

## Adrenal insufficiency in patients with decompensated cirrhosis

Apostolos KA Karagiannis, Theodora Nakouti, Chrysoula Pipili, Evangelos Cholongitas

Apostolos KA Karagiannis, Department of Endocrinology, Diabetes and Metabolism, Korgialeneio Mpenakeio Hospital, 11526 Athens, Greece

Theodora Nakouti, Evangelos Cholongitas, 4<sup>th</sup> Department of Internal Medicine, Medical School of Aristotle University, Hippokration General Hospital of Thessaloniki, 54642 Thessaloniki, Greece

Chrysoula Pipili, Division of Nephrology, Royal Infirmary of Edinburgh, Scotland EH16 4SA, United Kingdom

Author contributions: Karagiannis AKA and Nakouti T contributed equally in writing and editing of the article; Pipili C edited the article at the end; Cholongitas E supervised the article.

Conflict-of-interest: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Evangelos Cholongitas, MD, PhD, 4<sup>th</sup> Department of Internal Medicine, Medical School of Aristotle University, Hippokration General Hospital of Thessaloniki, Konstantinoupoleos 49, 54642 Thessaloniki, Greece. [cholongitas@yahoo.gr](mailto:cholongitas@yahoo.gr)

Telephone: +30-6936-378903

Fax: +30-2310-992940

Received: October 7, 2014

Peer-review started: October 7, 2014

First decision: December 17, 2014

Revised: January 12, 2015

Accepted: February 9, 2015

Article in press: February 11, 2015

Published online: May 18, 2015

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

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

### 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

Karagiannis AKA, Nakouti T, Pipili C, Cholongitas E. Adrenal insufficiency in patients with decompensated cirrhosis. *World J Hepatol* 2015; 7(8): 1112-1124 Available from: URL: <http://>

## INTRODUCTION

Cirrhosis is characterized by hyperdynamic circulatory failure, low arterial pressure, peripheral vasodilation and increased production of cytokines<sup>[1,2]</sup>. Although, the adrenal insufficiency (AI) among critically ill cirrhotics was firstly described in 1960 by Peterson *et al*<sup>[3]</sup>, there is still an increased interest in it during the last decade. Initially, Marik *et al*<sup>[4]</sup> 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<sup>[5,6]</sup>, in those with stable cirrhosis<sup>[7-9]</sup> and in liver transplant recipients<sup>[4,10]</sup>. 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)<sup>[11-16]</sup>, replaced later on by the term critical illness related corticosteroid insufficiency (CIRCI)<sup>[17]</sup>. This review aims to summarize the published data regarding AI in cirrhotics and in liver transplant recipients, additionally focusing in the diagnostic tools and the possible effectiveness of corticosteroids administration.

## 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*<sup>[7-9]</sup>. 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<sup>[18,19]</sup>. 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<sup>[20,21]</sup>. 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<sup>[22,23]</sup>. In addition, cirrhosis is characterized by the increased circulating pro-inflammatory cytokines, like tumor necrosis factor (TNF)- $\alpha$ , interleukin-6 (IL-6), IL-1 and endotoxin- like lipopolysaccharide<sup>[24-27]</sup>, which affect negatively the feedback of HPA axis. TNF- $\alpha$  reduces the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland, *via* completion with corticotrophin receptor and contributes to glucocorticoid deficiency<sup>[28,29]</sup> 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<sup>[30,31]</sup>. Finally, prolonged prothrombin time, a common finding in cirrhotic patients, could rarely lead to adrenal hemorrhage and impaired cortisol production<sup>[23]</sup>.

## ASSESSMENT OF HPA FUNCTIONALITY

Total cortisol consists of free and binding forms<sup>[32]</sup>. Only 10% of circulating cortisol is free and bioactive<sup>[33]</sup>. 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<sup>[34]</sup>. Salivary cortisol has been used as a surrogate marker of free cortisol but present limitations in cirrhotics<sup>[7,35-37]</sup> including the high incidence of oral candidiasis, gums bleeding and parotitis especially in alcoholics<sup>[38]</sup>. Finally, free cortisol index (FCI = total cortisol/CBG ratio) reflecting serum free cortisol levels has been used<sup>[39]</sup>. 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  $\mu$ g corticotrophin (Synacthen). If poststimulation cortisol exceeds 550 nmol/L, primary AI is excluded<sup>[40]</sup>. SST uses supraphysiological doses of corticotrophin and is preferred in critically ill patients<sup>[41]</sup>. In this patient group, AI is defined either by random total cortisol < 276 nmol/L or by delta cortisol < 250 nmol/L (CIRCI criteria)<sup>[42]</sup>. Delta cortisol is the difference between basal cortisol and cortisol measured 60 min after *iv* injection of corticotrophin analogue<sup>[43]</sup>.

### Low dose SST

Plasma cortisol is measured 30 min after stimulation with 1  $\mu$ g 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<sup>[41]</sup>.

### 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  $\mu$ g/kg corticotrophin-releasing

hormone given intravenously. High ACTH levels after stimulation suggest primary AI, while a more blunted response indicates a possible secondary AI<sup>[43]</sup>.

