

Evaluation of the blood ammonia level as a non-invasive predictor for the presence of esophageal varices and the risk of bleeding

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ABSTRACT

Background/Aims: The development of esophageal varices (EV) and resultant bleeding are the most critical complications of portal hypertension. Upper gastrointestinal endoscopy is the gold standard for diagnosis of EV. To find a non-invasive method for diagnosis of EV and to predict the bleeding risk is appealing and would decrease the cost and discomfort of upper endoscopy. The aim of our study was to evaluate the blood ammonia level as a predictor of the presence of EV and of a high risk of bleeding.

Materials and Methods: In this cross-sectional study, a total of 359 patients with cirrhosis were examined for the presence of EV by upper endoscopy. Abdominal ultrasonography, calculation of the Child-Pugh score, and measurement of blood ammonia were performed for each patient.

Results: The blood ammonia level was significantly higher in patients with EV than in those without it ($p < 0.001$), and in patients with a high risk of variceal bleeding than in those with a low risk ($p = 0.026$).

Conclusion: An increased blood ammonia level and splenic vein diameter are predictors for the presence of EV and bleeding risk factors. The blood ammonia level may be clinically useful as it correlates with and is an independent predictor for both the endoscopic risk signs and risk factors of bleeding, and therefore, it could be used in patients with cirrhosis to decrease the number of screening endoscopies they are subjected to.

Keywords: Esophageal varices, blood ammonia, bleeding risk factors, non-invasive predictors, gastrointestinal endoscopy

INTRODUCTION

Cirrhosis is a result of advanced liver disease, characterized by replacement of the liver tissue with fibrous tissue and regenerative nodules leading to loss of liver function (1).

Portal hypertension resulting from chronic liver disease is associated with the formation of portosystemic collaterals, of which varices are of the greatest clinical significance due to their severe complications (2). The hypertensive portal vein is decompressed by diverting up to 90% of the portal flow through portosystemic collaterals back to the heart, resulting in an enlargement of these vessels that are commonly located at the gastroesophageal junction, where they lie subjacent to the mucosa and present as gastric and esophageal varices (EV) (3).

Approximately 5%-15% of patients with cirrhosis devel-

op varices yearly, and most of them will develop gastrointestinal varices over their lifetime (4).

An increased portal pressure leads to an increased varix size and decreased varix wall thickness, thus leading to an increased variceal wall tension. Rupture occurs when the wall tension exceeds the elastic limits of the variceal wall. Varices are most superficial and have the thinnest wall at the gastroesophageal junction; thus, variceal hemorrhage mostly occurs in that area (3).

The EV bleeding stops spontaneously in up to 40% of patients, and although therapy has improved in recent years, the 6-week mortality rate is still $\geq 20\%$ (5).

The presence of a red risk signs (e.g., red wale markings and cherry red spots) and variceal size (medium-to-large grade) on endoscopy are indicators of the EV bleeding

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risk (6). Severity of liver dysfunction and the presence of ascites are also important risk factors for variceal bleeding (7).

Being able to predict the presence of EV in patients with cirrhosis by a non-invasive method would decrease the necessity of endoscopic screening and reduce health care costs (2).

Ammonia is a substance produced by intestinal bacteria and cells during the protein digestion. It is passed from the intestines to the liver through the portal vein. In the liver, ammonia is converted to glutamine, which is then metabolized into urea by the kidneys to be excreted. The reference range for ammonia is 11-35 $\mu\text{mol/L}$ (8,9).

In a diseased liver, the ammonia is not broken down, and it accumulates in the blood (10). A study conducted on 153 consecutive patients with liver cirrhosis of various etiologies have shown that the blood ammonia level correlates well with the severity of liver disease, as well as with the presence of different portosystemic shunts, particularly EV (11).

Therefore, we aimed to find out if there was a possibility to use the ammonia level measurement to predict the presence of EV as well as the varices at a high risk for bleeding.

MATERIALS AND METHODS

This cross-sectional study was conducted on 359 HCV positive cirrhotic patients attending the Tanta University School of Medicine Hospital. The sample size of 359 patients was calculated based on a previous study by Chiodi et al. (12), who found that the prevalence of EV in patients with cirrhosis was 63%, with 5% precision, and a 95% confidence level.

