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Original article

Fecal Calprotectin as Screening Parameter for Hepatic Encephalopathy

Ahmed M. Amin, Magdy A. Gad, Ahmed A. Negm

Department of Hepatology unit, department of internal medicine, Faculty of Medicine, Mansoura University, Egypt.

Corresponding to: Ahmed A. Negm, Department of Hepatology unit, department of internal medicine, Faculty of Medicine, Mansoura University, Egypt

Email:

negm1992@gmail.com

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Abstract

Background: Hepatic encephalopathy is a big neuropsychiatric problem that can happen with cirrhosis. It slowly happens in people with cirrhosis, starting with changes in their sleep patterns and moving on to asterixis, stupor, and coma**. Aim:** To evaluate the role of fecal calprotectin as a good screening parameter of hepatic encephalopathy in patients with cirrhosis of the liver**. Patients and methods:** This comparative cross-sectional research has been conducted on 80 subjects divided into both groups **Group I (N=60):** Cases with cirrhosis suffering hepatic encephalopathy and **Group II (N=20):** Healthy subjects as controls matched with study group in sex and age who were admitted at Department of Hepatology, Gastroenterology and Infectious Diseases, Damanhur Teaching Hospital. **Results:** With an area under the curve (AUC) of 0.929, fecal calprotectin (FC) can significantly predict the incidence of hepatic encephalopathy (HE) (P<0.001) at a cutoff value of >44.6 µg/mg, with a range of 16.7–640, showing 78.57% sensitivity, 92.11% specificity, 91.7% positive predictive value (PPV), and 79.5% negative predictive value (NPV). With an AUC of 0.966, serum ammonia (SA) can significantly predict the incidence of HE (P<0.001) at a cutoff value of >72.5 mcg/dL, with 90.00% sensitivity, 100.00% specificity, 100.0% PPV, and 76.9% NPV. There was no significant correlation between HE grades and FC levels, as FC levels did not differ significantly among HE grades. **Conclusion:** serum ammonia is better than fecal calprotectin as a predictor HE.

Key words: Fecal calprotectin; hepatic encephalopathy; cirrhosis

Introduction

Liver cirrhosis is an advanced stage of liver illness that results in the impairment of liver functions. This is caused by the development of scar tissue, which is called fibrosis, which can eventually replace normal functioning tissue as a result of the damage caused by liver illness [(1)].

A big neuropsychiatric problem that can happen with cirrhosis is hepatic encephalopathy. It slowly happens in people with cirrhosis, starting with changes in their sleep patterns and moving on to asterixis, stupor, and coma. The risk factors cause it include eating a lot of

protein, having stomach bleeding, taking sedatives, or having a transjugular intrahepatic portosystemic stent shunt [(2)].

It can only be diagnosed if there is confirmed liver disease, because the symptoms are similar to those of other encephalopathies. To tell the difference, abnormal liver function tests, an ultrasound that suggests liver disease, and ideally a liver biopsy are needed. The diagnosis is usually based on symptoms after other possible causes have been ruled out. It may be supported by blood ammonia levels, an electroencephalogram, or a computerized tomography scan of the brain [(3)].

The main cause of liver encephalopathy in people with cirrhosis may be changes in the structure of the intestinal mucosa, which makes the intestines more permeable and makes it easier for bacteria to move around, causing inflammation in the intestines. The amount of calprotectin in faeces is relative to the movement of neutrophils in the gut, so it is thought to be a sign of inflammation in the gut [(4)].

Calprotectin is a protein that binds to calcium and zinc (heterodimer S100A8/A9). It is a damage-associated molecular pattern protein and can kill microbes. It makes up 60% of the cytosolic material of neutrophils and can also be found in monocytes and macrophages. During inflammatory flare-ups, neutrophils gather in the mucosa. This causes calprotectin to be released in the stools, which makes it easy to measure [(5)].

Elevated levels of fecal calprotectin concentration have been observed in cirrhotic cases and are associated with the severity of liver illness. Furthermore, hepatic encephalopathy cases have significantly higher levels of fecal calprotectin concentration in comparison to cirrhotic cases without hepatic encephalopathy. Additionally, higher values of fecal calprotectin concentration have been observed as the degrees of hepatic encephalopathy rise, regarding the West-Haven criteria [(6)].