### Insulin-induced hypoglycemia test

It is considered the gold-standard to evaluate both the HPA axis growth hormone sufficiency, but it is not commonly used due to its contraindications, particularly in elderly people, those with cardiovascular disease and seizure disorders<sup>[44]</sup>. A dose of 0.15 IU/kg regular insulin is given *iv* causing symptomatic hypoglycemia or blood glucose levels < 40 mg/dL, while cortisol levels are measured at 15, 30, 45, 60 and 90 min after stimulation. Failure of cortisol to exceed 500-550 nmol/L suggests AI.

### Metyrapone test

This is the sensitive alternative test for ACTH reserve evaluation. Its utility is restricted by the limited availability of this compound in many countries. Metyrapone reduces cortisol production *via* blockage of 11 $\beta$  hydroxylase, the enzyme that catalyzes the conversion of 11-deoxycortisol to cortisol. Thirty milligram per kilogram metyrapone are administered at 11:00 pm and ACTH, plasma cortisol and 11-deoxycortisol are measured in the next morning. Values of 11-deoxycortisol < 202 nmol/L in combination with rising levels of ACTH indicate primary AI, while neither 11-deoxycortisol nor ACTH rising indicates pituitary or hypothalamus impairment<sup>[45,46]</sup>.

### Serum free and salivary cortisol

The thresholds concentrations of serum free cortisol that indicate AI in critically ill patients are < 50 nmol/L at baseline and < 86 nmol/L after SST<sup>[47]</sup>. AI is indicated when basal values of salivary cortisol are < 1.8 ng/mL or salivary cortisol after SST is < 12.7 ng/mL, or an increment of < 3 ng/mL<sup>[7,36]</sup>.

## 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<sup>[5,7,8,23]</sup>. 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 straight forward. 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 (EASL) 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*<sup>[41]</sup> 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<sup>[23]</sup>. Another study came from Thevenot *et al*<sup>[7]</sup> 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<sup>[48]</sup>, a higher proportion (76%) had AI compared to the study of Thevenot *et al*<sup>[7]</sup>. 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<sup>[49]</sup>, 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*<sup>[5]</sup> 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 cirrhotics was confirmed in two more studies<sup>[50,51]</sup>. AI (by using the SST) was found in 38% septic cirrhotics with severe variceal bleeding and in 73.5% non-septic critically ill cirrhotics.

In the study of du Cheyron *et al*<sup>[6]</sup>, 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<sup>[52]</sup> 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 <i>et al</i> <sup>[40]</sup>	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 AOFLD and ALF	SST to those required vasopressor administration or cardiovascular instability CIRCI: Basal cortisol < 275 nmol/L or delta cortisol < 250 nmol/L
Triantos <i>et al</i> <sup>[5]</sup>	Prospective, observational; NR; NR	20 patients; cirrhosis and variceal bleeding vs 74 controls (14 healthy and 60 stable cirrhosis)	SST: 6/20 30% LDST: 6/10 60% Healthy (SST and LDST): 0/14 0% Stable (LDST): 24/50 48% Stable (SST): 3/10 30% 3/30 10%	AI wasn't associated with outcome Those with AI and variceal bleeding had higher baseline and peak level of cortisol with stable cirrhotic, 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 LDST, for albumin > 2.5 mg/dL, AI: 6/10 (80%) with variceal bleeding vs 16/39 (41%) in cirrhosis control 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: Peak cortisol < 500 nmol/L in non-stressed patients and delta cortisol of < 250 nmol/L or a random total cortisol < 276 nmol/L in stressed patients LDST AI: Peak cortisol < 500 nmol/L in non-stressed patients and peak cortisol level of < 690 nmol/L or a delta cortisol < 250 nmol/L in stressed patients SST-AI: Post-SST SC < 510.4 nmol/L Salivary cortisol was also calculated
Thevenot <i>et al</i> <sup>[7]</sup>	Prospective; 2008-2009; France	30 patients; septic cirrhotic			
Arabi <i>et al</i> <sup>[48]</sup>	Randomized double blind; 2004-2007; Saudi Arabi	75 patients; septic shock and cirrhosis in ICU	57/75 76%		SST RAI: Delta cortisol < 250 nmol/L
du Cheyron <i>et al</i> <sup>[6]</sup>	Prospective; 2003-2005; France	50 patients; decompensated cirrhosis in ICU (critical ill with acute on chronic liver disease)	31/50 62%		SST AI: Baseline cortisol value < 414 nmol/L, or delta cortisol < 250 nmol/L with a baseline value between 414 and 938 nmol/L SST baseline cortisol < 414 nmol/L and/or delta cortisol < 250 nmol/L
Thierry <i>et al</i> <sup>[52]</sup>	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%		SST RAI: (1) Baseline cortisol concentration < 414 nmol/L or (2) delta cortisol < 250 nmol/L in patients with baseline cortisol concentration < 966 nmol/L SST AI: Baseline value < 414 nmol/L, or delta cortisol < 250 nmol/L with a baseline value between 414 and 938 nmol/L
Fernández <i>et al</i> <sup>[53]</sup>	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 <i>et al</i> <sup>[54]</sup>	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	