Patients were excluded from the study if they had hepatic encephalopathy or coma, active GI bleeding, or history of bleeding 2 weeks prior to entering the study, hepatocellular carcinoma, or portal vein thrombosis. Patients taking lactulose, beta blockers, and those for whom a previous intervention for varices such as band ligation or injection sclerotherapy had been performed were excluded as well as those with heart or renal failure.

In total, 532 cirrhotic patients were screened for study participation, and 173 were excluded from the study; of these, 149 had failures in exclusion criteria, and 24 de-

clined to participate. Thus, 359 patients were enrolled in the study. They were divided into two groups: Group I (EV group): 218 patients with EV; and Group II (Control group): 141 patients with no EV.

A detailed history was taken, and a full clinical examination, routine laboratory tests, and pelvic- abdominal ultrasonography were performed for all participating patients after obtaining an informed written consent.

To overcome a potential results bias, study collaborators who were not involved in the upper endoscopy procedures screened and enrolled the participants, and the endoscopists were blinded to the study outcome.

Upper GI endoscopy

Upper GI endoscopy was performed for all the patients, and varices were classified according to the Japanese classification (13). This involved recording of the location (L), form (F), color (C), and red color signs (RC) of the varices.

Measurement of the blood ammonia level

A venous blood sample was collected from each patient after at least 6 hours of fasting, and 9 hours avoidance of smoking, making sure that the patients had followed the instructions not to perform any physical exercise the day before. The samples were put into sterile specimen tubes containing EDTA as an anticoagulant.

The samples were transported on ice to the laboratory, separated within 15 minutes of collection, and analyzed immediately. These precautions are necessary as the ammonia content of standing blood increases spontaneously, due to generation and release of ammonia from red blood cells and, to a lesser extent, the deamination of amino acids by enzymes in the circulation.

Statistical analysis

The collected data were organized, tabulated, and statistically analyzed using the Statistical Package for Social Studies (SPSS) version 20 (IBM Corp.; Armonk, NY, USA). For numerical variable, the mean and standard deviation were calculated. Comparison of the mean values between the groups was performed using the analysis of variance (ANOVA). When the value of ANOVA (F) was found to be significant, Tukey's test was performed to test difference between each two groups. For categorical variables, the number and percentage were calculated, and the chi-squared test was used as a test of significance. A p-value of <0.05 was considered to be statistically significant.

Ethical considerations

All participating subjects provided written informed consents. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution’s Human Research Committee. The study was approved on March 31, 2015, by the Tanta University School of Medicine Ethics Committee (Approval Code: 30142/03/31).

RESULTS

A total of 532 cirrhotic patients were screened during the

period from January 2016 to June 2017 for study participation, and 173 were excluded from the study; of these, 149 had did not satisfy the exclusion criteria, and 24 declined to participate. Thus, 359 patients were enrolled in this cross-sectional study, and there were 249 males (69.33%) and 110 females (30.67%). The patients were divided into two groups: Group I (EV group): 218 patients with EV and Group II: 141 patients with no EV (control group).

Table 1. Difference between blood ammonia levels in cirrhotic patients with and without EV

| Groups | Blood Ammonia µg/dL | | t-Test | |
|---------------|---------------------|----------------|--------|---------|
| | Range | Mean±SD | t | p |
| EV (n=218) | 36-320 | 157.587±58.679 | 4.928 | <0.001* |
| No EV (n=141) | 25-563 | 103.232±72.760 | | |

*p<0.05 was considered to be significant
EV: esophageal varices

The measurement of blood ammonia revealed that it was significantly higher in patients with EV than those without (p<0.001) (Table 1). When using the receiver operator characterizing (ROC) curve, to differentiate between the patient group with EV and the control group, it was found that the best cutoff value for prediction of the presence of varices was >123 µg/dL, yielding a sensitivity and specificity of 70% and 92%, respectively, and an accuracy of 83.4% (Figure 1).

