Adrenal insufficiency in patients with decompensated cirrhosis

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Abstract

Adrenal reserve depletion and overstimulation of the hypothalamus-pituitary-adrenal (HPA) axis are causes for adrenal insufficiency (AI) in critically ill individuals. Cirrhosis is a predisposing condition for AI in cirrhotics as well. Both stable cirrhotics and liver transplant patients (early and later after transplantation) have been reported to present AI. The mechanisms leading to reduced cortisol production in cirrhotics are the combination of low cholesterol levels (the primary source of cortisol), the increased cytokines production that overstimulate and exhaust HPA axis and the destruction of adrenal glands due to coagulopathy. AI has been recorded in 10%-82% cirrhotics depending on the test used to evaluate adrenal function and in 9%-83% stable cirrhotics. The similarity of those proportions support the assumption that AI is an endogenous characteristic of liver disease. However, the lack of a gold standard method for AI assessment and the limitation of precise thresholds in cirrhotics make difficult the recording of the real prevalence of AI. This review aims to summarize the present data over AI in stable, critically ill cirrhotics and liver transplant recipients. Moreover, it provides information about the current knowledge in the used diagnostic tools and the possible effectiveness of corticosteroids administration in critically ill cirrhotics with AI.

Key words: Critically ill; Cirrhosis; Adrenal insufficiency; Corticosteroid

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Core tip: Adrenal insufficiency is present in both critically ill and stable cirrhotics and in liver transplant recipients early or later after transplantation. Due to certain difficulties in determining cortisol levels and lack of gold standard method, the incidence of adrenal failure varies and depends on each test used for assessment of adrenal function. Corticosteroid administration has not been elucidated whether it leads to beneficial outcome in critically ill cirrhotics.

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INTRODUCTION

Cirrhosis is characterized by hyperdynamic circulatory failure, low arterial pressure, peripheral vasodilatation and increased production of cytokines. Although, the adrenal insufficiency (AI) among critically ill cirrhotics was firstly described in 1960 by Peterson et al, there is still an increased interest in it during the last decade. Initially, Mark et al used the term “hepato-adrenal syndrome” to describe the AI found in the critically ill cirrhotic patients correlated with increased mortality. Nowadays, it is established that AI is found in critically ill cirrhotic patients with or without sepsis, in those with stable cirrhosis and in liver transplant recipients. There may be a deficient response of adrenal glands to the increased stress stimulation of hypothalamus-pituitary-adrenal (HPA) axis in critically ill patients named initially relative AI (RAI), replaced later on by the term critical illness related corticosteroid insufficiency (CIRCI). This review aims to summarize and to discuss the part of critical illness related adrenal insufficiency (CIRCI) in critically ill cirrhosis patients.

PATHOPHYSIOLOGY

AI has been described in all stages cirrhotic patients, critically ill and stable, implying that adrenal failure is a feature of liver dysfunction per se. However, the exact mechanism leading to AI in cirrhotic population is not yet clear. It is known that cholesterol is an important substrate for steroidogenesis and adrenal glands synthesize cortisol whenever is necessary. One main characteristic of cirrhotic patients is the low levels of total cholesterol, high density lipoprotein (HDL) and low density lipoprotein, which are correlated with the severity of liver disease. Thus, in cirrhosis, the adrenal glands cannot synthesize the adequate quantities of cortisol especially under stress conditions leading to “adrenal exhaustion syndrome” ending to AI. In addition, cirrhosis is characterized by the increased circulating pro-inflammatory cytokines, like tumor necrosis factor (TNF-α), interleukin-6 (IL-6), IL-1 and endotoxin-like lipopolysaccharides, which affect negatively the feedback of HPA axis. TNF-α reduces the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, via completion with corticotrophin receptor and contributes to glucocorticoid deficiency and the pro-inflammatory cytokines contribute to the decreased levels of HDL cholesterol via inhibition of apolipoprotein- A1 synthesis resulting in limited delivery to adrenal glands. Finally, prolonged prothrombin time, a common finding in cirrhotic patients, could rarely lead to adrenal hemorrhage and impaired cortisol production.

ASSESSMENT OF HPA FUNCTIONALITY

Total cortisol consists of free and binding forms. Only 10% of circulating cortisol is free and bioactive. The rest is mainly bound with corticosteroid-binding globulin (CBG) and less with albumin. In cirrhotic patients, hypoalbuminemia is positively correlated with the severity of liver disease leading to decrease of total cortisol and increase of the free bioactive fraction. Thus, the common methods for assessing adrenal function, based on total cortisol, may lead to overestimation of AI in patients with cirrhosis. In this case, the optimal method would be the direct evaluation of free cortisol, but its measurement is difficult in daily clinical practice. Indirectly free cortisol can be calculated by Coolens equation based on total cortisol and CBG. Salivary cortisol has been used as a surrogate marker of free cortisol but present limitations in cirrhotics including the high incidence of oral candidiasis, gums bleeding and parotitis especially in alcoholics. Finally, free cortisol index (FCI = total cortisol/CBG ratio) reflecting serum free cortisol levels has been used. FCI > 12 is indicative of normal adrenal function. However, it should be mentioned that none of these formulae/indexes takes into account albumin levels.