Marik <i>et al</i> <sup>[23]</sup>	Retrospective; NR; United States	221 patients; LTICU	At admission: 120/221 54% In 3 d: 16/101 16%	Low HDL could predict the development of AI	LDSST AI: (1) a random (stress) cortisol < 552 nmol/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 LDSST AI: (1) a random (stress) cortisol < 552 nmol/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
Marik <i>et al</i> <sup>[4]</sup>	Retrospective; 2002-2004; United States	340 patients; ALD, CLD, post OLT recently and remote LT	Overall: 245/340 72% ALD: 8/24 33% CLD: 97/146 66% Remote LT: 31/51 61% Recent LT: 109/119 92% Among those treated with vasopressors: 125/166 75% 73.5%	Low HDL could predict the development of AI	LDSST AI: (1) a random (stress) cortisol < 552 nmol/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
Nair <i>et al</i> <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	SST RAI: random basal TC ≤ 276 nmol/L or delta cortisol ≤ 250 nmol/L
Saffioti <i>et al</i> <sup>[51]</sup>	2009-2013	80; cirrhotic pre-LT	18/80 22.5%	Patients with AI had higher MELD (19 vs 15; <i>P</i> = 0.003), pre-LT INR, bilirubin and potassium, and lower AI: At least 2 of the following: baseline sodium and haemoglobin levels	SST cortisol < 148 nmol/L, peak cortisol < 550 nmol/L, delta cortisol < 250 nmol/L
Graupera <i>et al</i> <sup>[50]</sup>	Spain	37; cirrhotic with severe variceal bleeding	14/37 38%	6 wk survival 64% without and 31% with RAI No differences in overall survival	SST RAI: Baseline serum cortisol < 414 nmol/L or delta cortisol < 250 nmol/L

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; CIRC: 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.

out of 25<sup>[53]</sup> cirrhotics with sepsis. In the latter study, AI was related with the severity of liver disease (AI was found in 76% of in 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 glucocorticoid supplementation could lessen the mortality.

Summarizing the above data, SST was the commonly used test for adrenal function assessment. LDSST or both tests were used in three studies<sup>[4,5,23]</sup>. All studies reported values of total cortisol. The presence 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>[55]</sup>. DSST 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.*<sup>[5]</sup> in which both tests were applied. With the exception of sepsis, variceal bleeding was the complication of the underlying cirrhosis in two studies<sup>[50,56]</sup>. 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<sup>[23]</sup>. 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<sup>[4,23,49]</sup>. 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<sup>[49,54]</sup>, while others showed no association<sup>[5,50,51]</sup>. 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<sup>[56]</sup>, 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.*<sup>[57]</sup>, 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.*<sup>[10]</sup>, 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<sup>[7]</sup>. 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<sup>[8]</sup>, 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.*<sup>[9]</sup> 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<sup>[36]</sup> 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<sup>[58-64]</sup> confirmed that total cortisol overestimates AI in stable cirrhotics, compared to either FCI<sup>[58]</sup> or salivary cortisol<sup>[60]</sup> (Table 2). Interestingly, Privitera *et al.*<sup>[63]</sup> showed that total cholesterol contributed more to impaired cortisol production, compared to HDL. Nevertheless, in the study of Acevedo *et al.*<sup>[64]</sup>, 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<sup>[7,8,56]</sup>, although the included population were non-critically ill cirrhotics<sup>[63]</sup>. 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 presence of AI was overestimated in all studies (46%-70% vs 34.6%-40%<sup>[10]</sup>, 9.4% vs 7.4%-27.4%<sup>[7]</sup>, 60% vs

Table 2 Characteristics and outcomes of the included studies in not critically ill cirrhotic patients

Ref.	Study design; study period; country	No. of patients; type of liver disease	Adrenal failure	Other observations	Definition of adrenal failure
Fede <i>et al</i> <sup>[56]</sup>	Prospective, observational; NR; United Kingdom	79 patients; cirrhotics 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	LDST AI: Peak TC < 494 nmol/L at 20 or 30 min FC < 33 nmol/L FCI < 12
Acevedo <i>et al</i> <sup>[57]</sup>	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) RAI was correlated with worse outcome both during hospitalization and in 3 mo period AI was correlated with severity of liver disease	SST RAI: Delta cortisol < 250 nmol/L in patients with basal serum TC < 938 nmol/L
Kharb <i>et al</i> <sup>[10]</sup>	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 (65.4%), CLD: 23/50 (46%), post LT: 7/10 (70%)		SST AI: Basal cortisol levels < 83 nmol/L or a peak cortisol response < 500 nmol/L RAI: Delta cortisol < 250 nmol/L
Thevenot <i>et al</i> <sup>[7]</sup>	Prospective; 2008-2009; France	95 patients; hemodynamically stable cirrhotic mainly alcoholic	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) 0/41 (0%)	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 AI was 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	LDST 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 LDST, FCI, cFC AI: Peak (1) TC < 500 nmol/L (2) TC < 442 nmol/L (3) Delta cortisol < 250 nmol/L (4) FCI < 12
Fede <i>et al</i> <sup>[8]</sup>	Prospective, observational; NR; United Kingdom	101 patients; stable cirrhosis			
Tan <i>et al</i> <sup>[9]</sup>	Prospective, observational; 2008-2009; Australia	43 patients; stable cirrhosis	(1) 18/43 (39%) (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	SST (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 <i>et al</i> <sup>[36]</sup>	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 < 3 ng/mL

