48 Year-old Female with New Onset Liver Failure

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History of past illness:

- 48 y.o. female presented with c/o decreased appetite, abdominal distention and LE edema for 1 month.
- Her husband noticed jaundice 3 days prior to her presentation to ED of OSH.
- CT abdomen was performed and revealed liver cirrhosis with evidence of portosystemic collaterals and ascites.
- Ultrasound-guided paracentesis was unsuccessful at OSH.
- The pt was transferred to UofC for further work up and management.

History of past illness:

- Upon presentation to UofC, the pt revealed a hx of episodes of sweating and chills happening while she is fasting usually twice a year for the last twenty years.
- In last 2 months prior to admission she noticed that those episodes were happening more frequently (twice a week).
- Most recent episode was 2 weeks prior to her admission to UofC and happened while she was shopping with her friend, the episode happened 5 hrs after she had her breakfast. The pt went to her friend's house and checked her blood sugars, they were 55. The pt had juice and felt better.
- While inpatient the pt was placed accuchecks QAC and QHS, her blood sugars were in 80-144 range, no episodes of hypoglycemia while inpatient.

Past medical history:

- Asthma
- Hyperlipidemia

- ***Home medications:*** albuterol, singulair

- ***Family history:*** maternal grandmother with DM2, maternal cousin with thyroidectomy (poss due to hyperthyroidism), breast CA in her maternal grandmother and her sister.

- ***Social history:*** no history of smoking, alcohol abuse or any illegal drug use, married, does not work.

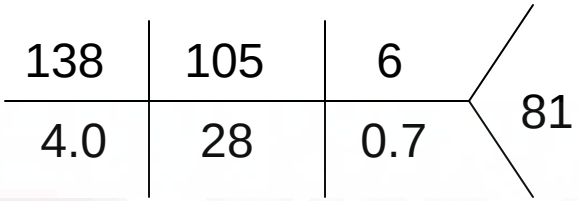
Review of systems:

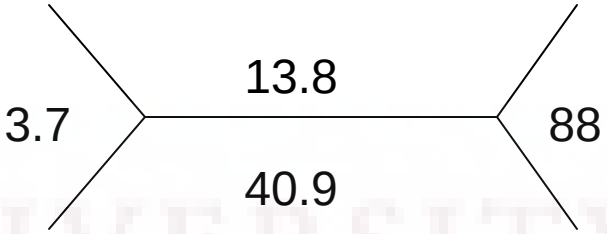
- Constitutional: **Weight loss 10lbs (intentional) in the last 6months**. **Episodes of sweating, nausea and lightheadedness, happening twice a week while she is fasting in the last two months (although has those episodes for years, but now they are more frequent)**
- Gastrointestinal: **+nausea, +abdominal pain,** no diarrhea.
- Musculoskeletal: No myalgias.
- Skin: No rash.

Physical exam:

- Vitals: BP 114/77, pulse 82, Temp 36.6 °C, Resp 18, Ht 162.6 cm, Wt 97.07 kg, BMI 36.73 kg/m2, SpO2 97%
- Eyes: **Sclerae icteric.**
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, **distended. Hepatomegaly 2cm below costal edge. + Mild ascitis.**
- Musculoskeletal/extremities: **LE edema 1+.**
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes.
- Skin: **+Jaundice.**

Labs:





Ca 8.4 (8.4-10.2 mg/dL),
Phos 4.3 (2.5-4.4 mg/dL)
Mg 1.9 (1.6-2.5 mg/dL)

LFTs:
Total Protein 7.1 (6-8.3 g/dL)
Albumin 2.1 (3.5-6 g/dL)
Total Bilirubin 4.3 (0.1-1 mg/dL)
Bilirubin, conjugated 2.1 (0-0.3 mg/dL)
Bilirubin, unconjugated 2.1 (0.1-1 mg/dL)
Alk Phos 155 (30-120 U/L)
AST 547 (8-37 U/L)
ALT 298 (8-35 U/L)

TSH 4.47 (0.3-4 mcU/mL), free T4 1.19 (0.9-1.7 ng/dL), total T3 91 (80-195 ng/dL) 02/12/13

TSH 0.49 (0.3-4 mcU/mL) 02/19/13

Total cholesterol 107 (120-199 mg/dL)
LDL 80 (60-129 mg/dL)
HDL 14 (40-80 mg/dL)
TG 64 (30-149 mg/dL)
HA1C 5%

Cortisol 0.5 mcg/dL (6AM)

Stim test:
Cortisol 3.8 mcg/dL, ACTH 15.2 pg/dL (9PM),

Cortisol 7.3 mcg/dL (10PM)

Labs:

ANA 160 (0-80 titer) homogeneous and speckled cytoplasmic antibodies present

Smooth muscle AB 400 (<25 titer)

Anti dsDNA <10 (<10 titer)

Hepatitis serology, iron studies, cerulloplasmin are unremarkable from OSH

Liver biopsy:

The findings are those of acute hepatitis with confluent parenchymal extinction.