Basal serum cortisol and ACTH

A basal standard total cortisol level < 138 nmol/L between 8.00–9.00 am indicates AI, while basal total cortisol > 415 nmol/L makes the diagnosis of AI unlikely. Primary AI is indicated by ACTH > 22 pmol/L, while normal values of ACTH could not rule out secondary AI.

Short synacthen test

Tetracosactide (Synacthen) and cosyntropin (Cortrosyn) are the analogues used for Short synacthen test (SST). Plasma cortisol is monitored at 0, 30 and 60 min after intravenous (iv) or intramuscular injection of 250 μg corticotrophin (Synacthen). If poststimulation cortisol exceeds 550 nmol/L, primary AI is excluded. SST uses supraphysiological doses of corticotropin and is preferred in critically ill patients. In this patient group, AI is defined either by random total cortisol < 276 nmol/L or by delta cortisol < 250 nmol/L (CIRCI criteria). Delta cortisol is the difference between basal cortisol and cortisol measured 60 min after iv injection of corticotropin analogue.

Low dose SST

Plasma cortisol is measured 30 min after stimulation with 1 μg corticotropin given iv. If peak cortisol exceeds 500 nmol/L, adrenal function is normal. This test seems to be more sensitive than SST and evaluates better the stable cirrhotic patients.

Corticotrophin-releasing hormone test

This is a test with high cost in which both cortisol and ACTH are measured at 0, 15, 30, 45, 60, 90 and 120 min after injection of 1 μg/kg corticotrophin-releasing
ADRENAL FAILURE AND LIVER DISEASE - CURRENT EVIDENCE

The percentage of AI in cirrhotic patients varies among different studies and depends on the methodology and criteria used to estimate adrenal function. The classification of trials according to critical illness, stability of cirrhosis, and whether or not researchers included liver transplant population makes the evaluation of existing data more straightforward. The relevant studies were extracted conducting research in the following databases until August 2014: PubMed/MEDLINE, gms, gms meetings and Scopus using the term “cirrhosis and AI”. Moreover we included the related posters and oral announcements of the European (EASLD) and American (AASLD) liver meetings of 2013 and 2014.

Critically ill cirrhotic patients

The data regarding the prevalence of AI in critically ill cirrhotic patients are summarized in Table 1. Marik et al. were the first who evaluated AI in 340 critically ill cirrhotic patients using LDSST. For highly stressed patients the applied cut-offs were random total cortisol < 552 nmol/L and for stressed patients the cut-offs were either random cortisol < 414 nmol/L or a 30 min post synachten level of cortisol < 552 nmol/L. AI was reported in 72% critically ill cirrhotics overall; 33% presented with acute liver failure; 66% with chronic liver failure (CLF), while 62% were short term liver transplant recipients and 92% long term recipients. HDL was the only predictive factor for the AI prevalence. The same authors reported 54% AI in a similar group of patients applying the aforementioned criteria. Another study came from Thevenot et al. who prospectively evaluated 30 septic cirrhotic patients. AI was found in 3 (10%), by using serum total cortisol < 510.4 nmol/L 60 min after SST. Salivary cortisol was also assessed. It was found to be significantly correlated with serum free cortisol (P < 0.0001) which was very high in patients with Child Pugh score C. The authors concluded that salivary cortisol was the most suitable marker adrenal function evaluation in patients with cirrhosis in the absence of serum-free cortisol availability. In another study including 75 cirrhotic patients with sepsis, a higher proportion (76%) had AI compared to the study of Thevenot et al. . The discrepancy between these two studies could be explained by the different criteria used to determine AI (in the latter study, AI was defined as delta cortisol < 250 nmol/L (Table 1).

In a prospective study conducted in United Kingdom from 2007 to 2009, 56 patients with ALF and 36 with acute on CLF (ACLF) underwent SST for adrenal function assessment. All were critically ill patients under vasopressor administration secondary to cardiovascular instability. According to CIRCI criteria, AI was found in 58% ACLF patients and it was related with HDL levels and with worse outcome. Triantos et al. conducted an observational prospective trial evaluating the presence of AI (using both SST and LDSST) in 20 critically ill patients with cirrhosis and variceal bleeding. This group was compared with 14 healthy individuals and 60 patients with stable cirrhosis. According to SST, AI was found in similar proportion (30%) in critically ill and stable patients, while according to LDSST (peak cortisol level < 690 nmol/L or delta cortisol < 250 nmol/L for critically ill cirrhotics and peak cortisol < 414 nmol/L for stable cirrhotics) AI was found in 60% critically ill patients vs 48% stable cirrhotics. Moreover, the hypothesis that CIRCI occur both in septic and non-septic cirrhics was confirmed in two more studies. AI (by using the SST) was found in 38% septic cirrhics with severe variceal bleeding and in 73.5% non-septic critically ill cirrhotics. In the study of du Cheyron et al. , AI was retrieved in 31 (62%) of 50 critically ill cirrhotics (according to the thresholds of 414 nmol/L for baseline cortisol and 250 nmol/L for delta cortisol, if baseline cortisol values were between 414 and 938 nmol/L). Using the same criteria, AI was found in 10 (77%) out of 14 and 17 (68%)...
Table 1 Characteristics and outcomes of the included studies in critically ill cirrhotics