Vincent <i>et al</i> <sup>[58]</sup>	Retrospective; NR; NR	26 patients; 15 CLD and 11 ALD	TC: 12/26 (46%) FCI: 3/26 (13%)	SST TC < 550 nmol/L FCI < 12 SST TC < 550 nmol/L
Shin <i>et al</i> <sup>[62]</sup>	Prospective; 2011-2012; South Korea	50 patients; stable cirrhosis	22/50 (44%)	AI was not related with the etiology of cirrhosis or alcohol consumption but only with the severity of liver disease
Privitera <i>et al</i> <sup>[63]</sup>	NR; NR; Italy	82 patients; cirrhotic stable	26/82 (32%)	LDSSST TC < 500 nmol/L
Cholongitas <i>et al</i> <sup>[60]</sup>	Prospective; 2010-2012; Greece	89 patients; stable decompensated cirrhosis	TC: 49/89 (55%) SC: 33/89 (37%)	SST TC, SC
Acevedo <i>et al</i> <sup>[59]</sup>	Prospective; 2007-2009; Spain	198 patients; 10 with compensated and 188 with decompensated cirrhosis	(1) 120/188 (64%), 8/10 (80%) (2) 51/188 (27%), 2/10 (22%)	No significant difference in mortality between patient SST with or without RAI RAI: Basal TC < 414 nmol/L and/or delta cortisol < 250 nmol/L (criteria 1) or delta cortisol < 250 nmol/L (criteria 2) SST RAI: Delta cortisol < 250 nmol/L
Acevedo <i>et al</i> <sup>[64]</sup>	Prospective; 2007-2010; Spain	166 patients; advanced cirrhosis	43/166 (26%)	Those with RAI had higher degree of circulatory dysfunction, SIRS ( $P = 0.01$ ), septic shock ( $P = 0.01$ ) and hospital mortality ( $P = 0.04$ ) AI was associated with reduced survival ( $P = 0.03$ )
Risso <i>et al</i> <sup>[61]</sup>	NR; NR; NR	85; stable cirrhotic with ascites	33/85 (39%)	SST RAI: Delta cortisol < 250 nmol/L and/or peak cortisol < 500 nmol/L

NR: Not reported; TC: Total cortisol; FC: Free cortisol; FCI: Free cortisol index; LDSSST: Low dose short synacthen test; SST: Short synacthen test; AI: Adrenal insufficiency; RAI: Relative adrenal insufficiency; ALD: Acute liver disease; CLD: Chronic liver disease; LT: Liver transplantation; cFC: Calculated free cortisol; HDL: High density lipoprotein; TRG: Triglycerides; CIRCI: Critical illness related adrenal insufficiency; SC: Salivary cortisol; HRS: Hepatorenal syndrome; MELD: Model for end-stage liver disease.

29%-38%<sup>[8]</sup>, 47% vs 12%-39%<sup>[9]</sup>). 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<sup>[8-10,62]</sup> and with worse outcome in a few studies<sup>[7,61,64]</sup>.

When plasma free cortisol was applied, AI was detected in a statistically lower proportion compared to the use of total cortisol<sup>[8,9,36,56,58,60]</sup>. However for values of albumin greater than 2.5 mg/dL, total cortisol was consistently correlated with free cortisol<sup>[36,60]</sup>. 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 cirrhotics (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*<sup>[10]</sup>, 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*<sup>[65]</sup> proved that the administration of 1000 mg methylprednisolone during the operation



**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 <i>et al</i> <sup>[10]</sup>	Cross sectional; 2010-2011; India	10; OLT	Post LT: 4/10 (40%) RAI: Post LT: 7/10 (70%)	SST AI: Basal cortisol levels < 83 nmol/L or a peak cortisol response < 500 nmol/L RAI: Delta cortisol < 250 nmol/L LDSST
Marik <i>et al</i> <sup>[4]</sup>	Retrospective; 2002-2004; United States	119 post OLT recently and 51 remote OLT	Recent LT: 109/119 (92%) Remote LT: 31/51 (61%)	AI: (1) a random (stress) cortisol < 552 nmol/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 <i>et al</i> <sup>[65]</sup>	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.

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*<sup>[4]</sup> 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<sup>[42,66,67]</sup>. A recent meta-analysis<sup>[68]</sup> 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<sup>[12]</sup>. The studies regarding the administration of cortisol in cirrhotics are presented in Table 4. Etogo-Asse *et al*<sup>[49]</sup> studied 51 vasopressor depended-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<sup>[48]</sup> of three years duration conducted in Saudi Arabi 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*<sup>[6]</sup>, 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*<sup>[53]</sup> 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 Marik *et al*<sup>[4]</sup> 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