The goal of this research has been to assess the role of fecal calprotectin as a useful screening parameter for hepatic encephalopathy in cases with cirrhosis

Patients and Methods

This comparative cross-sectional study was conducted on 80 subjects divided into two groups:

- Group I (n=60): Cirrhotic patients with hepatic encephalopathy (HE).
- Group II (n=20): Healthy controls matched for age and sex.

All participants were admitted to the Department of Hepatology, Gastroenterology, and Infectious Diseases at Damanhur Teaching Hospital during the period from July 2023 to May 2024.

Ethical Considerations:

This research was approved by the Institutional Ethical Committee of the Faculty of Medicine, Benha University, and informed consent was obtained from each patient {M.S.43.4.2023}.

Inclusion Criteria:

- Age above 18 years.
- Both sexes.
- Cirrhotic patients with HE.
- Patients who agreed to participate in the study.

Exclusion Criteria:

- Age below 18 years.
- History of inflammatory bowel diseases.
- Patients with hematemesis or melena.
- Chronic inflammatory conditions (e.g., rheumatoid arthritis).

- Active malignancy.
- Cardiovascular diseases.
- Pregnancy.

Diagnosis and Grading of Hepatic Encephalopathy (HE):

HE was diagnosed and graded according to the West-Haven criteria (Weissenborn, 2019). The grading was based on neurological and mental status assessments, ranging from Grade 0 (no symptoms) to Grade 4 (coma).

Abdominal Ultrasound:

All patients underwent abdominal ultrasound to assess liver size, echotexture, portal vein diameter, spleen size, and the presence of ascites or hepatic focal lesions. This was performed to confirm cirrhosis and exclude other liver pathologies.

Methods:

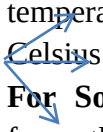
All cases were subjected to the following: Complete history taking, general and local examination and laboratory investigations. Hepatic encephalopathy has been observed regarding West-Haven criteria [7].

Laboratory investigations:

- Complete blood count (CBC)
- Liver enzymes (ALT, AST) (U/L).
- Serum ammonia (mcg/dl).
- Total and direct bilirubin (mg/dl).
- Coagulation profile test included Prothrombin time (PT): (seconds) & International normalized ratio (INR).
- Kidney function tests (Serum creatinine & urea). (mg/dl).
- C-reactive protein (CRP) (mg/L).
- Erythrocyte sedimentation rate (ESR) (mm/hr).

Calprotectin assay

The test, specimen, buffer and/or controls to reach room temperature fifteen to thirty degrees Celsius before testing were allowed. Adequate amount of feces (one to two milliliter or one to two gram) was obtained in a sterile and dry specimen collection container to ensure maximum antigens (if available). Optimal outcomes were achieved when **the examine** was conducted within six hours following collection of samples. If the specimen is not analyzed within six hours, it can be stored for a maximum of three days at a temperature of two to eight degree Celsius. Specimens should be stored at temperatures below minus twenty degrees Celsius f tion.



For Solid Specimens: Remove the cap from the specimen collection tube and insert the specimen collection applicator into the fecal specimen at a minimum of Three different sites collecting about fifty milligrams of feces (equal to 1/4 of a pea) in the process. Avoid collecting the fecal specimen using a scoop.

For Liquid Specimens: The dropper was held in a vertical position to aspirate fecal specimens. Subsequently, transfer two drops (about eighty microliters) were transferred into the specimen collection tube that already contained the extraction buffer. The cap was securely screwed onto the specimen collection tube, subsequently the tube was strongly shaken to thoroughly mixture the specimen and the extraction buffer. Allow the tube to remain undisturbed for a duration of two min. The pouch was allowed to be brought to room

temperature before being opened. The test cassette had been removed from the foil pouch and used within a span of one hour. Optimal outcomes were achieved when the test was conducted immediately following to opening the foil pouch. The specimen collecting tube was held in an upright position and the cap was removed from the tube. the specimen collection tube was invert and transfer two full drops of the extracted specimen (about eighty microliters) to each specimen well (S) of the test cassette, subsequently start the timer. Prevent trapping air bubbles in the specimen well (S). Illustration is provided below. The results were read within five min following the specimen was dispensed, and they were not read following ten min.

