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Serum Ascites Albumin Gradient (SAAG): A Non-Invasive Predictor of Esophageal Varices in Cirrhotic Patients

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Abstract

Background: The chronic liver disease is a disorder of high prevalence in South Asia. A potential outcome is liver cirrhosis associated with its adverse complications including esophageal varices. Several parameters related to clinical ultrasonography and biochemistry may be benefited for having diagnostic value in non-persistent evaluation of bleeding risk from varices. SAAG may be considered as a helpful mean in the forecasting the incidence of esophageal varices.

Objective: To determine the mean value of SAAG in DCLD patients and to compare it with patient characteristics and grades of esophageal varices.

Methods: This cross-sectional study took place in Department of Medicine, Holy Family Hospital Rawalpindi, Pakistan from June to December 2019. A total of 100 diagnosed patients of decompensated cirrhosis having ascites fulfilling the selection criteria was included in the study. Complete physical examination with investigations i.e. complete blood count, liver function tests, serum albumin, prothrombin time and viral profile (HbsAg, Anti-HCV) was done in all patients. Serum-ascites albumin gradient was calculated as per standard method. All the collected data was entered into SPSS version 21 and was analyzed.

Results: The mean age of patients was 46.22 ± 2.29 years with 47 (47%) female and 53 (53%) males in this study. The mean serum albumin was 2.82 ± 0.48 while mean albumin of Ascitic fluid was 0.84 ± 0.40 g/dl subsequently mean SAAG value was calculated to be 1.98 ± 0.62. Independent Sample t-test was applied to compare mean SAAG values among gender and age groups, the association was statistically not significant (p-value >0.05). Using One-way ANOVA to compare mean SAAG values between grades of esophageal varices, the association was found to be statistically significant (p-value <0.001).

Conclusion: Serum Ascitic Albumin Gradient (SAAG) can be considered as an oblique marker in predicting the incidence of esophageal varices.

Keywords: Hepatitis virus; Liver cirrhosis; Fibrosis; Esophageal varices; Portal hypertension; SAAG

Introduction

Cirrhotic liver patients develop complications including portal hypertension manifesting as esophageal varices (EV) which are dilated, tortuous and fragile vessels that connect portal venous and systemic venous circulation and located in sub mucosa of lower esophagus. The most dangerous presentation of EV is upper gastrointestinal bleeding. At the time of diagnosis, 30% of cirrhotic patients have EV that increase to 90%, after 10 years [1]. Gastroesophageal varices is a major complication of portal hypertension resulting from cirrhosis. Its prevalence is 25 to 35 percent in patients with chronic liver disease with 80 to 90 percent developing bleeding episodes. Variceal bleeding is associated with significant morbidity and mortality and carries higher economic burden.

The first episode of variceal bleeding has a high mortality

rate of up to 30 percent with rest of 70 percent developing subsequent episodes of bleeding within one year [2,3]. Variceal hemorrhage is a leading cause of morbidity and mortality in cirrhosis. Nonselective beta-blockers and endoscopic band ligation as a primary prophylaxis may reduce the risk of variceal bleeding. Current guidelines are of view that cirrhotic patients should be screened for esophageal varices at the time of diagnosis. If no varices are observed on initial endoscopy in patients with compensated cirrhosis, endoscopy should be repeated in 3 years; in decompensated cirrhotic patients, it should be repeated annually [4].

Serum-ascitic albumin gradient (SAAG) has been concluded in several studies as an oblique marker in approximating portal hypertension and its complications so it's a helpful mean in the forecasting of incidence of EV. Serum Albumin level and Ascitic fluid Albumin level taken from specimens taken less than 24 hours apart can be used to calculate SAAG value. If SAAG is equal or greater than 1.1 gm/dl (11mmol/L), the patient has likely portal hypertension; if SAAG is less than 1.1 gm/dl then the causes other than portal hypertension should be considered, like tuberculosis and malignancy etc. [5].

In clinical practice the cirrhotic patients are diagnosed for varices through diagnostic endoscopy. Endoscopy for esophageal varices in cirrhotic patients is invasive, expensive and causes significant discomfort to the patients. There is a need to make it possible to perform upper gastrointestinal endoscopy in preferred patients thus keep away from needless interference. The aim of present study was to find out the mean value of SAAG in DCLD patients and relation of mean value of SAAG with frequency of grades of esophageal varices so that it can help in risk stratification, diagnosis of esophageal varices and help in management of esophageal varices like primary and secondary prophylaxis.

Materials and Methods

This is a cross sectional study which took place in department of Medicine Holy Family Hospital Rawalpindi, Pakistan from June 2019 to December 2019.The sample size was calculated by using WHO sample size calculator taking confidence level 95%, population mean 2.01 [6], standard deviation 0.52 [6], absolute precision 0.25. The sample size turned out to be 100 patients. The sampling technique was non probability consecutive sampling. We included all the diagnosed patients of DCLD of both gender and having age between 20 – 50 years. We excluded patients already being treated on medicines for ascites, variceal bleed, patients having sclerotherapy or band ligation, patients suffering from Hepatocellular carcinoma, previous portosystemic anastomosis, portal vein thrombosis. We also excluded those patients who had ascites because of etiologies other than cirrhosis like tuberculosis, abdominal malignancy and congestive cardiac failure.