Given the reported positive ANA and the presence of hypergammaglobulinemia autoimmune hepatitis is regarded as the likely diagnosis.

- The pt was started on prednisone 60mg/day on discharge for autoimmune hepatitis
- She will follow up in endocrine clinic once she is tapered from prednisone

- Does this patient has adrenal insufficiency?
- How to interpret cortisol levels and stim test in liver disease?
- Is there a better diagnostic test for liver patients?
- Do low HDL levels correlate with adrenal insufficiency in liver disease?

Cortisol levels in liver disease:

- Free cortisol represents only 10% of serum total cortisol, the remaining 90% being linked to CBG and albumin
- Synthesis of these proteins is reduced in liver cirrhosis leading to reduction of total serum cortisol levels
- Free cortisol diffuses freely into saliva and might be a better estimate of cortisol levels in patients with liver disease

Table 3. Adrenal insufficiency prevalence according to serum total cortisol and salivary cortisol assays during corticotropin test.

	Adrenal insufficiency according to serum total cortisol	Adrenal insufficiency according to salivary cortisol	*p* Value
Adrenal insufficiency according to T0, n	12	6	
Adrenal insufficiency according to T60, n	10	3	
Adrenal insufficiency according to Δ, n	19	3	
Total number of patients with adrenal insufficiency, n (%)	29/88 (33.0%)	8/88 (9.1%)	0.001

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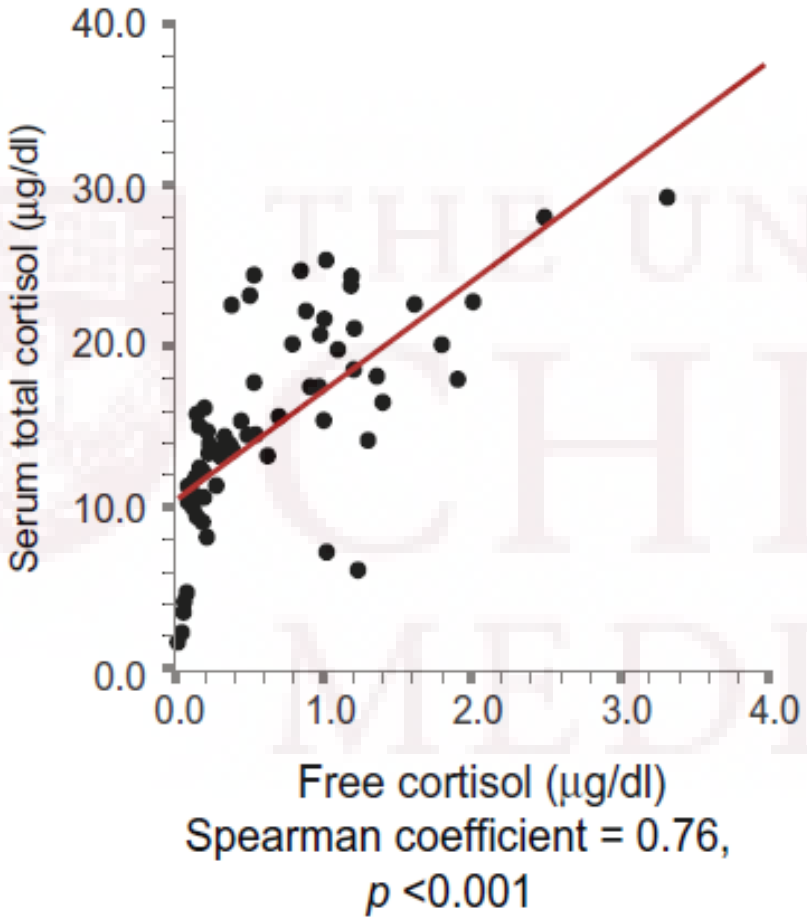