| Ref. | Study design; study period; country | No. of patients; type of liver disease | Adrenal failure | Other observations | Definition of adrenal failure |
|------|------------------------------------|----------------------------------------|----------------|------------------|-------------------------------|
| "Etogo-Asse et al\(^{[49]}\)" Prospective, observational; 2007-2009; United Kingdom | 163 patients; 89 ALF and 74 AOCLF; 56 ALF and 36 AOCLF underwent SST | AOCLF: 21/36 58% ALF: 27/56 48% | Among those with AI 17/32 (47%) with HDL < 0.1 mmol/L, vs 2/17 (12%) with HDL > 0.6 mmol/L, had increment < 250 nmol/L. HDL was lower in non survivors both in AOCLF and ALF. | SST to those required vasopressor administration or cardiovascular instability. CIRCI: Basal cortisol < 275 nmol/L or delta cortisol < 250 nmol/L. ALF: Peak cortisol < 300 nmol/L in non-stressed patients and delta cortisol of < 250 nmol/L or a random total cortisol < 276 nmol/L in stressed patients. AOCLF: 21/36 58% ALF: 27/56 48% | CIIRCI: Basal cortisol < 275 nmol/L or delta cortisol < 250 nmol/L. Alvarez et al. 2010. | | Triantos et al\(^{[5]}\) Prospective, observational; NR; NR | 20 patients; cirrhosis and variceal bleeding vs 74 controls (14 healthy and 60 stable cirrhosis) | SST: 6/20 30% LDSST: 6/10 60% Healthy (SST and LDSST): 0/14 0% Stable (LDSST): 24/50 48% Stable (SST): 3/10 30% | AI wasn't associated with outcome. Those with AI and variceal bleeding had higher baseline and peak level of cortisol with stable cirrhosis, but similar delta cortisol. With SST for albumin > 2.5 mg/dL, AI: 4/16 (25%) with variceal bleeding vs 1/8 (12.5%) in cirrhosis control. With LDSST, for albumin > 2.5 mg/dL, AI: 6/10 (80%) with variceal bleeding vs 16/39 (41%) in cirrhosis control. | SST AI: Peak cortisol < 300 nmol/L in non-stressed patients and peak cortisol level of < 690 nmol/L or a delta cortisol < 250 nmol/L in stressed patients. | | Thevenot et al\(^{[7]}\) Prospective; 2008-2009; France | 30 patients; septic cirrhotic | 3/30 10% | Significant correlation between salivary and serum free cortisol (P < 0.0001). Serum total cortisol were significantly lower in Child-Pugh score C than B or A, in contrary with free cortisol which had a non significant rise. | SST AI: Post-SST SC < 510.4 nmol/L Salivary cortisol was also calculated. | | Arabi et al\(^{[48]}\) Randomized double blind; 2004-2007; Saudi Arabia | 75 patients; septic shock and cirrhosis in ICU | 57/75 76% | RAI: Delta cortisol < 250 nmol/L. S | | | du Cheyron et al\(^{[6]}\) Prospective; 2003-2005; France | 50 patients; decompensated cirrhosis in ICU (critical ill with acute on chronic liver disease) | 31/50 62% | S | | | Thierry et al\(^{[8]}\) Prospective; March to December 2005; France | 34 patients; septic shock, 14 with and 20 without cirrhosis | Cirrhotic: 11/14 77% Non cirrhotic: 10/20 50% | | | | Fernández et al\(^{[9]}\) Prospective and retrospective; group 1 2004-2006, group 2 2001-2004 | Group 1: 25 patients; cirrhosis and septic shock Group 2: 50 patients; no assessment of adrenal function | 17/25 68% | | | | Tsai et al\(^{[10]}\) 2004-2005; Taiwan | 101; cirrhosis and severe sepsis required ICU | 52/101 51.4% Hemodynamically unstable: 43/54 79.61% Stable: 9/47 19.14% | ICU mortality: 71.4% vs 26.5%. Hospital mortality: 80.7% vs 36.7% (AI vs normal). Correlation with the severity of liver disease. | | |
| Authors | Study Description | Study Population | SST | LDSST | Results |
|--------|------------------|------------------|-----|------|---------|
| Marik et al<sup>35</sup> | Retrospective; NR, United States | 221 patients, LTICU | At admission: 120/221 (54%) | Low HDL could predict the development of AI | AI was related with the severity of liver disease (AI was found in 76% of patients with Child-Pugh class C vs 25% of patients with Child-Pugh class B, \( P = 0.08 \)), a finding which was confirmed by the trial of Tsai et al<sup>54</sup> evaluating 101 cirrhotics with sepsis as well. The common finding in the last four studies was the strong association between AI and outcome concluding that glyocorticoid supplementation could lessen the mortality. |
| Marik et al<sup>56</sup> | Retrospective; 2002-2004, United States | 340 patients, ALD, CLD, post OLT recently and remote LT | Overall: 245/340 (72%) | Low HDL could predict the development of AI | Serotonin and CRP were not associated with severity of liver disease, CRP or etiology of cirrhosis |
| Nair et al<sup>51</sup> | India | Critical ill cirrhotic in ICU, without sepsis | AI is not associated with severity of liver disease, CRP or etiology of cirrhosis |
| Saffioti et al<sup>58</sup> | 2009-2013 | 80, cirrhotic pre-LT | Patients with AI had higher MELD (19 vs 15, \( P = 0.003 \)), pre-LT INR, bilirubin and potassium, and lower sodium and haemoglobin levels |
| Graupera et al<sup>59</sup> | Spain | 37, cirrhotic with severe variceal bleeding | 14/37 (38%) | No differences in overall survival |

