



Inflammasome and extrahepatic organ failure in acute-on-chronic liver failure

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Comment on: Clària J, Stauber RE, Coenraad MJ, *et al.* Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology* 2016;64:1249-64.

Received: 15 February 2017; Accepted: 28 February 2017; Published: 31 March 2017.

doi: 10.21037/jphe.2017.03.02

View this article at: <http://dx.doi.org/10.21037/jphe.2017.03.02>

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute deterioration of liver function in patients with pre-existent chronic liver disease together with organ failure (OF). Six organs have been defined: brain, circulation, coagulation, kidneys, lungs and liver. Consequently, it is associated with high short-term mortality (1). The prevalence of ACLF is around 30% among patients with end-stage cirrhosis hospitalized with acute decompensation (AD). Patients are dynamically classified as having ACLF according to the number of OFs (corresponding to three grades of severity), with an increased risk of short-term death. Mortality correlates better with the early clinical course of ACLF than with the initial grade at presentation, especially between the third and seventh day after diagnosis (2). Bacterial infections and active alcoholism were the main precipitating factors, although up to 40% of cases the trigger was unknown. The systemic inflammatory response is a typical feature of this entity, as patients shown higher levels of plasma C-reactive protein and white cell count than those without ACLF even in the absence of infections, which also correlates with the number of OFs (1). Patients with advanced cirrhosis have abnormalities in the immune function because of the dynamic and paradoxical coexistence of exaggerated inflammatory response and immune paralysis (3). The former is mainly originated by gut-derived microorganisms' translocation into the circulation, and leads to the production of pro-inflammatory cytokines and

enhanced synthesis of nitric oxide (4). Released molecules by dying hepatocytes and other injured tissues damage-associated molecular patterns (DAMPs) also cause systemic inflammation. Immune paralysis, a compensatory anti-inflammatory mechanism to the exaggerated inflammation, occurs predominantly in severely decompensated cirrhosis and is common in ACLF. The degree of cellular immune depression is comparable in ACLF and sepsis. The study of Wasmuth *et al.* showed a decreased production of *ex vivo* TNF α and HLA-DR expression in both groups as compared to patients with stable cirrhosis and healthy controls (5).

The immune dysfunction plays a pathogenic role in several clinical manifestations of cirrhosis, and is related to hemodynamic derangement, increased susceptibility to bacterial infection, renal dysfunction, hepatic encephalopathy (HE) and ACLF (4-7). The main difference between ACLF and AD is the high short-term mortality associated to the presence of more than one OF (22% in ACLF-1 *vs.* 5-7% in AD) (1). Extrahepatic organ dysfunctions may be secondary to cell damage or hypoperfusion due to the effect of inflammatory mediators, in the setting of an exacerbation of the exaggerated inflammatory response presented in AD after a precipitating event (8). A better characterization of this mechanism could imply the search of new therapeutic targets to prevent and treat this syndrome.

The paper by Clària *et al.* supposes an advance in

this direction by analyzing the correlation between the course of inflammatory mediators and the presence and prognosis of ACLF in 522 patients with decompensated cirrhosis (237 suffering ACLF) and 40 healthy controls (9). Several cytokines and a marker of systemic oxidative stress human non-mercaptalbumin 2 (HNA2) were measured in patients with and without ACLF, and chronological relationship between these changes and ACLF severity were determined. Patients with cirrhosis showed higher levels of all cytokines. Those with ACLF had significantly higher levels of pro-inflammatory cytokines and HNA2 than those without it, with no differences in the remaining mediators. Baseline levels in ACLF were associated to short and mid-term mortality, and there was a progressive increase in IL-6, IL-8 and IL-1ra values from ACLF-1 to ACLF-3. These observations suggest a pathophysiological role of systemic inflammation in AD and ACLF, the higher severity of systemic inflammation the worse prognosis of ACLF.

The predominating cytokines profile in patients with ACLF varied with the precipitating event, suggesting different pathways depending on the trigger exacerbating the systemic inflammation. TNF α , IL-6 and IL-1ra levels were characteristically higher in bacterial infection-precipitated ACLF in contrast to the higher IL-8 values observed in patients with active alcoholism as trigger, especially if alcoholic hepatitis (AH) was present (10). Other precipitant events and those unidentified did not show any differential increased cytokine pattern, so they could rarely be attributed to covert bacterial infection. The association of systemic circulatory dysfunction with ACLF was also studied by measuring plasma renin concentration (PRC) levels. Despite PRC levels were higher in ACLF patients, they were not independently associated with ACLF as was the case with cytokines IL-6 and IL-8 and HNA2 values. There were also no differences between the PRC values across the three ACLF grades. In addition, there was an association between changes in systemic inflammation markers and the course of ACLF not observed with this systemic circulatory dysfunction indicator. These results support that ACLF developed within a further increase in systemic inflammation and systemic circulatory dysfunction presented in patients with AD, but the strength of the association between systemic inflammation and ACLF is much stronger than that from systemic circulatory