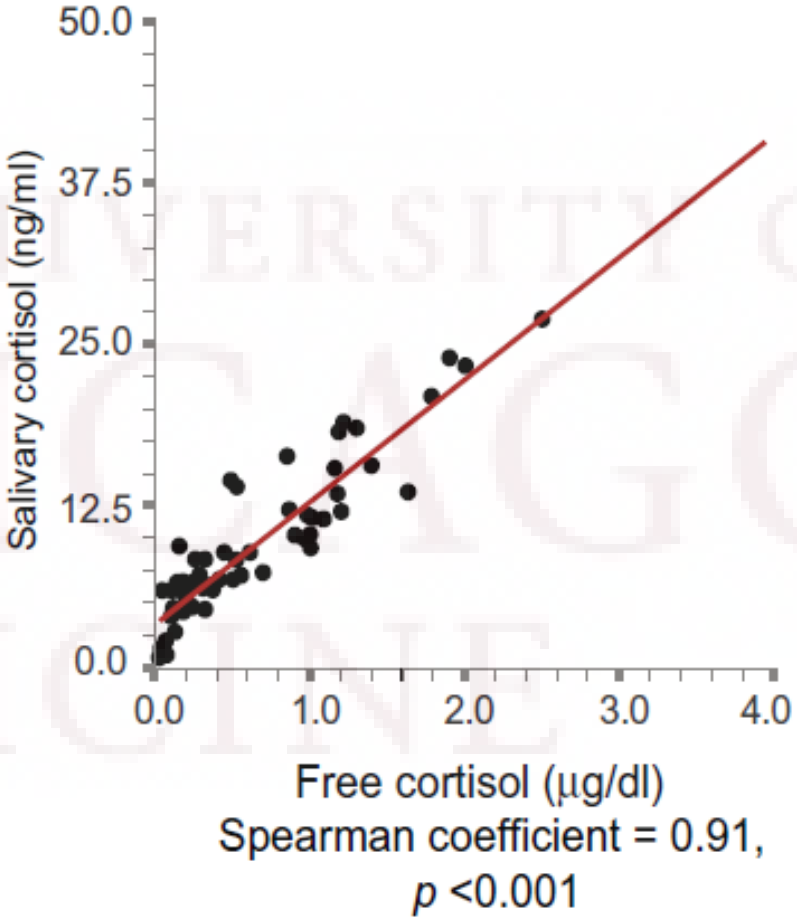

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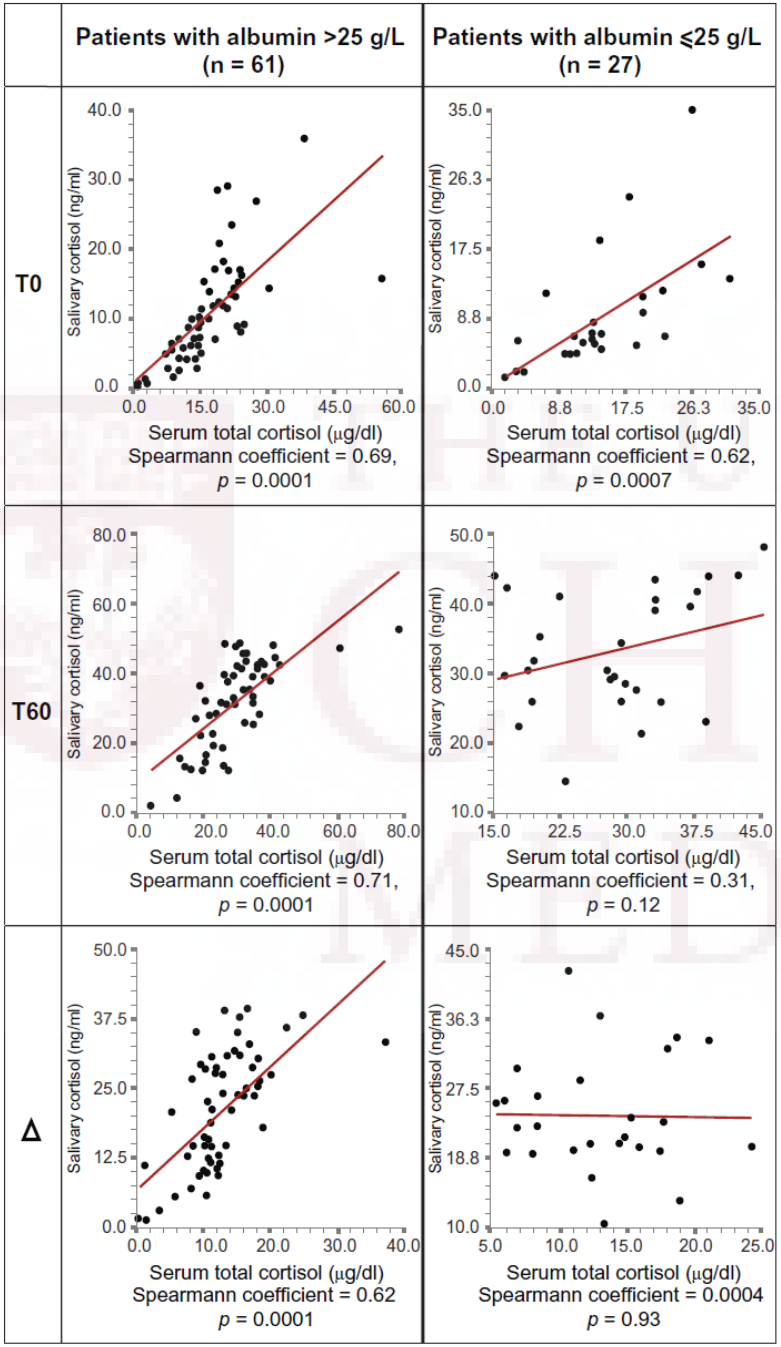

