EDITORIAL

Are We Ready to Evaluate Adrenal Function in Patients With Decompensated Cirrhosis and Acute-on-Chronic Liver Failure?

Cortisol is a pluripotent hormone responsible for orchestrating response to stress.[1] Relative adrenal insufficiency (RAI) is a condition characterized by inadequate levels of cortisol, which are not high enough to deal with the severity of illness.[1] Several studies have been reported assessing the prevalence and clinical impact of RAI in cirrhosis. In critically ill patients with cirrhosis, RAI is highly prevalent (51%–68%) and is associated with hemodynamic instability, renal failure, and increased mortality.[2,3] Moreover, studies have also been reported evaluating the presence and consequences of RAI in non–critically ill patients with decompensated cirrhosis; however, methods used to evaluate RAI in these studies were heterogeneous, and sample sizes were low.[4–6] The prevalence of RAI in these latter studies ranged between 7% and 60%, and possible association with clinical outcomes was not found consistently in all studies.[4–6] Therefore, there is need for further studies investigating the prevalence and clinical consequences of RAI in patients with decompensated cirrhosis.

A study by Piano et al[7] published in this issue of *Clinical Gastroenterology and Hepatology* evaluated the prevalence and significance of RAI in 160 patients with cirrhosis hospitalized for acute decompensation, excluding patients with septic shock.[7] To date, this is the largest study on RAI in non–critically ill patients with cirrhosis. Diagnosis of RAI was based on delta serum total cortisol <9 μg/dL in patients with basal serum total cortisol <35 μg/dL after 250 μg adrenocorticotropic hormone (ACTH) was given intravenously (short Synacthen test), which is the most currently accepted method to evaluate RAI.[8] The most relevant findings of this study are as follows: (1) Almost half of the patients (49%) had RAI, which is a prevalence higher than that reported in previous studies using the same methodology in patients with similar liver dysfunction.[6] Factors independently associated with RAI were age, high-density lipoprotein cholesterol levels, and leukocyte count. These findings are in keeping with the proposed pathogenic mechanisms of RAI in critically ill patients. Among other factors, cytokines and other peptides derived from blood cells may compete with ACTH on its receptor inducing resistance to glucocorticoids and, together with substrate deficiency due to low lipoprotein cholesterol levels, may lead to a disturbed adrenal stress response.[9] In fact, in the current cohort serum cholesterol levels were lower than those reported in previous cohorts,[6] which could account, at least in part, for the higher prevalence of RAI reported. (2) Patients with RAI had higher risk of new bacterial infections, sepsis, septic shock, and circulatory dysfunction, whereas other complications such as hepatic encephalopathy and acute kidney injury were not associated with the presence of RAI. That seems reasonable because cortisol is essential for maintaining vascular tone and immune function. (3) The probability of 90-day mortality was higher in patients with RAI compared with those without RAI (26% vs 10%; $P = .008$, respectively). These findings are consistent with those from previous studies, which suggest a significant clinical impact of RAI.[6]

Overall, the study by Piano et al[7] in a large series of non–critically ill patients with cirrhosis confirms that RAI is common and is associated with relevant clinical complications and high mortality. However, despite these and previous results, currently there are not enough data to support the use of corticosteroids to treat RAI in patients with cirrhosis. In contrast to the general population in which corticosteroids are recommended for patients with septic shock who are not responsive to fluid and vasopressor therapy,[10] treating RAI in critically ill patients with cirrhosis is not recommended in current guidelines because results are controversial.[8] On the other hand, to our knowledge, there are no studies evaluating the role of cortisol supplementation in non–critically ill patients with cirrhosis and RAI. Although the results of the present study are of clinical interest, we believe that RAI should not be incorporated into the routine diagnostic work-up for hospitalized patients with cirrhosis until there are data showing beneficial effects of treating RAI in this population. The results of the study by Piano et al should encourage the design of randomized controlled trials aimed at investigating the effects of treating RAI on clinically relevant outcomes in patients with decompensated cirrhosis.

The most novel part of the study by Piano et al[7] relies on the results showing relationship between RAI and risk of organ failures (OF) and acute-on-chronic liver failure (ACLF). The study shows that patients with RAI at baseline had higher incidence of new OF and ACLF within a 90-day follow-up period compared with that of patients without RAI. However, the specific type of new OF was not reported in the study. In this regard, Piano et al suggest incorporating RAI as a new OF in the current definition of ACLF. Definition of ACLF, according to the CANONIC study (European Association for the Study of the Liver–Chronic Liver Failure [EASL-CLIF] definition), is based on acute decompensation of cirrhosis in association with OF and high 28-day mortality rate

(>15%).[11] Patients with ACLF grade 3 have ≥3 OF, and those with ACLF grade 2 have 2 OF, whereas ACLF grade 1 includes 2 subgroups of patients: (1) patients with single renal failure and (2) patients with kidney dysfunction and/or mild hepatic encephalopathy plus a "non-renal" OF. Overall, 28-day mortality in patients from the CANONIC study with ACLF grade 1 was 22%. In the study by Piano et al, 28-day mortality of patients with RAI without ACLF was 10%. However, when considering RAI as another "non-renal" OF for the definition of ACLF grade 1, the association of RAI with mild renal dysfunction and/or mild/moderate hepatic encephalopathy increased 28-day mortality to 28% (RAI-ACLF definition). Therefore, 28-day mortality rate in patients with ACLF grade 1 was similar when comparing EASL-CLIF and RAI-ACLF definitions (22% vs 28%, respectively) and significantly higher than that of patients without ACLF (5%). As a result, authors suggest incorporating RAI as a "non-renal" OF for the diagnosis of ACLF. With the use of the new classification of ACLF, the number of patients with ACLF would increase by an absolute value of 11% compared with the EASL-CLIF classification.

Despite these interesting results, some important issues should be considered before implementing this modified classification in clinical practice. First, it should be noted that at baseline, the number of patients with ACLF, the number of OF, and liver function test results were similar between patients with and without RAI. This contrasts sharply with other studies in which the presence of RAI was associated with ACLF, high number of OF, and impaired liver function.[3] Moreover, in this study the presence of RAI was only evaluated at baseline and not at the time of development of new OF or ACLF. Therefore, development of ACLF during follow-up could not be assessed by using the new RAI-ACLF definition. Overall, this raises the question as to whether RAI represents a characteristic of ACLF that should be included in the definition or a risk factor for ACLF. Second, ACLF is a very dynamic syndrome, and reassessment of ACLF at days 3–7 after its onset is better to predict 28-day mortality compared with baseline ACLF.[12] In the study under discussion, evaluation of RAI was only performed at baseline; therefore, it would be interesting to explore the behavior of RAI during follow-up. Third, it seems reasonable that the effects of treatment of RAI in non–critically ill patients with decompensated cirrhosis should be elucidated before incorporating this condition as part of the ACLF definition. Finally, the proposed new definition of ACLF that includes assessment of RAI should be validated externally in future studies.

In conclusion, the prevalence of RAI in hospitalized patients with cirrhosis is high and associated with high short-term mortality and development of bacterial infections, sepsis, septic shock, OF, and ACLF. These findings pave the way for the design of future clinical trials to assess the benefit of treating RAI in non–critically ill patients with decompensated cirrhosis. Finally, a new classification of ACLF including RAI as a new OF has been proposed. However, despite its potential interest, more information is needed before RAI is incorporated into the definition of ACLF.

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Conflicts of interest
The authors disclose no conflicts.

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