Statistical analysis

A code sheet was created following data collection. The organization, presentation, tabulation, and analysis of data were performed using **SPSS (Statistical Package for the Social Sciences) V25** by IBM, USA.

- **Standard Deviation (S.D.):** This measures the degree of scatter or dispersion of individual values around the mean.
- **Mean value ($\bar{X}$):** The sum of all observations divided by the total number of observations.
- **Unpaired Student's t-test:** Used to compare two groups in quantitative data.
- **Chi-square (χ^2) Test:** This test assesses the independence of row and column variables, without indicating the strength or direction of the relationship. Both **Pearson chi-square** and **likelihood-ratio chi-square** tests were used.
- **Chi-square Test for Qualitative Data:** Employed for comparing two groups regarding qualitative data.
- A **two-tailed P-value < 0.05** was considered statistically significant.
- **Receiver Operating Characteristic (ROC) Curve Analysis:** This was performed to assess the diagnostic performance of **fecal calprotectin** and **serum ammonia** in predicting **hepatic encephalopathy (HE)**. **Area Under the Curve (AUC)**, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to evaluate the diagnostic accuracy.

Results

We included a total of 80 subjects, 52 (65%) were males and 28 (35 %) were females, their age ranged from 24 to 85 years with a mean of 57.35 ± 12.25 years. Regarding the demographic data, age was significantly higher in group I compared to group II (P<0.001). There was an insignificant difference between both groups regarding sex, height, weight, BMI, residence and smoking. None in either groups were alcohol consumers or taking OCP. Additionally, all subjects in both groups were married **(table, 1)**

A significant positive association was observed among ammonia and age, Respiratory rate, Temperature, ALT, direct bilirubin, serum creatinine, AST, total bilirubin, urea, PT, INR, CRP, ESR 1st hour and ESR 2nd hour. There was a significant negative correlation between ammonia and SBP, Hb, platelets and albumin. An insignificant association was observed among ammonia and the other parameters **(Table, 2)**

(Table, 3) shows that there was an insignificant relation between grades of encephalopathy and fecal calprotectin level, as fecal calprotectin level was insignificantly different among the grades of encephalopathy.

With AUC of 0.929, Fecal Calprotectin can significantly predict the incidence of hepatic encephalopathy (P<0.001), at cut off value >44.6µg/mg, with 78.57 sensitivity, 92.11% specificity, 91.7% PPV and 79.5% NPV. With AUC of 0.966, Serum ammonia can significantly predict the incidence of hepatic encephalopathy (P<0.001), at cut off value >72.5 mcg/dL, with ninety percent sensitivity, one hundred percent specificity, 100.0% PPV and 76.9% NPV **(Table, 4).**