Regarding the variceal appearance on endoscopy, the blood ammonia levels were found to be significant-

Table 2. Blood ammonia levels regarding endoscopic features among cirrhotic patients with EV

| Cirrhotic patients with EV (n=218) | | Blood Ammonia µg/dL | | T-Test or ANOVA | |
|------------------------------------|--------------------------------------|---------------------|----------------|-----------------|--------|
| | | N | Mean±SD | T or F | p |
| EV grading | Grade 1 | 83 | 145.737±63.403 | 2.853 | 0.041* |
| | Grade 2 | 94 | 156.644±50.872 | | |
| | Grade 3 | 39 | 178.056±57.160 | | |
| | Grade 4 | 2 | 280.000±60.514 | | |
| EV location (L) | LI (Inferior) | 118 | 169.635±57.272 | 2.852 | 0.063 |
| | LM (Medialis) | 85 | 140.728±53.497 | | |
| | LS (Superior) | 15 | 158.571±80.977 | | |
| EV form (F) | F1 | 123 | 143.995±61.108 | 3.902 | 0.023* |
| | F2 | 74 | 171.353±47.051 | | |
| | F3 | 21 | 186.900±64.171 | | |
| EV color (C) | Cw | 166 | 149.404±57.617 | -2.550 | 0.012* |
| | Cb | 52 | 183.500±55.440 | | |
| EV red color sign (RC) | Rc0 | 124 | 147.661±60.239 | 1.782 | 0.156 |
| | Hematocystic spots (HCS) | 26 | 163.000±37.878 | | |
| | Cherry red spots(CRS) | 26 | 159.583±60.484 | | |
| | Red wale markings (RWM) | 42 | 182.684±59.471 | | |
| Endoscopic risky signs | Patients with no risk signs | 124 | 146.921±58.039 | -2.669 | 0.009* |
| | Patients with one or more risk signs | 94 | 179.242±54.616 | | |

*p<0.05 was considered significant
EV: esophageal varices

Table 3. Child class and endoscopic appearances in cirrhotic patients with bleeding risk factors

| Child Class and Endoscopic Features | Patients With Risk Factors (n=147) | % |
|-------------------------------------|------------------------------------|-------|
| Child Class | | |
| Child A | 39 | 26.53 |
| Child B | 81 | 55.10 |
| Child C | 27 | 18.37 |
| EV grading | | |
| Grade 1 | 44 | 29.93 |
| Grade 2 | 64 | 43.53 |
| Grade 3 | 37 | 25.17 |
| Grade 4 | 2 | 1.36 |
| EV red color signs | | |
| None (Rc0) | 57 | 38.78 |
| Hematocystic spots (HCS) | 26 | 17.69 |
| Cherry red spots (CRS) | 26 | 17.69 |
| Red wale markings (RWM) | 38 | 25.85 |
| EV Form | | |
| F1 | 64 | 43.54 |
| F2 | 62 | 42.18 |
| F3 | 21 | 14.29 |

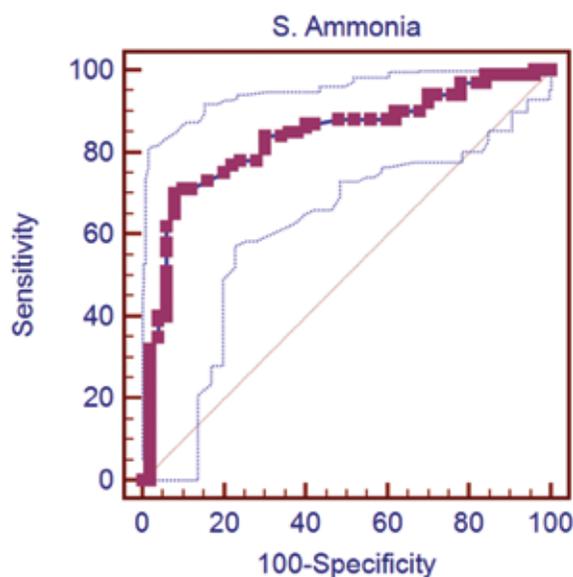


Figure 1. ROC curve giving the best cutoff value for prediction of presence of varices in cirrhotic patients

