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Correlation between Serum-Ascites Albumin Gradient and Esophageal Varices in Portal Hypertension due to Cirrhosis of Liver

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ABSTRACT

Introduction: Cirrhosis of the liver is a major health problem in our country. Patients with cirrhosis are at risk of developing esophageal varices and variceal bleeding with high mortality. They must undergo routine upper gastrointestinal endoscopy to screen for the presence of varices. This poses an economic, social, and medical burden. Thus, this warrants a non-invasive predictor of esophageal varices in a cirrhotic patient. The aim of this study was to find the correlation between SAAG and esophageal varices in portal hypertension due to cirrhosis of liver.

Methods: Patients (45 males and 35 females) above 18 years of age and with cirrhosis of the liver underwent cross sectional observational study at Nepal Medical College Teaching hospital between October 2015 and December 2017 AD. Serum albumin and ascitic fluid albumin were analyzed on the same day and serum-ascites albumin gradient (SAAG) was calculated. Upper GI endoscopy was done to evaluate for the presence of esophageal and gastric varices. Pearson's chi-square test was applied to see the relation between SAAG and esophageal varices.

Results: Among the 80 patients studied, 56.2% were male and 93.75% had varices. Majority of the patients who had esophageal varices had SAAG of more than 1.1 g/dL. A positive correlation was found between serum-ascites-albumin gradient and esophageal varices but was statistically not significant. A cut-off of >1.6 for SAAG to discriminate between presence and absence of varices yielded a sensitivity of 78.66% and a positive predictive value of 92.18%.

Conclusions: This study highlighted that SAAG has a positive correlation with esophageal varices with high sensitivity and positive predictive value in estimating the presence of varices but without statistical significance. It has a low specificity. Due to statistically insignificant correlation and low specificity, SAAG cannot be used in place of upper GI endoscopy in diagnosing gastroesophageal varices.

INTRODUCTION

Liver cirrhosis is defined histologically as a bridging fibrosis leading to deranged liver architecture and regenerative nodules and is considered the end stage of a variety of chronic liver diseases, and is irreversible in its advanced stages.[1] The pathophysiological features of cirrhosis involve progressive liver injury and fibrosis resulting in portal hypertension (PHTN) and decompensation, including ascites,

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spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), variceal hemorrhage, hepatorenal syndrome (HRS), and hepatocellular carcinoma (HCC).[2] Ascites is the most common of the three major complications of cirrhosis, the other complications being hepatic encephalopathy and variceal hemorrhage and its development may be the first evidence of the presence of cirrhosis.[3] Portal hypertension (PHTN) is the increase in portosystemic pressure gradient in any portion of the portal venous system which could result from prehepatic abnormalities (e.g., portal or splenic vein thrombosis), post-hepatic abnormalities (e.g., Budd-Chiari syndrome) or intrahepatic causes (e.g., schistosomiasis, sinusoidal obstruction syndrome). Cirrhosis is by far the most common cause of portal hypertension and, as such, has been the most widely investigated.[4]non-selective b-blockers are recommended, while patients with medium/large varices can be treated with either b-blockers or esophageal band ligation. Standard of care for acute variceal hemorrhage consists of vasoac-tive drugs, endoscopic band ligation and antibiotics prophylaxis. Transjugular intrahepatic portosystemic shunt (TIPS Portal hypertension is responsible for the more severe and often lethal complications of cirrhosis such as bleeding from esophageal varices (EV) which occurs in almost 35% - 70% of patients.[5]. The practice guidelines from the American College of Gastroenterology (ACG) and the American Association for the Study of Liver Diseases (AASLD) for gastroesophageal varices suggest that all patients with hepatic cirrhosis should be screened for varices at least every other year.[3] Screening should be done to determine the size of esophageal varices because patients with varices ≥ 5 mm in diameter are at the greatest risk for bleeding and should receive prophylaxis.[6] Upper GI endoscopy should be repeated at 2-3 yearly intervals whereas for those with compensated cirrhosis with EV, upper GI endoscopy should be repeated 1-2 yearly and for those with decompensated cirrhosis, more frequent screening endoscopy may be warranted.[5] Endoscopic band ligation is indicated for patients who are at high risk for bleeding and for those who have already bled. To avoid costly and invasive endoscopic screening, there are a number of studies on non-invasive means of predicting the presence and future development of esophageal varices in high risk population. These non-invasive means would decrease the number of endoscopies performed thus restricting the performance of endoscopy to only those patients with a high probability of having varices. This would avoid endoscopy in those at low risk patients.[6] SAAG was proposed to be a factor which determined the degree of portal hypertension and prognosis in alcohol induced cirrhosis.[7] Several prediction models such as combination of platelet count and Child-Pugh class, platelet count and splenomegaly, and spleen width and portal vein diameter were also investigated. However, different studies performed in cirrhotic patients have yielded different results.[6] Serum-ascites albumin gradient (SAAG) has been concluded in several studies like a surrogate marker in estimating portal hypertension and its complications and it can be a helpful means in predicting incidence of EV.[7]