NR: Not reported; AI: Adrenal insufficiency; HDL: High density lipoprotein; SC: Serum cortisol; ICU: Intensive care unit; ALF: Acute liver failure; AOCLF: Acute on chronic liver failure; SST: Short synacthen test; LDSST: Low dose short synacthen test; NR: Not reported; CIRCI: Critical illness related adrenal insufficiency; RAI: Relative adrenal insufficiency; LTICU: Liver transplant intensive care unit; OLT: Orthotopic liver transplantation; CLD: Chronic liver disease; ALD: Acute liver disease; LT: Liver transplantation; MELD: Model for end-stage liver disease; CRP: C-reactive protein; INR: International normalized ratio.

The prevalence of AI ranged from 10% to 77% according to SST and 54% to 72% according to LDSST. This wide variation in the AI prevalence could be explained by the variant thresholds used. When more strict criteria for the AI diagnosis were applied, AI prevalence appeared low around 22.5%<sup>58</sup>. LDSST overestimated AI, when performed in stressed patients and was more reliable for the detection of subclinical AI in stable cirrhotics. This assumption was confirmed.
in the study of Triantos et al\textsuperscript{(5)} in which both tests were applied. With the exception of sepsis, variceal bleeding was the complication of the underlying cirrhosis in two studies\textsuperscript{(50,56)}. In the latter group of cirrhotics with variceal bleeding, AI was diagnosed in 30%-38% with SST and in 60% with LDSST. It was LDSST again, which overestimated the prevalence of AI. Furthermore, the fact that Marik detected AI in non-adrenal insufficient cirrhotics three days after the first evaluation, indicated that adrenal function is a dynamic process and critically ill cirrhotics should be re-assessed\textsuperscript{(21)}. The common study endpoints were that low HDL levels predict the presence of AI in critically ill cirrhotics and that impaired adrenal function was associated with the outcome\textsuperscript{(8,23,49)}. AI was also more apparent in patients with more severe liver disease. It should be mentioned that these studies calculated total cortisol without taking into account the low levels of serum albumin. Some of the studies defined adrenal failure as an independent risk factor for worse outcome\textsuperscript{(49,54)}, while others showed no association\textsuperscript{(53,50,51)}. Interestingly, there was no correlation between AI and worse outcome in cirrhotic patients with variceal bleeding. Since the number of patients was low, safe conclusions could not be drawn.

**Not critically ill cirrhotic patients**

AI is present in stable patients with decompensated cirrhosis and its prevalence varies according to the applied diagnostic test (SST or LDSST). The data regarding the prevalence of AI in stable cirrhotic patients are indicated in Table 2.

In a prospective trial\textsuperscript{(56)}, adrenal function was evaluated in 79 stable cirrhotics. All patients underwent LDSST and AI was recorded in 34%, 28%, 30% of patients using as definition the presence of peak total cortisol < 494 nmol/L, peak free cortisol < 33 nmol/L at 30 min after stimulation or FCI < 12, respectively. Similarly to critically ill cirrhotics, total cortisol overestimated AI potentially due to the low levels of CBG and albumin, while FCI was correlated with free cortisol. No significant association was highlighted between the presence of AI and the outcome.