Table 1: Demographics and Organ Function Tests of the Examined Groups

		Group I (number=sixty)	Group II (number=twenty)	P-value
Age (years)	**Mean± SD**	61.68 ± 9.22	44.35 ± 11.08	**<0.001***
	Range	24 - 85	26 - 65	
Sex	**Male**	36 (60%)	16 (80%)	0.175
	Female	24 (40 %)	4 (20 %)	
Weight (Kg)	**Mean± SD**	73.9 ± 8.5	71.3 ± 8.55	0.241
	Range	60 - 89	61 - 88	
Height (m)	**Mean± SD**	1.70 ± 0.04	1.71 ± 0.04	0.115
	Range	1.63 - 1.78	1.62 - 1.77	
BMI (Kg/m^2)	**Mean± SD**	25.72 ± 3.66	24.26 ± 2.82	0.109
	Range	19.57 - 33.5	19.92 - 28.58	
Residence	**Urban**	38 (63.33%)	8 (40%)	0.117
	Rural	22 (36.67 %)	12 (60 %)	
Smoking		2 (3.33%)	0 (0%)	1.00
Alcohol		0 (0%)	0 (0%)	---
Marital status	**Married**	60 (100%)	20 (100%)	---
	Not	0 (0 %)	0 (0 %)	
OCP		0 (0%)	0 (0%)	---
ALT (U/L)	Mean± SD	57.79 ± 80.3	22.17 ± 7.28	0.002*
	Range	9.3 - 568.6	10.4 - 36	
	Median (IQR)	32.9 (20.1-57.8)	21.0 (17.8-27.5)	
AST (U/L)	Mean± SD	99.38 ± 124.86	30.77 ± 10.08	<0.001*
	Range	19.7 - 851.2	16.9 - 60	
	Median (IQR)	59.8(40.0-105.6)	29.0 (25.0-35.5)	
Total bilirubin (mg/dL)	Mean± SD	3.87 ± 4.54	0.76 ± 0.18	<0.001*
	Range	0.27 - 25.96	0.49 - 1.1	
	Median (IQR)	2.18 (1.28-4.46)	0.79 (0.60-0.90)	
Direct bilirubin (mg/dL)	Mean± SD	2.42 ± 3.42	0.22 ± 0.12	<0.001*
	Range	0.12 - 18.25	0.1 - 0.5	
	Median(IQR)	1.20(0.49-2.82)	0.19 (0.14-0.26)	
Albumin (g/dL)	Mean± SD	4.72 ± 16.85	3.66 ± 0.37	<0.001*
	Range	1.49 - 133	3.1 - 4.49	
	Median(IQR)	2.4 (2.1-3.0)	3.6 (3.4-3.8)	
Serum creatinine (mg/dL)	Mean± SD	1.65 ± 1.21	0.92 ± 0.34	0.004*
	Range	0.5 - 8.1	0.08 - 1.42	
	Median(IQR)	1.3 (0.9 -2.1)	0.9 (0.7 -1.1)	
Urea (mg/dL)	Mean± SD	78.5 ± 50.28	36.59 ± 6.66	<0.001*
	Range	19.2 - 250	27.7 - 47	
	Median(IQR)	59.9(44.6-107.2)	35.0 (30.9-44.0)	

BMI: body mass index, OCP: oral contraceptive pills, *: statistically significant as p value <0.05. ALT: alanine aminotransferase, AST: aspartame aminotransferase, *: statistically significant as p-value less than 0.05.

Table 2: Spearman association among Ammonia and different parameters

	Ammonia (mcg/dL)	
	r	P
Age (years)	0.342	0.002*
BMI (Kg/m2)	-0.212	0.059
SBP (mmHg)	-0.464	<0.001*
DBP (mmHg)	-0.007	0.951
Pulse (beat/min)	-0.170	0.133
RR (breath/min)	0.285	0.010*
Temperature (o c)	0.324	0.003*
Hb (g/dL)	-0.325	0.003*
Platelets (*109/L)	-0.498	0.000
WBCs (*109/L)	-0.081	0.474
ALT (U/L)	0.384	<0.001*
AST (U/L)	0.503	<0.001*
Total bilirubin (mg/dL)	0.436	<0.001*
Direct bilirubin (mg/dL)	0.439	<0.001*
Albumin (g/dL)	-0.409	<0.001*
Serum creatinine (mg/dL)	0.355	0.001*
Urea (mg/dL)	0.404	<0.001*
PT (sec)	0.356	0.001*
INR	0.305	0.006*
CRP (mg/L)	0.311	0.005*
ESR 1st hour (mm/hr)	0.299	0.007*
ESR 2nd hour (mm/hr)	0.302	0.007*
MELD	0.075	0.567

SBP: systolic blood pressure, DBP: diastolic blood pressure, INR: international normalized ratio, RR: respiratory rate, Hb: hemoglobin, WBCs: white blood cells, PT: prothrombin, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, *: statistically significant as p-value less than 0.05.

Table 3: Relation between grades of encephalopathy and Fecal Calprotectin level

		Grade 1 (number=six)	**Grade 2 (number=thirty-seven)**	**Grade 3 (number=sixteen)**	**Grade 4 (number=one)**	**P-value**
Fecal Calprotectin (µg/mg)	Mean± SD	75.8 ± 70. 8	110.94 ± 145.38	121.03 ± 158.34	144.2 ± 0	0.880
	Range	25.1 - 188	10 - 640	18.11 -596.3	144.2	
	Median (IQR)	35(28.4 - 153.5)	31.9(31.9- 203.5)	42.4(42.4- 182.1)	--	

IQR: interquartile range.