After seeking approval from Institutional Research forum and ethical committee of RMU, a total of 100 diagnosed patients of decompensated liver cirrhosis having ascites fulfilling the selection criteria was included in the study. The patients fulfilling the inclusion criteria were enrolled through OPD of Holy family hospital Rawalpindi, Pakistan. All the patients were explained the study purpose and procedure after which informed written consent was taken.

Complete physical examination was done in all patients followed by blood sampling for the investigations i.e. complete blood count, liver function tests, serum albumin, prothrombin time and viral profile (HbsAg, Anti-HCV).

Diagnostic paracentesis was done under aseptic measures within 30 minutes of taking blood samples. All the tests were performed in uniform lab and were verified by pathologist. Serum-ascites albumin gradient was calculated by; SAAG = (serum albumin) - (albumin level of ascitic fluid). Abdominal ultrasound was performed to evaluate the coarse echogenic texture of liver parenchyma, splenomegaly and ascites. Endoscopic evaluation of all patients was done by a gastroenterologist and was graded as; Grade 1(F1): Small straight varices, Grade 2(F2): Enlarged tortuous varices occupying less than one third of the lumen, Grade 3(F3): Large coiled-shaped varices occupying more than one third of the lumen. Demographic information including name, age, gender and all other information regarding all investigations was recorded on a predesigned Performa.

All the collected data was entered into SPSS version 21 and was analyzed. Mean and standard deviation was calculated for quantitative variables like, age, Serum Albumin, Ascitic fluid Albumin and SAAG value. Qualitative variables like Esophageal Varices grades were presented in the form of frequency and percentage. Effect modifiers like age and gender was controlled by stratification. Post stratification independent sample t-test was applied. Grades of varices were compared for mean SAAG by ANOVA test. P-value ≤ 0.05 was considered significant.

Results

The mean age of patients was 46.22 ± 2.29 years with minimum and maximum age of 42 and 50 years respectively. There were 47% (N=47) female and 53% (N=53) males in this study. The mean serum albumin was 2.82 ± 0.48 with

minimum and maximum serum albumin was 1.90 and 3.50 g/dl. The mean ascitic fluid albumin was 0.84 ± 0.40 g/dl, with minimum and maximum value of 0.10 and 1.95 g/dl. The mean SAAG value was 1.98 ± 0.62 with minimum and maximum value was 0.60 and 3.15. On endoscopy17% (N=17) had no esophageal varices 21% (N=21) had Grade 1, 38% (N=38) had Grade 2, 24 (N=24) had Grade 3 esophageal varices Table 1.

Table 1: *Characteristics of Studied Patients.*

Variable	N (%)
Gender	
Male	53 (53%)
Female	47 (47%)
Age (years)	
Mean (SD)	46.22 (±2.29)
Serum Albumin (g/dl)	
Mean (SD)	2.82 (±0.48)
Ascitic Fluid Albumin (g/dl)	
Mean (SD)	0.84 (±0.40)
SAAG (g/dl)	
Mean (SD)	1.98 (±0.62)
Esophageal varices	
Present	83 (83%)
Absent	17 (17%)
Grades of Esophageal varices	
Grade 0	17 (17%)
Grade 1	21 (21%)
Grade 2	38 (38%)
Grade 3	24 (24%)

Using Independent Sample t-test, the mean SAAG values in age group 40-44 and 45-50, 1.96 ± 0.70 and 1.99 ± 0.60 respectively were found to be statistically similar in both age groups (p-value >0.05). The mean SAAG values in female and male groups were also statistically same, 1.90 ± 0.67 and 2.05 ± 0.58 respectively. (p-value >0.05). The mean SAAG in patients with esophageal varices was significantly higher 2.17 ± 0.49 when compared to non- esophageal varices 1.08 ± 0.33 (p-value <0.001) Table 2. Mean SAAG

Table 2: *Comparison of SAAG value according to variables.*

Variable	SAAG (mg/dl) Mean (SD)	t (p-value)*
Gender		-1.20 (0.233)
Male	2.05 (±0.58)	
Female	1.90 (±0.67)	
Age groups		0.309 (0.846)
40-44 years	1.96 (±0.70)	
45-50 years	1.99 (±0.60)	
Esophageal varices		8.68 (<0.001)
Present	2.17 (±0.49)	
Absent	1.08 (±0.33)	
*Independent Sample t-test was applied to calculate p-value		

values of different grades of esophageal varices showed an increasing trend with Grade 0, 1, 2 and 3 having 1.07 ±0.34, 2.03 ±0.56, 2.13 ±0.44 and 2.33 ±0.49 respectively. One-way ANOVA was applied to compare mean SAAG values as per grades of esophageal varices, the association was found to be significant Table 3.