METHODS

The study was approved by the ethical committee of Nepal Medical College and Teaching Hospital, and consent was taken from the participants. Based on inclusion and exclusion criteria eighty patients with cirrhosis of liver, attending the medical wards and outpatient departments of Nepal Medical College and Teaching Hospital were enrolled in the study.

All patients in the study underwent a full clinical evaluation. History and physical examination findings were recorded. All patients underwent biochemical tests, like liver function test, complete blood count, renal function test, prothrombin time, and ultrasonography of the abdomen to confirm the presence of cirrhosis. Ascitic fluid (10 ml) was drawn using aseptic technique and sent to analyze total count, differential count, total protein, albumin, LDH and glucose. Child-Pugh score was calculated for all patients. All patients underwent upper gastrointestinal endoscopy to evaluate for the presence and grading of esophageal varices. The grading of esophageal varices was done according to the AASLD guidelines as mentioned above. Data collected was analyzed using SPSS and Microsoft word and Excel were used to generate graphs and tables etc.

RESULTS

Out of total 80 patients included in the study, more than one third of the patients were from 51 to 60 years of age. The mean age was 51.41 ± 10.14 years with age range from 30 to 78 years. Most patients were male (56.20%). On reviewing the clinical data of the studied patients, general examination revealed that 95% had jaundice which was the most common symptom. Pedal edema, abdominal distension, pain abdomen, fatigue, melena, weight loss, oliguria and symptoms of hepatic encephalopathy were the other presenting complaints (Table 1).

TABLE1. Distribution of patients according to presenting complaints.

Clinical symptoms*	No. of patients (N=80)	Percentage (%)
Jaundice	76	95.00
Pedal edema	62	77.50
Abdominal distension	68	85.00
Pain abdomen	25	31.25
Fatigue	40	50.00
Melena	20	25.00
Oliguria	17	21.25
Weight loss	27	33.75
Symptoms of HE	13	16.25

*Multiple responses

Icterus was the most common presenting sign (95%). Ascites (68%), pallor (81.25%) and pedal edema (77.5%) were the other common signs observed. On abdominal examination, 75% of the patients had splenomegaly. Mild ascites was detected in 18.75%, moderate ascites in 56.25% and severe ascites in 25% patients. Regarding the hepatitis markers of the studied patients, HCV antibody and HBsAg were positive in only two and three patients respectively. The most common cause of cirrhosis of liver was alcohol (93.75%). Only 6.25% of patients had positive viral markers, hepatitis B in 3.75% and hepatitis C in 2.50%. Regarding Child-Pugh classification, 5 patients (6.25%) were in Child class A, 55 patients (68.75%) were in Child class B and 20 patients (25%) were in Child class C. Regarding the biochemical analysis of the ascitic fluid, the ascitic fluid albumin ranged between 0.4-1.8 (mean albumin 0.72) gm/dL. Serum albumin ranged from 1.6-4.1 (mean albumin 2.68) gm/dL. Serum-ascites albumin gradient (SAAG) was calculated in all of the patients and it ranged between 0.9-3.0 (mean SAAG 1.27) gm/dL. Most patients had SAAG in the range of 2.5-2.9 g/dL. Only a few number of patients had SAAG in the range of 4.0-4.4 g/dL group (Fig 4).