In the study of Acevedo et al\textsuperscript{(57)}, RAI was found in 37 (26%) of the 143 non-critically ill cirrhotics with acute decompensation. SST was also used for RAI determination. Interestingly, patients with RAI had longer duration of hospitalization, higher risk for infections, sepsis and hepatorenal syndrome (HRS) type I and higher mortality (during hospitalization and after three months of follow up) compared to those without RAI. In addition, RAI was not associated with the severity of liver disease and the type of decompensation with exception to type I HRS. The latter group of patients had a trend towards higher frequency of RAI. However, in the study of Kharb et al\textsuperscript{(10)}, AI was more frequent in patients with more severe liver disease as estimated by the Child-Pugh score. Moreover, low HDL cholesterol was associated with the presence of AI.

The LDSST was used in a study with 95 hemo-
dynamically stable cirrhotic patients\textsuperscript{(7)}. The thresholds were firstly basal serum total cortisol < 138 nmol/L and total cortisol 30 min after stimulation < 440 nmol/L, secondly serum total cortisol <500 nmol/L at 30 min after LDSST and thirdly delta cortisol < 250 nmol/L. The AI prevalence according to each of the above criteria was 7.4%, 19%, 27.4% and 49.4% respectively. Serum free cortisol was also measured and its levels were significantly associated with mortality. Patients with ascites and more severe liver disease had higher free cortisol (basal and after stimulation). In another study, using the same criteria for AI in 101 stable cirrhotics\textsuperscript{(8)}, AI was reported in 38%, 29% and 60%, respectively. Again, there was a strong relationship between AI and severity of liver disease.

Tan et al\textsuperscript{(5)} evaluated the presence of AI based on total and free cortisol in 43 stable cirrhotics using SST. AI was found in 39%, 47% and 23% of patients by using peak total cortisol < 500 nmol/L, CIRCI criteria (delta cortisol < 250 nmol/L) and FCI (< 12), respectively. In addition, AI was reported in only 12% of subjects by applying peak plasma free cortisol < 33 nmol/L. Therefore, there was a significant discrepancy of AI proportions by using variant diagnostic criteria. Plasma free cortisol was significantly associated with higher MELD score and mortality. In another study\textsuperscript{(36)} 88 stable, mainly alcoholic cirrhotics were evaluated with SST. AI was assessed with total cortisol (basal value < 250 nmol/L or peak total cortisol after stimulation < 500 nmol/L or delta cortisol < 250 nmol/L) and with salivary cortisol (basal values < 1.8 ng/mL or peak cortisol at 60 min < 12.7 ng/mL or an increase between these two values < 3 ng/mL). AI was overestimated by using total cortisol, compared to salivary cortisol (33% vs 9%), particularly in patients with albumin < 2.5 mg/dL. Ascites and HDL levels were independently associated with the presence of AI. The relatively low prevalence of AI in this study was attributable to the high proportion of patients with alcoholic cirrhosis. Alcohol caused pseudo-cushing syndrome potentially leading to compensation in regards to AI secondary to cirrhosis.

In total, seven studies\textsuperscript{(58-64)} confirmed that total cortisol overestimates AI in stable cirrhotics, compared to either FCI\textsuperscript{(58)} or salivary cortisol\textsuperscript{(60)} (Table 2). Interestingly, Privitera et al\textsuperscript{(61)} showed that total cholesterol contributed more to impaired cortisol production, compared to HDL. Nevertheless, in the study of Acevedo et al\textsuperscript{(64)}, RAI (defined by SST as delta cortisol < 250 nmol/L) HDL was significantly associated with severe infections ($P = 0.01$), septic shock ($P = 0.01$) and mortality ($P = 0.04$).