dysfunction. This implied that potential therapeutic targets aimed to prevent the deleterious effect in organ functions in patients with AD, or to treat ACLF if established, should also focus on systemic inflammation. As mentioned above, there are different ways of measuring systemic inflammation. Those mediators most related to ACLF and their advantages and disadvantages, if any, regarding their usefulness in this syndrome are represented in *Table 1*.

Enhancing or decreasing immune system therapies have already been tested in patients with cirrhosis. In this regard, bacterial decontamination has shown to reduce systemic inflammation, spontaneous bacterial peritonitis prevalence, hepatorenal syndrome (HRS), HE and mortality (11). Anti-inflammatory drugs such as infliximab and corticosteroids have shown to be beneficial in AH (12,13), and even treatment with non-selective beta-blockers has been associated with reduced severity of systemic inflammation and improved survival in ACLF by increasing gut motility and reducing bacterial translocation (14). Granulocyte colony-stimulating factor (G-CSF) therapy has shown an improvement in short-term survival in patients with ACLF. The effectiveness may be due to hepatic regeneration through stem cells migration from the bone marrow to the liver, traduced by an improvement in the hepatic function. G-CSF therapy has also been related to a lower incidence of HRS and sepsis. The increased peripheral neutrophil count observed may be the reason of this finding, as neutrophil dysfunction has been related to HRS and sepsis in patients with ACLF (15). The accurate mechanisms of each OFs and their chronological correlation to systemic inflammation and systemic circulatory dysfunction requires further investigation. Establishing these complex pathways may permit to find a bridge therapy until liver transplantation in potential candidates. Given the parallel changes in systemic inflammation markers and the course of ACLF observed in the mentioned study, sequential measurements of systemic inflammation mediators could assess treatment effectiveness and prognosis.

In conclusion, the study by Clària *et al.* emphasizes the role of systemic inflammation in the presence, course and prognosis of ACLF. It also identifies characteristic profiles of cytokines depending on the precipitating event. Further studies on this basis could improve outcomes by identifying patients with AD at greatest risk of developing OFs.

Table 1 Systemic inflammation and systemic circulatory dysfunction mediators in ACLF

Mediators	Advantages	Disadvantages
Systemic inflammation		
IL-6	Strongly associated with ACLF; related to severity, increasing parallelly from ACLF-1 to ACLF-3; baseline values associated with short-term mortality; higher levels if ACLF trigger was bacterial infection	–
IL-8	Strongly associated with ACLF; related to severity, increasing parallelly from ACLF-1 to ACLF-3; baseline values associated with short-term mortality; higher levels if ACLF trigger was active alcoholism; associated with ACLF-RF	–
HNA2	Strongly associated with ACLF; baseline values associated with short-term mortality; associated with ACLF-RF	No significant changes from ACLF-1 to ACLF-3
TNF α	Higher levels if ACLF trigger was bacterial infection; <i>ex vivo</i> secretion is reduced in ACLF patients (cellular immune depression)	Not independently associated with ACLF
IL-1ra and IL-10	The only identified anti-inflammatory cytokines with higher levels in patients with than without ACLF; IL-1ra; related to severity, increasing parallelly from ACLF-1 to ACLF-3; higher levels if ACLF trigger was bacterial infection	Not independently associated with ACLF; unbalance in favor of pro-inflammatory cytokines
SIRS	Easy to measure	Not shown by most patients with ACLF
Systemic circulatory dysfunction		
PRC	Higher levels in ACLF patients; sensitive to changes in effective circulating volume; not influenced by GFR	Not independently associated with ACLF; changes not associated with ACLF course; no significant changes from ACLF-1 to ACLF-3
PCC	Higher levels in ACLF patients; sensitive to changes in effective circulating volume	Influenced by GFR in ACLF-RF patients

ACLF, acute-on-chronic liver failure; HNA2, human non-mercaptalbumin 2; PRC, plasma renin concentration.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Public Health and Emergency*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jphe.2017.03.02>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jphe.2017.03.02

Cite this article as: Sendra C, Ampuero J, Romero-Gómez M. Inflammasome and extrahepatic organ failure in acute-on-chronic liver failure. *J Public Health Emerg* 2017;1:34.