**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
Etogo-Asse <i>et al</i> <sup>[49]</sup>	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 corticosteroid
Arabi <i>et al</i> <sup>[48]</sup>	Randomized double blind; 2004-2007; Saudi Arabi	75 patients; septic shock and cirrhosis in ICU	39 patients received 200 mg hydrocortisone <i>iv</i> /d vs 36 patients receiving normal saline until shock resolution	Shock reversal: 24/39 (62%) with hydrocortisone vs 14/36 (39%) with placebo ( $P = 0.05$ ) Shock relapse after tapering: 13/39 (34%) vs 5/36 (14%) ( $P = 0.03$ ) 28 d mortality: 33/39 (85%) vs 26/36 (72%), ( $P = 0.19$ ) Increase in gastrointestinal bleeding ( $P = 0.02$ ) in hydrocortisone group
du Cheyron <i>et al</i> <sup>[6]</sup>	Prospective; 2003-2005; France	31 AOCLD with AI	14 treated with stress doses of cortisol vs 17 not treated	30 d mortality: 7/14 (50%) of those treated vs 12/17 (70%) not treated ( $P = 0.29$ )
Fernández <i>et al</i> <sup>[53]</sup>	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 62% in group 2 in ICU ( $P = 0.03$ ), 36% vs 68% ( $P = 0.003$ ) in hospital Septic shock resolved in 96% vs 58% in group 2 ( $P = 0.001$ )
Marik <i>et al</i> <sup>[4]</sup>	Retrospective; 2002-2004; United States	140 patients vasopressor depended with ALD or CLD and AI	300 mg hydrocortisone/d	Reduction in dose of norepinephrin in the 24 h ( $P = 0.02$ ) in those with AI treated with hydrocortisone and increase in those with AI not treated ( $P = 0.04$ ) Mortality: 26% in those treated with steroids and 46% in not treated ( $P = 0.002$ )
Harry <i>et al</i> <sup>[69]</sup>	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	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.

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*<sup>[69]</sup> contrasted 20 cirrhotics with ALD or decompensated cirrhosis, vasopressor dependent on 300 mg/d hydrocortisone with a group of 20 cirrhotics with similar characteristics not treated with steroids. The steroids group required less norepinephrine doses, but showed 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 depended 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<sup>[6,49,69]</sup> were similar secondary to shock relapse and infection increase. However, opposite results come from two other studies<sup>[4,53]</sup>, 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 cirrhotics 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 indentify 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

before long and supraphysiological corticosteroid doses are applied in patients with severe liver disease.