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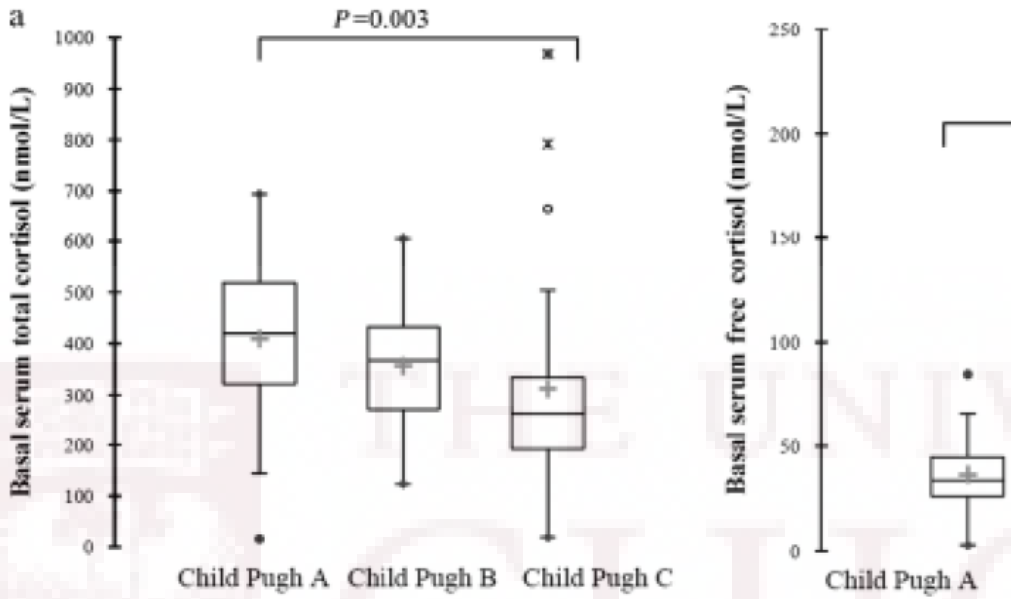