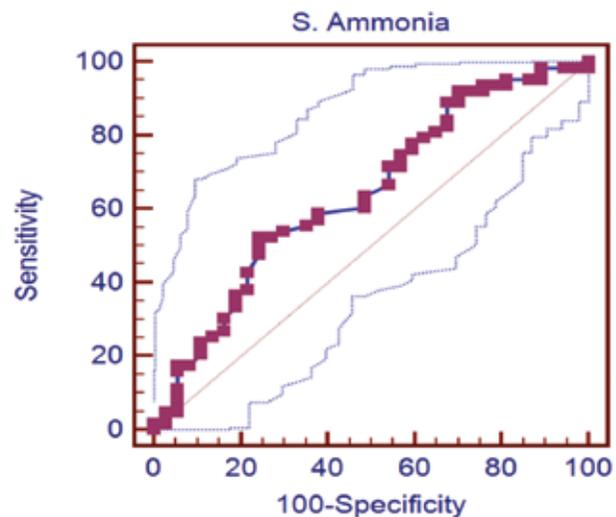


Figure 2. ROC curve for serum ammonia cutoff level for prediction of high risk esophageal varices

ly higher with an increasing grade and form of the varices ($p=0.041$ and 0.023 , respectively), as well as with blue-colored varices when compared with white-colored varices ($p=0.012$). Blood ammonia levels showed no significant differences related to varix location or any of the red color signs (Table 2).

The Child class and endoscopic appearances related to the bleeding risk in our EV patients are shown in Table 3.

It is known that the main factors posing a bleeding risk in cirrhotic patients with EV are a high Child class (Child B and C), the presence of large varices (Grade 3 or 4), F3 varices, and presence of red color signs (Cherry red spots, hematocystic spots, and red wale markings). Therefore, we recorded these risk factors in our patients with EV (Table 3).

We studied blood ammonia levels regarding the presence of endoscopic risk signs for esophageal varix bleeding, and we noted that the mean blood ammonia was significantly higher among patients having one or more of these endoscopic signs than in patients having none of them ($p=0.009$) (Table 2).

When we compared the patients having risk factors for EV bleeding (Child B and C as well as endoscopic risk signs) with those having no risk factors, we found a statistically significant difference in blood ammonia levels ($p=0.026$) (Table 4). A ROC curve revealed that a blood

Table 4. Comparison between patients having EV with or without bleeding risk factors and patients with no varices regarding ammonia levels and ultrasound findings

| | Presence of Risk Factors in EV (n=218) | | | ANOVA | | TUKEY'S Test | | |
|---------------------|-------------------------------------------|-------------------|----------------------|--------|---------|--------------|---------|---------|
| | I No (n=71) | II Yes (n=147) | III NO EV (n=141) | F | p | I&II | I&III | II&III |
| | Mean±SD | Mean±SD | Mean±SD | | | | | |
| Blood ammonia µg/dL | 140.668±56.748 | 167.524±57.939 | 103.232±72.760 | 14.524 | <0.001* | 0.026* | 0.019* | <0.001* |
| PVD (mm) | 13.246±1.725 | 13.700±1.605 | 11.756±2.119 | 16.598 | <0.001* | 0.452 | 0.001* | <0.001* |
| SLD (cm) | 15.630±1.795 | 15.898±1.672 | 14.284±2.658 | 9.046 | <0.001* | 0.807 | 0.009* | <0.001* |
| SVD (mm) | 10.924±1.021 | 11.278±1.081 | 8.552±1.912 | 57.816 | <0.001* | 0.445 | <0.001* | <0.001* |

I: EV with no risk factors

II: EV with risk factors

III: No EV

*p<0.05 was considered significant; EV: esophageal varices; PVD: portal vein diameter; SLD: splenic longitudinal diameter; SVD: splenic vein diameter

Table 5. Variables associated with the presence of EV

| | Unstandardized Coefficients | | Standardized Coefficients | | |
|---------------|-----------------------------|------------|---------------------------|--------|---------|
| | B | Std. Error | Beta | T | p |
| Blood ammonia | -0.001 | 0.000 | -0.211 | -3.377 | 0.001* |
| PVD (mm) | -0.011 | 0.018 | -0.049 | -0.622 | 0.535 |
| SLD (cm) | 0.037 | 0.017 | 0.173 | 2.170 | 0.032* |
| SVD (mm) | -0.182 | 0.024 | -0.718 | -7.657 | <0.001* |
| Child Score | -0.069 | 0.046 | -0.252 | -1.497 | 0.137 |

Dependent Variable: Groups

*p<0.05 was considered significant

EV: esophageal varices; PVD: portal vein diameter; SLD: splenic longitudinal diameter; SVD: splenic vein diameter

ammonia cutoff value of >156 µg/dL could predict high-risk EV with 52.38% sensitivity, 75.68% specificity, and 64.2% accuracy (Figure 2).