## REFERENCES

- Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008; **371**: 838-851 [PMID: 18328931 DOI: 10.1016/S0140-6736(08)60383-9]
- Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther* 2001; **89**: 221-231 [PMID: 11516477]
- Peterson RE. Adrenocortical steroid metabolism and adrenal cortical function in liver disease. *J Clin Invest* 1960; **39**: 320-331 [PMID: 14432260 DOI: 10.1172/JCI104043]
- Marik PE, Gayowski T, Starzl TE. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med* 2005; **33**: 1254-1259 [PMID: 15942340]
- Triantos CK, Marzigue M, Fede G, Michalaki M, Giannakopoulou D, Thomopoulos K, Garcovich M, Kalafateli M, Chronis A, Kyriazopoulou V, Jelastopoulou E, Nikolopoulou V, O'Beirne J, Burroughs AK. Critical illness-related corticosteroid insufficiency in patients with cirrhosis and variceal bleeding. *Clin Gastroenterol Hepatol* 2011; **9**: 595-601 [PMID: 21545846 DOI: 10.1016/j.cgh.2011.03.033]
- du Cheyron D, Bouchet B, Cauquelin B, Guillotin D, Ramakers M, Daubin C, Ballet JJ, Charbonneau P. Hyperreninemic hypoaldosteronism syndrome, plasma concentrations of interleukin-6 and outcome in critically ill patients with liver cirrhosis. *Intensive Care Med* 2008; **34**: 116-124 [PMID: 17906854 DOI: 10.1007/s00134-007-0864-z]
- Thevenot T, Borot S, Remy-Martin A, Sapin R, Cervoni JP, Richou C, Vanlemmens C, Cleau D, Muel E, Minello A, Tirziu S, Penfornis A, Di Martino V, Monnet E. Assessment of adrenal function in cirrhotic patients using concentration of serum-free and salivary cortisol. *Liver Int* 2011; **31**: 425-433 [PMID: 21281437 DOI: 10.1111/j.1478-3231.2010.02431.x]
- Fede G, Spadaro L, Tomaselli T, Privitera G, Piro S, Rabuazzo AM, Sigalas A, Xirouchakis E, O'Beirne J, Garcovich M, Tsochatzis E, Purrello F, Burroughs AK. Assessment of adrenocortical reserve in stable patients with cirrhosis. *J Hepatol* 2011; **54**: 243-250 [PMID: 21056503 DOI: 10.1016/j.jhep.2010.06.034]
- Tan T, Chang L, Woodward A, McWhinney B, Galligan J, Macdonald GA, Cohen J, Venkatesh B. Characterising adrenal function using directly measured plasma free cortisol in stable severe liver disease. *J Hepatol* 2010; **53**: 841-848 [PMID: 20739086 DOI: 10.1016/j.jhep.2010.05.020]
- Kharb S, Garg MK, Puri P, Nandi B, Brar KS, Gundurthi A, Pandit A. Assessment of adrenal function in liver diseases. *Indian J Endocrinol Metab* 2013; **17**: 465-471 [PMID: 23869304 DOI: 10.4103/2230-8210.111643]
- Fleseriu M, Loriaux DL. "Relative" adrenal insufficiency in critical illness. *Endocr Pract* 2009; **15**: 632-640 [PMID: 19625244 DOI: 10.4158/EP09180.RA]
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580-637 [PMID: 23353941]
- Moraes RB, Czepielewski MA, Friedman G, Borba EL. Diagnosis of adrenal failure in critically ill patients. *Arq Bras Endocrinol Metabol* 2011; **55**: 295-302 [PMID: 21881811]
- Hebbar KB, Stockwell JA, Leong T, Fortenberry JD. Incidence of adrenal insufficiency and impact of corticosteroid supplementation in critically ill children with systemic inflammatory syndrome and vasopressor-dependent shock. *Crit Care Med* 2011; **39**: 1145-1150 [PMID: 21336126 DOI: 10.1097/CCM.0b013e31820eb4e4]
- Manji RA, Kumar A. Determining relevant cortisol concentrations in critically ill patients. *Crit Care* 2010; **14**: 113 [PMID: 20156331 DOI: 10.1186/cc8225]
- Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; **348**: 727-734 [PMID: 12594318]
- Marik PE. Critical illness-related corticosteroid insufficiency. *Chest* 2009; **135**: 181-193 [PMID: 19136406]
- van der Voort PH, Gerritsen RT, Bakker AJ, Boerma EC, Kuiper MA, de Heide L. HDL-cholesterol level and cortisol response to synacthen in critically ill patients. *Intensive Care Med* 2003; **29**: 2199-2203 [PMID: 14566456 DOI: 10.1007/s00134-003-2021-7]
- Kraemer FB. Adrenal cholesterol utilization. *Mol Cell Endocrinol* 2007; **265-266**: 42-45 [PMID: 17208360 DOI: 10.1016/j.mce.2006.12.001]
- Tsai MH, Peng YS, Chen YC, Lien JM, Tian YC, Fang JT, Weng HH, Chen PC, Yang CW, Wu CS. Low serum concentration of apolipoprotein A-I is an indicator of poor prognosis in cirrhotic patients with severe sepsis. *J Hepatol* 2009; **50**: 906-915 [PMID: 19304335 DOI: 10.1016/j.jhep.2008.12.024]
- Murch O, Collin M, Hinds CJ, Thiemermann C. Lipoproteins in inflammation and sepsis. I. Basic science. *Intensive Care Med* 2007; **33**: 13-24 [PMID: 17093985 DOI: 10.1007/s00134-006-0432-y]
- Gui D, Spada PL, De Gaetano A, Pacelli F. Hypocholesterolemia and risk of death in the critically ill surgical patient. *Intensive Care Med* 1996; **22**: 790-794 [PMID: 8880248 DOI: 10.1007/BF01709522]
- Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. *Intensive Care Med* 2006; **32**: 275-280 [PMID: 16432671 DOI: 10.1007/s00134-005-0005-5]
- Khoruts A, Stahnke L, McClain CJ, Logan G, Allen JI. Circulating tumor necrosis factor, interleukin-1 and interleukin-6 concentrations in chronic alcoholic patients. *Hepatology* 1991; **13**: 267-276 [PMID: 1995437]
- Devière J, Content J, Denys C, Vandenbussche P, Schandene L, Wybran J, Dupont E. Excessive in vitro bacterial lipopolysaccharide-induced production of monokines in cirrhosis. *Hepatology* 1990; **11**: 628-634 [PMID: 2184115]
- Soares JB, Pimentel-Nunes P, Roncon-Albuquerque R, Leite-Moreira A. The role of lipopolysaccharide/toll-like receptor 4 signaling in chronic liver diseases. *Hepatol Int* 2010; **4**: 659-672 [PMID: 21286336 DOI: 10.1007/s12072-010-9219-x]
- Sekiyama KD, Yoshida M, Thomson AW. Circulating proinflammatory cytokines (IL-1 beta, TNF-alpha, and IL-6) and IL-1 receptor antagonist (IL-1Ra) in fulminant hepatic failure and acute hepatitis. *Clin Exp Immunol* 1994; **98**: 71-77 [PMID: 7923888]
- Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009; **360**: 2328-2339 [PMID: 19474430 DOI: 10.1056/NEJMr0804635]
- Charmandari E, Kino T, Ichijo T, Chrousos GP. Generalized glucocorticoid resistance: clinical aspects, molecular mechanisms, and implications of a rare genetic disorder. *J Clin Endocrinol Metab* 2008; **93**: 1563-1572 [PMID: 18319312 DOI: 10.1210/jc.2008-0040]
- O'Beirne J, Holmes M, Agarwal B, Bouloux P, Shaw S, Patch D, Burroughs A. Adrenal insufficiency in liver disease - what is the evidence? *J Hepatol* 2007; **47**: 418-423 [PMID: 17629587 DOI: 10.1016/j.jhep.2007.06.008]
- Bornstein SR, Briegel J. A new role for glucocorticoids in septic shock: balancing the immune response. *Am J Respir Crit Care Med* 2003; **167**: 485-486 [PMID: 12588709 DOI: 10.1164/rccm.2211010]
- Rosner W. Plasma steroid-binding proteins. *Endocrinol Metab Clin North Am* 1991; **20**: 697-720 [PMID: 1778174]
- Torpy DJ, Ho JT. Value of free cortisol measurement in systemic infection. *Horm Metab Res* 2007; **39**: 439-444 [PMID: 17578761 DOI: 10.1055/s-2007-980200]
- Coolens JL, Van Baelen H, Heyns W. Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin. *J Steroid Biochem* 1987; **26**: 197-202 [PMID: 3560936]
- Inder WJ, Dimeski G, Russell A. Measurement of salivary cortisol in 2012 - laboratory techniques and clinical indications. *Clin Endocrinol (Oxf)* 2012; **77**: 645-651 [PMID: 22812714 DOI: 10.1111/j.1365-2265.2012.04508.x]
- Galbois A, Rudler M, Massard J, Fulla Y, Bennani A, Bonnefont-Rousselot D, Thibault V, Reigner S, Bourrier A, Poynard T, Thabut D. Assessment of adrenal function in cirrhotic patients: salivary