Summarizing the above results, SST was used in 10 studies and LDSST in 4\textsuperscript{(7,8,56)}, although the included population were non-critically ill cirrhotics\textsuperscript{(62)}. The prevalence of AI ranged from 26% to 80% according to the SST and 7.4% to 38% according to LDSST. When the CIRCI criteria were applied, the prevalence of AI was overestimated in all studies (46%-70% vs 34.6%-40%\textsuperscript{(10)}, 9.4% vs 7.4%-27.4%\textsuperscript{(7)}, 60% vs...
| Ref.        | Study design; study period; country | No. of patients; type of liver disease | Adrenal failure | Other observations | Definition of adrenal failure |
|------------|-------------------------------------|---------------------------------------|----------------|-------------------|------------------------------|
| Fede et al | Prospective, observational; NR; United Kingdom | 79 patients; cirrhosis for pretransplantation or decompensation of cirrhosis | TC: 27/79 (34%) FC: 22/79 (28%) [for FC < 25: 15/79 (19%)] FCI: 24/79 (30%) | AI was not correlated with the outcome | LDSST AI: Peak TC < 494 nmol/L at 20 or 30 min FC < 33 nmol/L FCI < 12 |
| Acevedo et al | Prospective, observational; 2008-2010 Spain | 143 patients; acute decompensation of cirrhosis - follow up for 3 mo | 37/143 (26%) | RAI was similar between different Child-Pugh scores and various causes of decompensations with the exception of HRS type-1 (trend for higher proportions) | SST RAI: Delta cortisol < 250 nmol/L in patients with basal serum TC < 938 nmol/L |
| Kharb et al | Cross sectional; 2010-2011; India | 25 ALD, 50 CLD, 10 post liver transplanted | ALD: 9/25 (34.6%) CLD: 20/50 (40%) (18/30 with child 2, 3 and 2/20 with child 1) Post LT: 4/10 (40%) RAI: ALD: 17/25 (68.4%), CLD: 23/50 (46%), post LT: 7/10 (70%) | AI was correlated with severity of liver disease | SST AI: Basal cortisol levels < 83 nmol/L or a peak cortisol response < 500 nmol/L RAI: Delta cortisol < 250 nmol/L |
| Thevenot et al | Prospective; 2008-2009; France | 95 patients; hemodynamically stable cirrhotic mainly alcoholic | 7/95 (7.4%) 18/95 (19%) 26/95 (27.4%) 47/95 (49.4%) (According each threshold) (1) 38/101 (38%) (2) 29/101 (29%) (3) 61/101 (60%) (4) 4/41 (10%) | Patients with Child C cirrhosis and those with ascites had higher non significant rise in basal and stimulated serum FC Serum FC levels were directly associated with the risk of non transplant-related mortality | LDSST AI: (1) basal serum TC < 138 nmol/L and a T30 serum TC < 440 nmol/L; (2) T30 serum TC < 500 nmol/L; (3) delta cortisol < 250 nmol/L |
| Fede et al | Prospective, observational; NR; United Kingdom | 101 patients; stable cirrhosis | AI more frequent in hypoalbuminemic patients, according TC and delta cortisol and related with the severity of liver disease TC and cFC were significantly related FCI was lower in patients with AI | | LDSST, FCI, cFC AI: Peak (1) TC < 500 nmol/L (2) TC < 442 nmol/L (3) Delta cortisol < 250 nmol/L (4) FCI < 12 |
| Tan et al | Prospective, observational; 2008-2009; Australia | 43 patients; stable cirrhosis | (1) 18/43 (43%) (2) 20/43 (47%) (3) 5/43 (12%) (4) 25/43 (58%) (5) 10/43 (23%) | With serum FC criteria, patients with AI had significantly higher MELD score (P = 0.03) and mortality (P = 0.0007) Serum TC was correlated well with serum FC in pts with albumin both > and < 30 g/L Serum FC correlated significantly with FCI at baseline but less strongly with peak FC Overall survival at 6 and 12 mo was similar between AI and non AI group according TC Serum FC correlated with SC A number of criteria were independent risk factors for AI | LDSST, FCI, cFC (1) Standard criteria: peak TC < 500 nmol/L (2) CIRCI criteria: delta cortisol < 250 nmol/L (3) Peak serum FC < 33 nmol/L (4) Any set of criteria (5) FCI < 12 |
| Galbois et al | Prospective, observational; 2006-2009; France | 88 patients; complication of cirrhosis - alcoholic mainly | TC: 29/88 (33%) SC: 8/88 (9.1%) | There was correlation between cFC and SC Between SC and TC there was correlation for alb > 2.5 mg/dL whereas for alb < 2.5 mg/dL there was correlation for T0 but no for T60 or delta cortisol Acites and HDL were independent risk factors for AI | SST TC: basal TC < 250 nmol/L or in T60 < 500 nmol/L or delta cortisol < 250 nmol/L SC: T0 < 1.8 ng/mL or T60 < 12.7 ng/mL or delta cortisol < 5 ng/mL |
AI based on plasma free cortisol, FCI and salivary cortisol was detected in 12%-28%, 0%-30% and 9.1%-37%, respectively. Predictive factors for the presence of AI were ascites, HRS-1, total and HDL cholesterol. AI was positively correlated with the severity of liver disease in the vast majority of studies [8-10,62] and with worse outcome in a few studies [7,61,64].

When plasma free cortisol was applied, AI was detected in a statistically lower proportion compared to the use of total cortisol [8,9,36,56,58,60]. However for values of albumin greater than 2.5 mg/dL, total cortisol was consistently correlated with free cortisol [36,60]. Moreover, plasma free cortisol was associated with FCI, salivary cortisol and calculated free cortisol. FCI is considered more appropriate diagnostic test for AI in stable cirrhics (when it is available) compared to total cortisol. In critically ill cirrhotics, the CIRCI criteria are recommended for Adrenal function evaluation; in case free cortisol is used, the thresholds are the same with those used in healthy individuals. Nevertheless, their implementation in stable cirrhotics is doubtful, so more studies are needed to define the gold standard method for AI diagnosis in non-critically ill cirrhotics.

