Prevalence and clinical significance of relative adrenal insufficiency in decompensated cirrhosis

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Relative adrenal insufficiency (RAI) is characterised by insufficient production of cortisol relative to organ demand. It frequently occurs in people hospitalised with cirrhosis, but there is uncertainty over the true prevalence and clinical significance of RAI in this complex group of patients.

For example, a recent prospective study of 160 inpatients with decompensated cirrhosis (defined as jaundice, ascites, variceal haemorrhage or hepatic encephalopathy) found RAI in 78 cases (49%). The diagnosis of RAI was associated with a higher risk of sepsis, shock, organ failure and 90-day mortality, with similar prognostic value to nonrenal organ failures.[1]

In this issue of *JRCPE*, Nandish et al.[2] describe the prevalence of RAI in patients with decompensated liver cirrhosis in the intensive care unit (ICU) without associated sepsis or haemodynamic instability. RAI or critical illness-related corticosteroid insufficiency refers to an inadequate cortisol response for the physiological need. It develops in states of systemic inflammation and haemodynamic compromise such as septic shock. In the general patient population with septic shock, RAI is associated with further haemodynamic instability and increased mortality and so steroid treatment is recommended with an associated survival benefit.[3,4]

In liver disease, however, the situation is more complex as adrenal insufficiency can be a feature of liver disease per se.[5] The exact mechanisms are unclear, but the systemic inflammation and haemodynamic disturbance that characterise septic shock and increase the prevalence of RAI are also present to a lesser extent in the pathophysiology that may drive decompensation of cirrhosis. Bacterial translocation from the gut is thought to increase proinflammatory cytokines systemically, promoting peripheral arterial vasodilation and cardiomyocyte dysfunction leading to relatively low circulating volume.[6]

The severity of this systemic inflammation increases with liver disease severity and decompensation events. Of the proinflammatory cytokines, tumour necrosis factor-α reduces adrenocorticotropic hormone (ACTH) secretion and so may reduce cortisol secretion in turn. Advanced chronic liver disease is also associated with low cholesterol and high-density lipoprotein and thus reduced substrates for cortisol synthesis and lower levels of corticosteroid-binding globulin and albumin, factors required to bind and transport cortisol. Indeed RAI has been associated with increased liver disease severity and lower high-density lipoprotein in several studies.[7]

Adrenal insufficiency has 15–80% prevalence in noncritically ill patients with cirrhosis, whilst RAI has 10–77% prevalence in critically ill patients with cirrhosis.[7–9] When patients are categorised by aetiology of critical illness, RAI has 10–77% prevalence in sepsis, 2–60% prevalence in variceal bleeding and 58–62% in acute-on-chronic liver failure.[10,11]

The paper by Nandish et al.[2] contributes to this field by describing a 60% prevalence of RAI in critically ill patients with decompensated cirrhosis in the absence of sepsis, haemodynamic instability or acute-on-chronic liver failure.

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Their cohort comprised 24% of ICU admissions with cirrhosis, largely due to variceal bleeding and/or hepatic encephalopathy.

A major limitation of studies surrounding RAI in patients with cirrhosis is the variation in methods and criteria used to define RAI, giving rise to wide variation in reported prevalence and outcomes. RAI definitions have been based on baseline cortisol levels, short Synacthen test (SST), low-dose SST, corticotrophin-releasing hormone test, metyrapone test and insulin-induced hypoglycaemia test. Different cutoff levels have been used in some studies and cortisol measurement has also varied between total plasma cortisol, free serum cortisol and salivary cortisol.

Within the same patient cohort, RAI prevalence can vary from 30% to 60% in cirrhosis with variceal bleeding or from 7.4% to 49.4%, 9% to 33% and 29% to 60% in stable cirrhosis using different methods to define RAI.[7] Such wide variation makes it difficult to evaluate Nandish et al.'s data[2] in the context of studies using different methodology, but one study by Chawlani et al.[12] using similar methods showed 58% RAI prevalence in patients with cirrhosis in the absence of sepsis, haemodynamic instability or acute-on-chronic liver failure who were admitted to the gastroenterology department rather than ICU. This implies the need for ICU-level care is not associated with an increased RAI prevalence, although Nandish et al.[2] do not report measures of their patients critical illness (e.g. APACHE II) or the type of intensive care support required.

There is no gold standard identification of RAI in patients with cirrhosis. In critically ill patients without cirrhosis, the favoured methods have been narrowed down to the change in total plasma cortisol <9 μg/dl pre and 60 min post 250 μg of synthetic ACTH (SST) and a random total plasma cortisol of <10 μg/dl,[3] criteria that were used by Nandish et al.[2] in addition to a post synthetic ACTH total plasma cortisol of >20 μg/dl. However, these parameters may be less accurate in patients with cirrhosis, due to overestimation of biologically active cortisol using total rather than free plasma cortisol. Only free cortisol is biologically active, whereas the majority of cortisol exists biologically inactive, bound to corticosteroid-binding globulin and albumin.[13] These binding protein levels reduce with worsening liver disease severity, thus lowering total cortisol.[14,15] Correspondingly, multiple studies have shown significantly higher estimates of adrenal insufficiency using total vs free cortisol SSTs.[3] Nandish et al.'s data[2] may therefore overestimate RAI prevalence, supported by the lower serum albumin found in their RAI vs non-RAI group.

RAI has been associated with worse clinical outcomes and mortality in most studies.[1,7,12] However, the results from Nandish et al.'s study[2] did not show an association of RAI with short-term mortality, leading the authors to conclude that screening for RAI is not indicated in their studied patient group and therefore steroid treatment is unlikely to be beneficial.[2] Even in patients with cirrhosis and septic shock, the only double-blind randomised controlled trial conducted to date showed that steroids reduced vasopressor requirement, but not mortality,[16] whilst cohort studies of patients with cirrhosis and vasopressor-dependence showed mixed results on survival benefit with steroid therapy.[7]

In conclusion, Nandish et al.'s study[2] has contributed to the reporting of an increased prevalence of RAI in patients with cirrhosis. A wider consensus on RAI diagnostic criteria is still needed for the most accurate investigation of RAI prevalence across the spectrum of cirrhosis and critical illness, its relevance to clinical outcomes and whether steroid treatment could offer clinical benefit in selected patient groups.

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