Abdominal ultrasound revealed that the liver size was normal (11-15 cm) in 35 patients (43.75%), enlarged (>15 cm) in 8 patients (10%) and shrunken (<11 cm) in 37 patients (46.25%). On ultrasonography, the spleen was slightly enlarged (13-16 cm) in 51 patients (63.75%), moderately enlarged (16-20 cm) in 25 patients (31.25%) and hugely enlarged (>20 cm) in 4 patients (5.0%). 85% had ascites and most of them had moderate ascites as confirmed by shifting dullness and ultrasonogram. Upper GI endoscopy revealed varices in 75 patients (93.75%) and no varices in five patients (6.25%). Among those with varices, 9 patients had additional gastric varices. Twenty-six patients (34.66%) had grade I EV, 20 patients (26.66%) had grade II EV, 29 cases (38.66%) had grade III EV. Portal hypertensive gastropathy (PHG) was observed in 45 patients (56.25%). Rest of the patients had no evidence of portal gastropathy. Among them, 30 patients (66.66%) had severe portal hypertensive gastropathy whereas 15 patients (33.33%) had mild gastropathy.

According to the SAAG values, patients were divided into two groups:

-High SAAG: 73 Patients (91.25%) were with high SAAG (≥1.1 g/dL)

-Low SAAG: 7 patients (8.75%) were with low SAAG (<1.1 g/dL)

Upper GI endoscopy revealed varices in 68 patients (93.15%) of high SAAG group and all patients (100%) of low SAAG group. Although hundred percentages of the low SAAG group had esophageal varices but it was statistically insignificant (P value = 0.48) as shown in Table 2. Among the patients who had varices, most (90.66%) had high value of SAAG.

Table 2. Comparison between high SAAG and low SAAG group with varices.

Presence of varices	High SAAG (N=73)		Low SAAG (N=7)		P value
	N	%	N	%	
Yes	68	93.15	7	100	0.48
No	5	6.85	0	0.00	

Among the 68 patients with varices in the high

SAAG group, 59 patients (86.76%) had isolated esophageal varices and 9 patients (13.23%) had esophageal varices with gastric extension (gastroesophageal varices). Among the 7 patients with varices in the low SAAG group, none of them had gastric varices. Comparison between patients with different grades of varices with regard to SAAG showed no significant statistical difference (P value = 0.24) as shown in Table 3.

TABLE 3. Comparison between different grades of varices with SAAG.

Esophageal varices	High SAAG with varices (N=68)		Low SAAG with varices (N=7)		P value
	N	%	N	%	
Grade 1	21	30.88	5	71.43	0.24
Grade 2	19	27.94	1	14.29	
Grade 3	28	41.17	1	14.29	

Comparison between patients with varices as regards to serum albumin, ascitic albumin and SAAG showed no significant statistical difference (Table 4).

TABLE 4. Comparison between patients with or without varices as regards to serum albumin, ascites albumin and SAAG.

Variables	No varices (N=5)	Varices (N=75)	P value
	Mean	Mean	
Serum albumin (g/dL)	2.69	2.52	0.90
Ascites albumin (g/dL)	0.73	0.66	0.96
SAAG	1.96	1.86	0.06

Correlation between different groups of SAAG and the size of varices was calculated which showed that there is no statistically significant correlation between SAAG groups and the size of varices. The Pearson's chi-square test value between the grading of esophageal varices and serum-ascites albumin gradient was 0.24 i.e. a weak positive correlation. So, as the gradient increased, the grading of esophageal varices also increased, but it was statistically insignificant (significant p value considered 0.01). This analysis is tabulated below (Table 5).

TABLE 5. Distribution according to the grade of esophageal varices and the degree of SAAG.

Esophageal varices	SAAG value (g/dL)										P value
	< 1.1		1.1-1.5		1.6-2.0		2.1-2.5		2.6-3.0		Total		
	N	%	N	%	N	%	N	%	N	%	N	%	
Grade 1	5	6.67	3	4.00	9	12.00	6	8.00	3	4.00	26	34.67	0.24
Grade 2	1	1.33	4	5.33	5	6.67	8	10.67	2	2.67	20	26.67	
Grade 3	1	1.33	2	2.67	11	14.67	13	17.33	2	2.67	29	38.66	
Total	7	9.33	9	12.00	25	33.34	27	36.00	7	9.34	75	100.00	