Patients after liver transplantation
The results of the studies evaluating the AI prevalence in liver transplant recipients are summarized in Table 3. In the study by Kharb et al [20], AI was presented in 4 (40%) of the 10 liver transplant recipients (defined as basal cortisol levels < 80 nmol/L or levels of peak cortisol after stimulation < 500 nmol/L using SST). Using the criterion of delta cortisol < 250 nmol/L, RAI was detected in 70% of patients. These results indicated the possible need of corticosteroid administration in liver transplant recipients post operatively and until the liver function is fully restored. Moreover, Patel et al [65] proved that the administration of 1000 mg methylprednizolone during the operation...
was associated with better outcome, less need of vasopressors, invasive ventilation and renal replacement therapy. This supports the assumption that RAI is present in liver transplant patients as well. Marik et al[10] estimated AI by using LDSST in liver transplant recipients post operatively and later after transplantation. AI was reported in 109 (92%) of 119 and in 31 (61%) of 51 subjects, respectively. Liver transplant recipients recorded later after transplantation were treated with steroid-free immunosuppressive regimens. The high prevalence of AI was explained by the fact that the LDSST was the preferred test in stable patients, and thus AI was overestimated in stressed subjects.

**Treatment with steroids**

The data on corticosteroid administration in critically ill patients, especially in those with septic shock are controversial[52,66,67]. A recent meta-analysis[68] showed that low dose hydrocortisone improved shock reversal and short term mortality, but not 28-d mortality. Potential explanations were infections, gastrointestinal bleeding and hyperglycaemia observed during steroid administration. The recent International Guidelines for Management of Severe Sepsis and Septic Shock recommend the administration of low dose hydrocortisone intravenously for septic patients remaining hemodynamically unstable despite fluid resuscitation and vasopressor therapy.[12] The studies regarding the administration of cortisol in cirrhotics are presented in Table 4. Etoo-Asse et al[49] studied 51 vasopressor dependent-critically ill cirrhotics receiving hydrocortisone in a median dose of 200 mg/d. Interestingly, the mortality rate (65%) was similar between those and the group who did not receive corticosteroid supplementation. The only randomized double blind trial[69] of three years duration conducted in Saudi Arabic and included 75 cirrhotics with septic shock. Thirty nine patients receiving hydrocortisone (50 mg intravenously every six hours until shock resolution) compared with 36 patients receiving placebo. Although there was improvement in hemodynamic parameters ($P = 0.05$) in the hydrocortisone group, no difference was noticed regarding 28-d, intensive care unit (ICU) and hospital mortality. Controversially, the hydrocortisone group had higher frequency of shock relapse ($P = 0.03$) and gastrointestinal bleeding ($P = 0.02$). Alike, du Cheyron et al[70], found similar 30-d mortality between 14 patients who were treated with stress doses of cortisol and 17 who were not treated (50% vs 70%, respectively, $P = 0.29$).

Fernández et al[71] reported AI in 17 of 25 cirrhotics with septic shock treated with 50 mg hydrocortisone four times per day. This group was compared with a historical group with similar characteristics who was not on hydrocortisone. The hydrocortisone group presented higher rates of shock resolution (96% vs 58%, $P = 0.001$), ICU-survival (68% vs 38%, $P = 0.03$) and hospital-survival (64% vs 32%, $P = 0.003$). In the study of Mark et al[47] hydrocortisone (300 mg/d) administered in 140 vasopressor-dependent cirrhotics with acute liver disease (ALD) and chronic liver disease. The mortality rate was significantly lower in patients on hydrocortisone compared to those not treated with

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**Table 3 Characteristics and outcomes of the included studies in post transplanted patients**

| Ref. | Study design; study period; country | No. of patients; type of liver disease | Adrenal failure | Definition of adrenal failure |
|------|------------------------------------|----------------------------------------|----------------|------------------------------|
| Kharb et al[34] | Cross sectional; 2010-2011; India | 10; OLT | Post LT: 4/10 (40%) | AI: Basal cortisol levels < 83 nmol/L or a peak cortisol response < 500 nmol/L |
| | | | RAI: Post LT: 7/10 (70%) | RAI: Delta cortisol < 250 nmol/L |
| Marik et al[10] | Retrospective; 2002-2004; United States | 119 post OLT recently and 51 remote OLT | Recent LT: 109/119 (92%) | AI: (1) a random (stress) cortisol < 552 nmol/L/L in patients with hypoxemic respiratory failure, hypotension or requiring vasopressor agents and (2) a random level < 414 nmol/L or a 30-min post-low-dose cosyntropin stimulation test level of < 552 nmol/L in non-highly stressed patients |
| Patel et al[40] | Retrospective; NR; United Kingdom | 90 patients; ICU post OLT; 45 patients received bolus dose of 1000 ng methylprednisolone intraoperative vs 45 patients not receiving | First group: significant reduced requirements for fluid administration ($P = 0.02$), vasopressors ($P = 0.01$), renal replacement therapy ($P = 0.001$), invasive ventilation ($P = 0.01$), and ICU stay ($P = 0.02$), compared to the second group |

AI: Adrenal insufficiency; RAI: Relative adrenal insufficiency; SST: Short synacthen test; LDSST: Low dose short synacthen test; OLT: Orthotopic liver transplantation; LT: Liver transplantation; ICU: Intensive care unit; NR: Not reported.