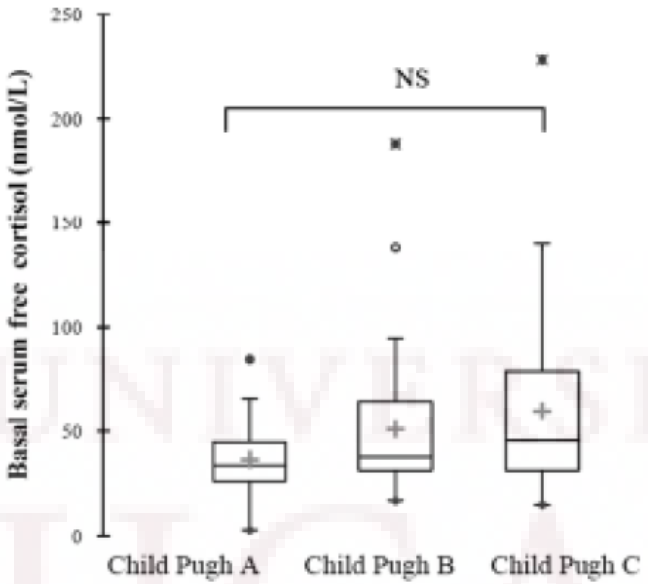

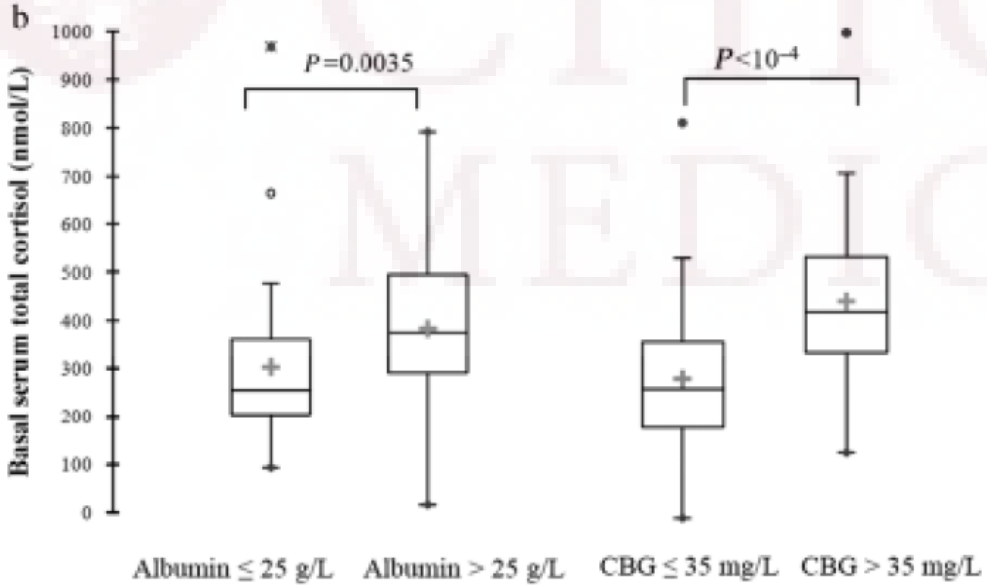

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Low HDL and adrenal insufficiency in liver disease:

	Normal adrenal function Group 1 ($n = 85$)	Adrenal exhaustion Group 2 ($n = 16$)	
	Baseline	Baseline	Time 2
APACHE II score	16 ± 4	21 ± 5*	–
Total bilirubin µmol/l	8.2 ± 9.4	7.9 ± 7.7	12.5 ± 11.7
INR	1.8 ± 0.8	1.4 ± 0.17	1.7 ± 0.3
Serum albumin g/l	2.5 ± 0.6	2.4 ± 0.7	2.1 ± 0.5
LDL mg/dl	65.8 ± 54.3	48.2 ± 25.2	36.0 ± 12.4
HDL mg/dl	28.4 ± 14.4	11.7 ± 7.0*	5.6 ± 6.3†
S-cortisol µg/dl	30.4 ± 19.5	24.7 ± 6.6	8.2 ± 2.3‡