Table 4: Diagnostic accuracy for prediction of hepatic encephalopathy

	Cut-off	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**	**P value**
Fecal Calprotectin (µg/mg)	>44.6	78.57	92.11	91.7	79.5	0.929	<0.001*
Ammonia (mcg/dL)	>72.5	90.0	100.0	100.0	76.9	0.966	<0.001*

PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve.

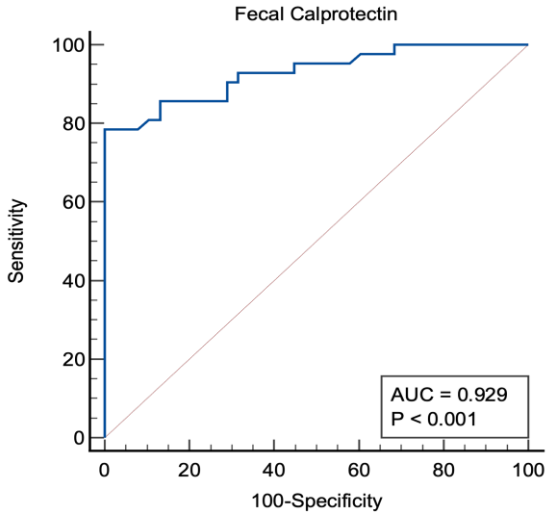


Figure 1: ROC curve analysis of fecal calprotectin for prediction of hepatic encephalopathy

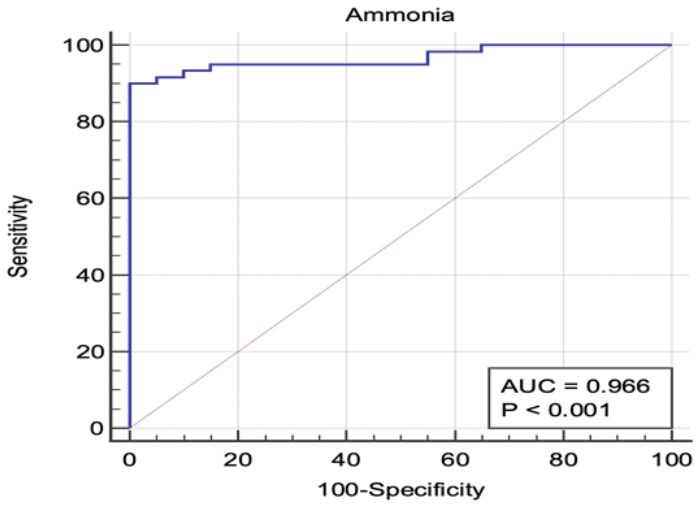


Figure 2: ROC curve analysis of Ammonia for prediction of hepatic encephalopathy

Discussion

Regarding the demographic data, age was significantly greater in group I compared to group II (P-value < 0.001). An insignificant variance was observed among both groups according to sex, height, weight, body mass index, residence, and smoking. None in either group were alcohol consumers or taking OCP. Additionally, all subjects in both groups were married. ALT, AST, total and direct bilirubin, albumin, serum creatinine, and urea were significantly greater in group I compared to group II (P < 0.05). Also, fecal calprotectin was significantly higher in group I compared to group II.

This was in agreement with [8] who conducted a cross-sectional study on 90 patients to assess: the value of fecal calprotectin in the diagnosis of hepatic encephalopathy, and the relationship

between the level of fecal calprotectin and the degree of hepatic encephalopathy. They reported that the mean age of the study groups was 49.92 ± 8.86 years, and the age was significantly higher in the hepatic encephalopathy group than the control group. In terms of gender, males were significantly higher in the studied patients (54 males and 36 females) [8].

In the present study, vital signs in the studied patients, the mean respiratory rate was 20.2 ± 2.32 breaths/min, the mean heart rate was 76.42 ± 7.48, the mean temperature was 37.37 ± 0.76, the mean SBP was 101.33 ± 12.68, and the mean DBP was 70.5 ± 8.32.

In the present study, 39 patients had pallor, 13 patients had palmar erythema, and 27 patients had jaundice.

In agreement with us, a study was conducted to know the spectrum of cutaneous changes and their correlation with liver function tests in 303 patients with disorders of the hepatobiliary system. They reported that 131 (43.02%) patients had pallor, 25 (8.2%) patients had palmar erythema, and 241 (79.5%) patients had jaundice [9].