Regarding the PVD, SLD, and SVD, they were significantly higher in all patients with EV than in patients with cirrhosis without EV, yet there was no difference between those with and those without risk factors for bleeding.

A multivariate regression analysis was used to evaluate the factors associated with the presence of EV and the risk of bleeding. Blood ammonia, SLD, and SVD were independent predictors for the presence of EV (Table 5). Blood ammonia was the only independent predictor of the EV presence with endoscopic risk signs for bleeding (Table 6). Blood ammonia and SVD were found to be independent predictors for EV with risk factors for bleeding (endoscopic risk signs, as well as the Child B or C class cirrhosis) (Table 6).

DISCUSSION

The development of EV is the most critical complication of portal hypertension. Rupture of the varices leads to hemorrhage that surpasses all other types of upper gastrointestinal bleeding considering morbidity, mortality, and hospital costs (14).

In patients with cirrhosis, portosystemic shunts remove most of the ammonia from the portal to the systemic circulation, raising the blood ammonia level. This could render blood ammonia measurement useful to reflect the presence of portal hypertension and portosystemic collaterals (15).

Our study aimed to determine if the blood ammonia level could be used as a non-invasive predictor for the presence of EV and the high risk of bleeding.

Measurement of blood ammonia revealed that it was significantly higher in patients with EV than in those without

Table 6. Variables associated with the presence of risky EV

| | Unstandardized Coefficients | | Standardized Coefficients | | |
|---------------------------|-----------------------------|------------|---------------------------|--------|---------|
| | B | Std. Error | Beta | t | p |
| Endoscopic risk signs | | | | | |
| Blood ammonia | 0.002 | 0.001 | 0.200 | 2.041 | 0.044* |
| PVD (mm) | 0.026 | 0.033 | 0.088 | 0.809 | 0.420 |
| SLD (cm) | 0.001 | 0.035 | 0.004 | 0.035 | 0.972 |
| SVD (mm) | 0.097 | 0.059 | 0.109 | 1.646 | 0.103 |
| Risk factors for bleeding | | | | | |
| Blood ammonia | -0.001 | 0.001 | -0.297 | -3.315 | 0.031* |
| PVD (mm) | -0.016 | 0.034 | -0.043 | -0.482 | 0.631 |
| SLD (cm) | 0.040 | 0.032 | 0.114 | 1.241 | 0.217 |
| SVD (mm) | -0.224 | 0.041 | -0.549 | -5.425 | <0.001* |

*p <0.05 was considered significant

EV: esophageal varices; PVD: portal vein diameter; SLD: splenic longitudinal diameter; SVD: splenic vein diameter

EV ($p < 0.001$). Our finding is congruent with that of Ali et al. (16), who also detected an increase in the mean values of blood ammonia in patients suffering from cirrhosis with varices in comparison to patients without varices.

Impairment of liver function and uptake leads to the accumulation of ammonia in splanchnic vessels, resulting in their vasodilatation and an increased portal blood flow generating portal hypertension (17-18).

It is known that the hepatic stellate cell activation and altered function play an important role in the occurrence of liver fibrosis and portal hypertension (19-20).

In 1998, Bod et al. (21) stated that high ammonia levels may have detrimental effects on stellate cell function. Recently, it has been reported that abnormally high ammonia levels cause significant alteration in proliferation and metabolic activity of stellate cells in vitro. Therefore, elevation of ammonia seems to be part of a vicious circle. It results from the presence of portal hypertension and portosystemic collaterals and leads to a further increase in portal hypertension (22).