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**Table 3** Characteristics and outcomes of the included studies in post transplanted patients
hydrocortisone (26% vs 46%, \( P = 0.002 \)). Furthermore, patients with AI on hydrocortisone required less doses of norepinephrine over the first 24 h \(( P = 0.02)\) compared to those without AI \(( P = 0.62)\) while patients with AI not receiving hydrocortisone required increased doses of vasopressors compared also with the non AI group \(( P = 0.04)\). Finally, Harry et al\(^{[6]}\) contrasted 20 cirrhotics with ALD or CLD and no benefit in survival and higher bacterial infections.

Summarizing the data of five non-randomized trials, glucocorticoids (200-300 mg/d) were usually administered in vasopressor dependant critically ill cirrhotics. In three studies, there was a temporary reduction of vasopressor doses in patients treated with steroids but mortality rates between those treated and those not treated with steroids\(^{[69,63,33]}\) were similar secondary to shock relapse and infection increase. However, opposite results come from two other studies\(^{[6,53]}\), reporting significant improvement in hemodynamic stability and mortality of cirrhotics treated either with 200 mg or 300 mg of corticosteroid.

### CONCLUSION

Based on recent data, AI is present in cirrhotics either due to the various parameters associated with the primary disease or as a characteristic of cirrhosis per se. The fact that AI prevalence is high not only in critically ill but also in stable cirrhosis further supports these data. So far, there has not been a consensus about the appropriate method for the precise AI diagnosis. The results vary according to each test used to evaluate adrenal function. Furthermore, the thresholds in patients with liver disease might be different from other populations and free cortisol cannot be not easily estimated and is costly. Salivary cortisol could be an alternative approach, although it has limitations as well. Additional double blind randomized studies should be recruited in order to identify the reliable cortisol cut offs. Moreover the benefits of cortisol administration should be further elucidated towards the appropriate given dose and administrative period in hospitalized patients. Ultimately, extreme caution should be urged and cost effectiveness should be taken into account.

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Table 4 Characteristics and outcomes of the included studies of patients treated with steroids

| Ref.                  | Study design; study period; country | No. of patients; type of liver disease | Hydrocortisone                  | Outcome |
|-----------------------|-------------------------------------|---------------------------------------|---------------------------------|---------|
| Etoo-Ase et al\(^{[1]}\) | Prospective, observational; 2007-2009; United Kingdom | 51 critical ill cirrhotic patients required vasopressors | 31 received hydrocortisone of a median dose of 200 mg/d | Mortality: 13/20 (65%) in those who did not and 20/31 (65%) in those who received corticosterone |
| Arbi et al\(^{[2]}\) | Randomized double blind; 2004-2007; Saudi Arabi | 75 patients; septic shock and cirrhosis in ICU | 39 patients received 200 mg hydrocortisone iv/d vs 36 patients receiving normal saline until shock resolution | Shock relapse after tapering: 13/39 (34%) with placebo \(( P = 0.05)\) |
| du Cheyron et al\(^{[3]}\) | Prospective; 2003-2005; France | 31 AOCLD with AI | 14 treated with stress doses of cortisol iv vs 17 not treated | Increase in gastrointestinal bleeding \(( P = 0.02)\) in hydrocortisone group |
| Fernández et al\(^{[4]}\) | Prospective and retrospective; group 1 2004-2006, group 2 2001-2004 | Group 1: 17 patients; cirrhosis and septic shock and AI Group 2: 50 patients; no assessment of adrenal function | 17 patients of group 1 treated with 200 mg hydrocortisone/d vs 50 patients not treated | Mortality: group 1 32% vs \( \geq 62\% \) in group 2 in ICU \(( P = 0.03)\), 36% vs 68% \(( P = 0.003)\) in hospital |
| Marik et al\(^{[5]}\) | Retrospective; 2002-2004; United States | 140 patients vasopressor dependent with ALD or CLD and AI | 300 mg hydrocortisone/d | Reduction in dose of norepinephrine in the 24 h \(( P = 0.02)\) in those with AI treated with hydrocortisone and increase in those with AI not treated \(( P = 0.04)\) |
| Harry et al\(^{[6]}\) | Retrospective; 1999-2001; United Kingdom | 40 patients with ALD or AOCLD required vasopressors | 20 patients treated with 300 mg hydrocortisone/d vs 20 patients not treated | Mortality: 26% in those treated with steroids and 46% in not treated \(( P = 0.002)\) In the group of 20 patients treated, there was reduction in doses of norepinephrin, higher risk of infections and no benefit in survival compared with the 20 patients not treated |

CLD: Chronic liver disease; ICU: Intensive care unit; ALD: Acute liver disease; AOCLD: Acute on chronic liver disease; AI: Adrenal insufficiency.
before long and supraphysiological corticosteroid doses are applied in patients with severe liver disease.

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