Regarding laboratory investigations in the studied groups, the mean Hgb was 10.39 ± 2.02, the mean Plt was 173.43 ± 119.9, and the mean WBCs was 8.9 ± 5.26.

This was in agreement with [8] who reported that the mean Hgb was 10.7 ± 1.06, the mean Plt was 133.4 ± 61.64, and the mean WBCs was 6.41 ± 2.22.

This is consistent with research performed by [10] on cases with cirrhosis and elevated cytokines. The objective of the research was to assess serum fecal calprotectin in cases hospitalized for complications of cirrhosis, such as hepatic encephalopathy. It is a prospective cohort study that involved two hundred participants who were hospitalized due to complications related to cirrhosis, and fecal calprotectin was estimated by enzyme-linked immunosorbent assay. They reported high levels of fecal calprotectin, C-reactive protein (CRP), total bilirubin, direct bilirubin, and erythrocyte sedimentation rate (ESR). Also, high levels of fecal calprotectin were associated more with hepatic encephalopathy and correlated with variables related to the severity of cirrhosis.

Furthermore, another study by [11] that included 94 subjects, 63 of them had cirrhosis. It was discovered that cases with cirrhosis had high levels of direct and total bilirubin, international normalized ratio, and C-reactive protein.

0ur study found that fecal calprotectin concentrations were significantly higher in group I compared to group II. The mean fecal calprotectin level in group I was 182.46 ± 190.64, the mean fecal calprotectin level in group II was 30.89 ± 11.41

Consistently, research done by [6] assessed the role of fecal calprotectin in diagnosing severity and onset of hepatic encephalopathy in cases with cirrhosis. It included sixty-one cirrhotic patients and forty-two subjects served as a control. Fecal calprotectin concentrations were found to be greater in cirrhotic cases than the control group. More importantly, this research found a positive correlation between the severity of hepatic encephalopathy and fecal calprotectin. Moreover, a prospective observational study was performed by [12] to assess the function of fecal calprotectin in cases suffering from cirrhosis of the liver. It found that cases with chronic liver illness had very high concentrations of fecal calprotectin compared to healthy

individuals, but since it was only done on 35 subjects, larger research is required to determine the potential function of fecal calprotectin in those with chronic liver disease.

Our study found that ammonia levels were significantly higher in group I compared to group II.

A retrospective observational study done by [13], including four hundred and forty-six patients with liver cirrhosis hospitalized for complications related to liver cirrhosis such as ascites, upper gastrointestinal bleeding, and more importantly, hepatic encephalopathy. They reported high levels of ammonia in patients with liver failure, and also patients who had ammonia levels higher than 152 μmol/L had a high risk for poor prognosis.

Our study detected a significant positive correlation between fecal calprotectin, total bilirubin, direct bilirubin, CRP, ESR 1st hour and ESR 2nd hour, and ammonia.

There was an insignificant relation between grades of encephalopathy and fecal calprotectin level, as fecal calprotectin level was insignificantly different among the grades of encephalopathy. Also, a significant positive association was observed between fecal calprotectin and ammonia.

In agreement with our findings, a study performed by [14] on 60 patients with liver cirrhosis in Serbia found that patients suffering from cirrhosis had exceptionally high levels of fecal calprotectin and ammonia, but they confirmed that fecal calprotectin is more sensitive than ammonia concentrations as an indicator of hepatic encephalopathy.

With AUC of 0.929, fecal calprotectin can significantly predict the incidence of hepatic encephalopathy ($P < 0.001$), at a cutoff value >44.6 μg/mg, with a range of 16.7-640, with 78.57% sensitivity, 92.11% specificity, 91.7% PPV, and 79.5% NPV. With AUC of 0.966, serum ammonia can significantly predict the incidence of hepatic encephalopathy ($P < 0.001$), at a cutoff value >72.5 mcg/dL, with 90.00% sensitivity, 100.00% specificity, 100.0% PPV, and 76.9% NPV. There was an insignificant relation between grades of encephalopathy and fecal calprotectin level, as fecal calprotectin level was insignificantly different among the grades of encephalopathy.

Conclusion

Serum ammonia is better than fecal calprotectin as a predictor HE.

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