The best blood ammonia cutoff value for the detection of EV in the present study was 123 $\mu\text{g/dL}$, and this value had a sensitivity of 70% and a specificity of 92%.

Other studies have been performed on this point. El-Hefny et al. (23) reported a cutoff value of 77.5 $\mu\text{mol/L}$ (108.5 $\mu\text{g/dL}$) ammonia with 100% sensitivity and 95% specific-

ity for the detection of EV, whereas Tarantino et al. 2009 (11) reported a different cutoff value of 42 $\mu\text{mol/L}$ (58.8 $\mu\text{g/dL}$) with a sensitivity 97% and a specificity 43%.

Montasser et al. (24) found that the level of ammonia was significantly higher in patients with varices and portosystemic collaterals as seen by an abdominal ultrasound than in patients with EV and no collaterals or patients with neither EV nor collaterals. They concluded that the cutoff ammonia level of 113 $\mu\text{g/dL}$ could predict the presence of EV, while 133 $\mu\text{g/dL}$ was capable of predicting the existence of both EV and abdominal collaterals.

There is an increased risk of EV rupture with certain endoscopic signs; the presence of larger sized varices, increased number of varices, and red color signs (6-25). Therefore, we studied the levels of ammonia in relation to these parameters. Regarding variceal appearance on endoscopy, ammonia levels were found to be significantly higher with an increasing grade and form of the varices ($p = 0.041$ and 0.023 , respectively) as well as with blue-colored varices when compared to white-colored varices ($p = 0.012$). Blood ammonia levels showed no significant differences related to varix location or any of the red color signs.

The main risk factors for the occurrence of variceal bleeding are large varices with red color signs and high Child scores of cirrhosis (26).

We found that the mean blood ammonia level was higher in patients with bleeding risk factors of EV (Child B or C,

high variceal grade, high variceal form, and red color signs) than in patients without risk factors of bleeding with a significant difference between the two groups (p -value =0.026) and a cutoff value >156 $\mu\text{g/dL}$ with sensitivity and specificity of 52.38% and 75.68%, respectively.

Dilated portal and splenic veins as well as splenomegaly are suggestive of portal hypertension (27). These ultrasound findings of PVD, SLD, and SVD were significantly higher in all patients with EV than in patients with cirrhosis without EV.

A multivariate regression analysis was used to evaluate the factors associated with the EV presence. Blood ammonia, SLD, and SVD were found to be independent predictors for the presence of EV (p =0.001, 0.032, and <0.001, respectively).

A multivariate regression analysis to evaluate the factors associated with an EV risk of bleeding proved that blood ammonia was the only independent predictor of the presence of EV with endoscopic risk signs for bleeding (the presence of one or more of the following: high variceal grade, high variceal form, and red color signs) (p =0.044).

Blood ammonia and SVD were found to be independent predictors for the EV presence with risk factors for bleeding (endoscopic risk signs as well as the Child B or C class cirrhosis) (p =0.031, and p <0.001, respectively). These statistical findings confirm the predictive value of ammonia measurement for the presence of EV as stated by previous studies. The present study, to the best of our knowledge, is the only one to evaluate and record the importance of blood ammonia levels as a predictor of the EV bleeding risk in cirrhosis.

Our study is limited by being a single center study and by the inability to measure the portal pressure in our patients.

An increased blood ammonia level and splenic vein diameter are predictors for the presence of EV and risk factors for bleeding. The blood ammonia level may be clinically useful as it correlates with and is an independent predictor for both endoscopic risk signs and risk factors of bleeding, and therefore, it could be used in cirrhotic patients to decrease the number of screening endoscopies they are subjected to.

Ethics Committee Approval: Ethics committee approval was received for this study from the Tanta University School of Medicine Ethics Committee (Approval Code: 30142/03/31).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - F.E., L.M.; Design - F.E., L.M., A.E.; Supervision - F.E., L.M., H.M.; Resources - A.E., H.M.; Materials - H.M., A.E.; Data Collection and/or Processing - A.K., A.E.; Analysis and/or Interpretation - A.K., A.E., L.M.; Literature Search - A.E.; Writing Manuscript - F.E., A.K., A.E.; Critical Reviews - F.E., A.K.

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