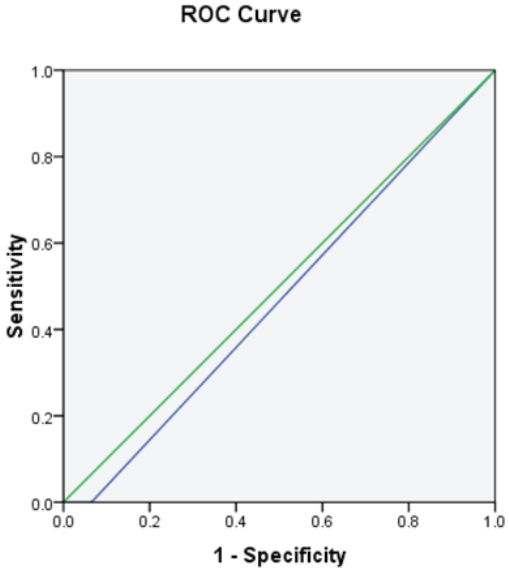

FIGURE 1. ROC curve for the prediction of varices with SAAG

Serum-ascites albumin gradient was not a strong predictor for the presence or absence of varices, as the area under the curve (AUC) = 0.468 which is statistically not significant (Figure 1).

DISCUSSION

In our study, the incidence of cirrhosis was maximum in the age group of 41-60 yrs. Overall, the mean age was 51.41 yrs (SD 10.14 yrs). Males predominated in each of the age group studied. This showed that males because of their more drinking habit in our society have more prevalence of cirrhosis.[8] Among the patients studied, the most common cause of cirrhosis was alcoholism (93.75%). Viral markers were positive only in 5 patients (6.25%). Majority of patients belonged to Child class B (68.75%). In this present study, 73 patients (91.2%) had high SAAG and 7 patients (8.8%) had low SAAG. Upper GI endoscopy revealed varices in 68 patients (93.15%) with high SAAG and all patients (100%) with low SAAG but there was no significant statistical difference.

In this present study EV were present in 9 of 9 patients (100%) with SAAG values 1.10-1.49 g/dL, 25 of 30 patients (83.33%) with SAAG values 1.50-1.99 g/dL, 27 of 27 patients (100%) with SAAG values 2.10-1.50 g/dL, 7 of 7 patients with SAAG values 2.6-3.0 g/dL. This study also showed a positive correlation between SAAG and esophageal varices but it was statistically insignificant (p value = 0.24). There was also no significant correlation between grades of esophageal varices and serum albumin, ascitic albumin, ascitic fluid total protein or SAAG level. In this study, Receiver Operating Characteristic (ROC) curve was displayed in order to discriminate between presence and absence of varices which showed that serum-ascites albumin gradient was not a strong predictor for the presence or absence of varices (AUC = 0.468).

The discrepancy in the results of SAAG level and its relation to portal hypertension may be attributed to two factors. Firstly, the 3.3% error in its diagnostic accuracy is due to the very narrow range of the level of ascitic fluid albumin concentration (0 to 1 g/dL in most cases).[9] Secondly, the discrepancy in the results of SAAG level may be caused by usual methods of estimation of albumin concentration (dye binding and shift in color when a dye is bound by albumin). More appropriate methods for the determination of albumin concentration in the body fluids where albumin concentration is normally low (i.e., urine and CSF) includes several formats of electrophoresis, radioimmunoassay (RIA) and immunoassay.[10] These investigations need special equipments, which are not available in ordinary clinical laboratories, particularly in developing countries.[11] A cutoff value of >1.6 for SAAG to discriminate between presence and absence of varices yielded a sensitivity of 78.66% and a positive predictive value of 92.18% but it was not specific. This means that we can predict the presence of varices with a sensitivity of 78.66% without any significant specificity.

CONCLUSIONS

Serum-ascites albumin gradient (SAAG) has been considered as a surrogate marker for predicting esophageal varices. Many studies have shown a positive correlation between SAAG and esophageal varices. This study has shown that SAAG has a positive correlation with esophageal varices. It has both high sensitivity and positive predictive value in estimating the presence of varices but without statistical significance. As well as, it has a low specificity. Due to statistically insignificant correlation and a low specificity, SAAG cannot be used in place of upper GI endoscopy in diagnosing gastroesophageal varices. These findings have been in accordance with the conclusion drawn by American Association for the Study of Liver Diseases, European Association for the Study of the Liver and American College of Gastroenterology. It is thus advised not to use SAAG as a substitution for upper GI endoscopy to diagnose and manage esophageal varices in cirrhosis.

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