Time 2 = data at time diagnosed with adrenal failure

* $p < 0.001$ for baseline group II compared to baseline group I

† $p = 0.01$ for baseline group II compared to time 2

‡ $p < 0.001$ for baseline group II compared to time 2

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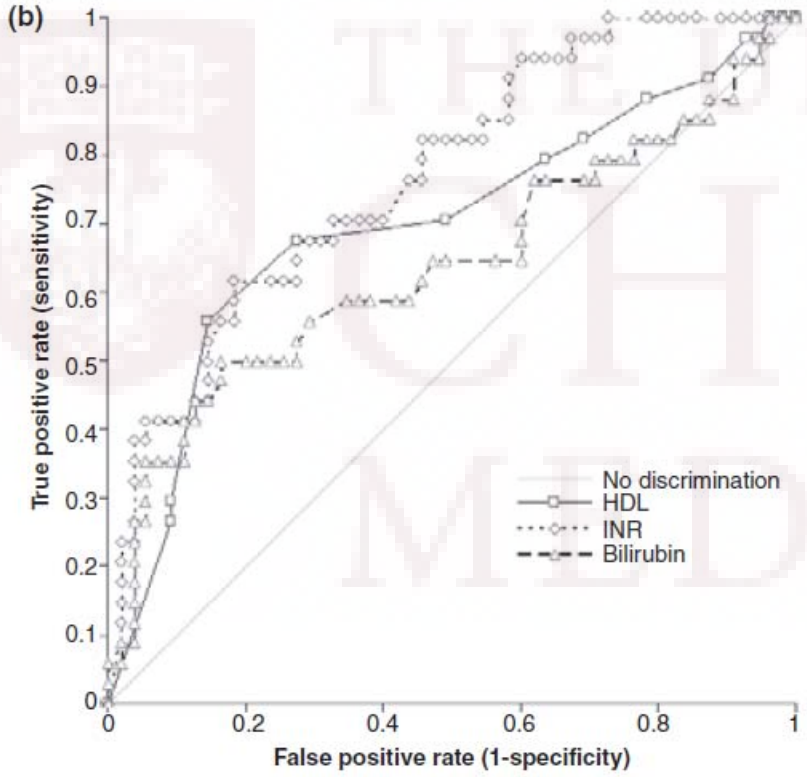
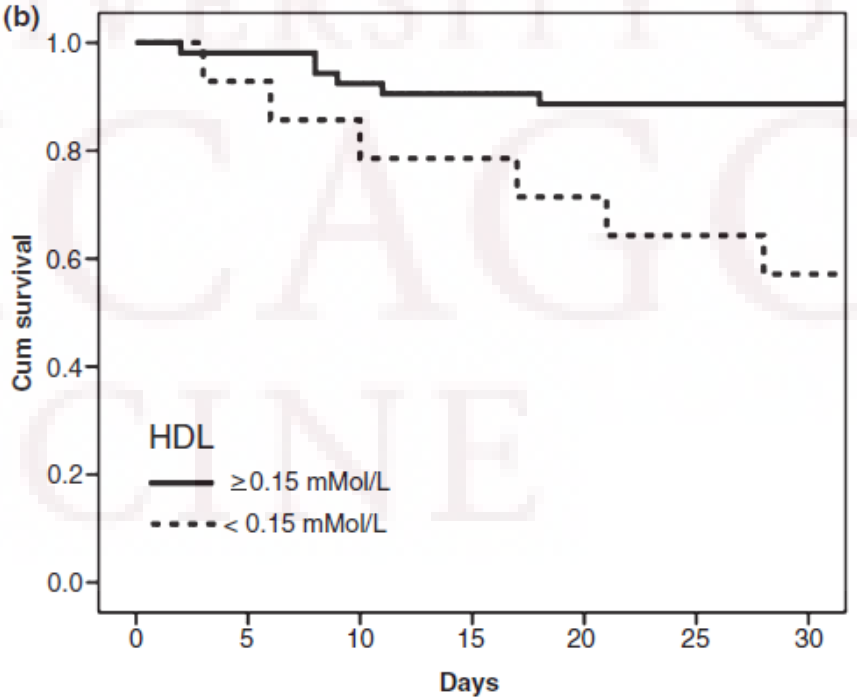
Low HDL and adrenal insufficiency in liver disease:

- Adrenal burnout syndrome: adrenal insufficiency in end-stage liver disease due to decreased cortisol production related to low steroidogenic substrate
- HDL is the preferred cholesterol source of steroidogenic substrate in the adrenal gland
- Low levels of HDL could be suggestive of low steroidogenic substrate





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Hepatoadrenal syndrome:

- In patients with cirrhosis, adrenal insufficiency during critical illness is associated with increased mortality, leading to what is termed “hepato-adrenal syndrome.”
- Liver failure can contribute to AI by increasing levels of endotoxin and impairing cholesterol synthesis.
- Bacterial infections that occur in patients with cirrhosis might be related to altered synthesis of adrenal cortisol, and bacterial and viral products that modify glucocorticoid tissue sensitivity and activation of peripheral cortisol metabolism.

Take home points:

- Adrenal insufficiency is common in patients with liver disease not only during acute critical illness (ie. Sepsis, shock, and variceal bleeding), but also during stable cirrhosis.
- There is no consensus on a best test for diagnosis of adrenal insufficiency in patients with liver failure
- Salivary cortisol might be a better estimate of cortisol levels in patients with liver disease
- Low levels of HDL could be a predictor of adrenal insufficiency in liver disease and also a predictor of mortality

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