- cortisol should be preferred. *J Hepatol* 2010; **52**: 839-845 [PMID: 20385427 DOI: 10.1016/j.jhep.2010.01.026]
- 37 **Arafah BM**, Nishiyama FJ, Tlaygeh H, Hejal R. Measurement of salivary cortisol concentration in the assessment of adrenal function in critically ill subjects: a surrogate marker of the circulating free cortisol. *J Clin Endocrinol Metab* 2007; **92**: 2965-2971 [PMID: 17535998 DOI: 10.1210/jc.2007-0181]
  - 38 **Trifan A**, Chiriac S, Stanciu C. Update on adrenal insufficiency in patients with liver cirrhosis. *World J Gastroenterol* 2013; **19**: 445-456 [PMID: 23382623 DOI: 10.3748/wjg.v19.i4.445]
  - 39 **le Roux CW**, Chapman GA, Kong WM, Dhillon WS, Jones J, Alaghband-Zadeh J. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab* 2003; **88**: 2045-2048 [PMID: 12727952 DOI: 10.1210/jc.2002-021532]
  - 40 **Parker KL**, Kowwacs WJ. Addison's disease (adrenal insufficiency). In: Wass JA, Shalet SM, editors. *Oxford Textbook of Endocrinology and Diabetes*. New York: Oxford University Press, 2002: 837-844
  - 41 **Kazlauskaitė R**, Evans AT, Villabona CV, Abdu TA, Ambrosi B, Atkinson AB, Choi CH, Clayton RN, Courtney CH, Gonc EN, Maghnie M, Rose SR, Soule SG, Tordjman K. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab* 2008; **93**: 4245-4253 [PMID: 18697868 DOI: 10.1210/jc.2008-0710]
  - 42 **Marik PE**, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; **36**: 1937-1949 [PMID: 18496365 DOI: 10.1097/CCM.0b013e31817603ba]
  - 43 **Dorin RI**, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; **139**: 194-204 [PMID: 12899587]
  - 44 **Agha A**, Tomlinson JW, Clark PM, Holder G, Stewart PM. The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab* 2006; **91**: 43-47 [PMID: 16249286 DOI: 10.1210/jc.2005-1131]
  - 45 **Berneis K**, Staub JJ, Gessler A, Meier C, Girard J, Müller B. Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. *J Clin Endocrinol Metab* 2002; **87**: 5470-5475 [PMID: 12466339 DOI: 10.1210/jc.2001-011959]
  - 46 **Fiad TM**, Kirby JM, Cunningham SK, McKenna TJ. The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal axis. *Clin Endocrinol (Oxf)* 1994; **40**: 603-609 [PMID: 8013141 DOI: 10.1111/j.1365-2265.1994.tb03011.x]
  - 47 **Hamrahian AH**, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med* 2004; **350**: 1629-1638 [PMID: 15084695 DOI: 10.1056/NEJMoa020266]
  - 48 **Arabi YM**, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, Knawy BA, Hajeer AH, Tamimi W, Cherfan A. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ* 2010; **182**: 1971-1977 [PMID: 21059778 DOI: 10.1503/cmaj.090707]
  - 49 **Etogo-Asse FE**, Vincent RP, Hughes SA, Auzinger G, Le Roux CW, Wendon J, Bernal W. High density lipoprotein in patients with liver failure; relation to sepsis, adrenal function and outcome of illness. *Liver Int* 2012; **32**: 128-136 [PMID: 22098564 DOI: 10.1111/j.1478-3231.2011.02657.x]
  - 50 **Graupera I**, Hernandez-Gea V, Rodriguez J, Colomo A, Poca M, Llaó J, Rigla M, Aracil C, Guarner C, Villanueva C. Incidence and prognostic significance of relative adrenal insufficiency in cirrhotic patients with severe variceal bleeding. *Hepatology* 2010; **52** Suppl 1: 267A
  - 51 **Nair HNH**, Shyamsundar S, Menon A, Mumtaz K, Harishkumar K, Vallath B. Adrenal insufficiency in critically ill cirrhotic patients: Prevalence, risk factors and impact on mortality. *J Hepatol* 2014; **60**: S215-S359 [DOI: 10.1016/S0168-8278(14)60637-1]
  - 52 **Thierry S**, Giroux Leprieur E, Lecuyer L, Brocas E, Van de Louw A. Echocardiographic features, mortality, and adrenal function in patients with cirrhosis and septic shock. *Acta Anaesthesiol Scand* 2008; **52**: 45-51 [PMID: 17996000]
  - 53 **Fernández J**, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, Lacy AM, Ginès P, Arroyo V. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology* 2006; **44**: 1288-1295 [PMID: 17058239 DOI: 10.1002/hep.21352]
  - 54 **Tsai MH**, Peng YS, Chen YC, Liu NJ, Ho YP, Fang JT, Lien JM, Yang C, Chen PC, Wu CS. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006; **43**: 673-681 [PMID: 16557538 DOI: 10.1002/hep.21101]
  - 55 **Saffioti FTE**, O'Beirne J, Agarwal B, Thorburn D, Jeffrey G, Burroughs AK. Does pre-transplant adrenal function have an impact on post-transplant renal function? *J Hepatol* 2014; **60**: S215-S359 [DOI: 10.1016/S0168-8278(14)61081-3]
  - 56 **Fede G**, Spadaro L, Tomaselli T, Privitera G, Scicali R, Vasianopoulou P, Thalassinou E, Martin N, Thomas M, Purrello F, Burroughs AK. Comparison of total cortisol, free cortisol, and surrogate markers of free cortisol in diagnosis of adrenal insufficiency in patients with stable cirrhosis. *Clin Gastroenterol Hepatol* 2014; **12**: 504-512.e8; quiz e23-24 [PMID: 23978347]
  - 57 **Acevedo J**, Fernández J, Prado V, Silva A, Castro M, Pavesi M, Roca D, Jimenez W, Ginès P, Arroyo V. Relative adrenal insufficiency in decompensated cirrhosis: Relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. *Hepatology* 2013; **58**: 1757-1765 [PMID: 23728792 DOI: 10.1002/hep.26535]
  - 58 **Vincent RP**, Etogo-Asse FE, Dew T, Bernal W, Alaghband-Zadeh J, le Roux CW. Serum total cortisol and free cortisol index give different information regarding the hypothalamus-pituitary-adrenal axis reserve in patients with liver impairment. *Ann Clin Biochem* 2009; **46**: 505-507 [PMID: 19726458]
  - 59 **Acevedo JFJ**, Castro M, Roca D, Gines P, Arroyo V. Prognostic value of relative adrenal insufficiency in decompensated cirrhosis. *J Hepatol* 2010; **54**: S61
  - 60 **Cholongitas EGJ**, Kokonis G, Nakouti T, Rakitzi P, Chalevas P, Slavakis A, Akriviadis E. Assessment of adrenal function in patients with stable decompensated cirrhosis using salivary and total serum cortisol. *J Hepatol* 2013; **58**: S229-S407 [DOI: 10.1016/S0168-8278(13)60579-6]
  - 61 **Risso AAC**, Elia C, Mezzabotta L, Andrealli A, Spandre M, Morgando A, Marzano A, Rizzetto M. Adrenal dysfunction in nonseptic cirrhotic patients with ascites: Impact on survival. *Dig Liv Dis* 2011; **43** Suppl 2: S74-S75 [DOI: 10.1016/S1590-8658(11)60031-5]
  - 62 **Shin SR**. Evaluation of adrenal insufficiency in cirrhotic patients in Korea. *J Hepatol* 2013; **58**: S229-S407 [DOI: 10.1016/S0168-8278(13)60229-9]
  - 63 **Privitera G**. Assessment of lipoprotein subfractions in liver cirrhosis: relationship with basal and ACTH induced cortisol. *J Hepatol* 2013; **58**: S229-S407 [DOI: 10.1016/S0168-8278(13)60231-7]
  - 64 **Acevedo JFJ**, Castro M, Roca D, Gines P, Arroyo V. Impact of relative adrenal insufficiency on circulatory function and mortality in advanced cirrhosis. *J Hepatol* 2011; **54**: S61 [DOI: 10.1016/S0168-8278(11)60141-4]
  - 65 **Patel SBR**, Butt T, O'Beirne J, Mallett S. Steroids administration during liver transplantation (LT) reduces the need for physiological support post operatively. More evidence for relative adrenal insufficiency in liver failure. *Eur J Anaesthesiol* 2010; **27**: 176 [DOI: 10.1097/00003643-201006121-00563]
  - 66 **Annane D**, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 2009; **301**: 2362-2375 [PMID: 19509383]
  - 67 **Briegel J**, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K. Stress doses of hydrocortisone reverse hyperdynamic septic shock:



- a prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; **27**: 723-732 [PMID: 10321661]
- 68 **Wang C**, Sun J, Zheng J, Guo L, Ma H, Zhang Y, Zhang F, Li E. Low-dose hydrocortisone therapy attenuates septic shock in adult patients but does not reduce 28-day mortality: a meta-analysis of randomized controlled trials. *Anesth Analg* 2014; **118**: 346-357 [PMID: 24445635]
- 69 **Harry R**, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int* 2003; **23**: 71-77 [PMID: 12654129]

**P- Reviewer:** Kovacs SJ, Ukena SN **S- Editor:** Tian YL  
**L- Editor:** A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