Table 3*: Comparison of SAAG value according to Grades of Esophageal Varices.*

Variable	SAAG (mg/dl) Mean (SD)	F (p-value)*
Grades of Esophageal Varices		27.39 (<0.001)
Grade 0	1.07 (±0.34)	
Grade 1	2.03 (±0.56)	
Grade 2	2.13 (±0.44)	
Grade 3	2.33 (±0.49)	
*One way ANOVA was applied to calculate p-value		

Discussion

Cirrhosis is a diffuse and reversible pathologic process in which normal structure of the liver is replaced by regenerative nodules of hepatocytes separated by bands of fibrosis. Cirrhosis may result from various forms of chronic hepatic insult. Clinical features of cirrhosis are derived from the morphologic alterations and often reflect the severity of hepatic damage rather than the etiology of the underlying liver disease [7]. Cirrhosis initially may develop without giving rise to signs or symptoms. Compensated cirrhosis may progress, however, and has 2 major pathophysiologic consequences: portal hypertension and hepatic failure. After the diagnosis of cirrhosis, the probability of developing decompensated cirrhosis by 10 years is approximately 60%, and the 10-year survival rate is approximately 50% [8].

Proper diagnosis and management of the complications of portal hypertension are vital to improving quality of life and reducing mortality. Ascites, the abnormal accumulation of fluid in the abdominal cavity, is one of the most common complications of advanced liver disease. In general, ascites carries a poor prognosis with high mortality. In the United States, approximately 8 in every 10 patients develop ascites as a consequence of cirrhosis of the liver [9]. In patients with compensated cirrhosis, ascites develops at a 5-year cumulative rate of approximately 30% [10]. Once ascites has developed, the 1-year survival rate is approximately 50% compared with 90% in patients with compensated cirrhosis [10].

Prognosis is particularly poor in patients who develop refractory ascites or hepatorenal syndrome [11]. The treatment of ascites does not appear to prolong life in the cirrhotic patient; it does, however, improve the quality of life and protect the patient from spontaneous infections of the fluid that convey high death rates.12 The consequences of ascites are related to the high risk of spontaneous infection in the fluid, the development of abdominal hernias with incarceration or rupture, difficulty breathing due to pressure of the abdomen on the thoracic cavity, decreased food intake with progressive malnutrition, and decreased physical activity [12].

Successful treatment depends on an accurate diagnosis of the cause of ascites. Paracentesis with analysis of ascitic fluid is the most rapid and cost-effective method of diagnosis. It should be done in patients with ascites of recent onset, cirrhotic patients with ascites admitted to hospital, or those with clinical deterioration. The most important analyses are cell count, fluid culture, and calculation of the serum: ascites albumin gradient (SAAG), which reflects differences in oncotic pressures and correlates with portal venous pressure. If SAAG is greater or equal to 1.1 g/dL (or 11 g/L), ascites is ascribed to portal hypertension with approximately 97% accuracy [13]. Patients with cirrhosis and ascites are also at risk of developing infections, particularly spontaneous bacterial peritonitis (SBP). SBP occurs in approximately 10% of hospitalized cirrhotic patients [14], with an associated mortality of 20–40% if untreated [15].

Variceal hemorrhage occurs in 25 to 35% of cirrhotic patients and is associated with significant morbidity and mortality and elevated hospital costs. A total of 76.47% of the patients were men and 23.53% were women.

The median age was 52.8 ±12.4 years [16]. In current study the mean age of patients was 46.22 ±2.29 years 47(47%) female and 53(53%) males in this study. These statistics are comparable to the above findings. Esophageal varices (EV) were found in 85.29% of the patients [16]. We in this study found that esophageal varices was seen in 83(83%) of the patients which are almost similar to the above cited study. A local study reported almost similar statistics i.e. Out of 73 patients, 51 (69.9%) were males and 22 (30.1%) were females. Forty-four (60.3%) patients were having esophageal varices on endoscopy and 29 (39.7%) patients were having no varices. Out of 44 patients, small varices were found in 28 (63.6%) patients while large varices were found in 16 (36.4%) patients [17]. We in this study found that grades 1 was seen in 21 (21%), grade 2 was seen in 38 (38%) and grade 3 was seen in 24 (24%) of the patients.

One more study was designed to determine the correlation between the level of serum-ascites albumin concentration gradient (SAAG) and the complications of portal hypertension (PHTN), manifested by the presence and grade of esophageal varices (EV). They found that 25 of 32 (78.13%) patients had High SAAG and 7 of 32 (21.87%) had Low SAAG. Esophageal varices were present in 18 of 25 (72%) patients with High SAAG and in none of 7 (0%) patients with Low SAAG ($p < 0.001$). Among patients with High SAAG, EV were present in four of 8 patients (50%) with SAAG values of 1.10-1.49 g/dl; in four of seven patients (57.1%) with SAAG values of 1.50-1.99g/dl; and in ten of ten (100%) with SAAG values of > 2.0g/dl ($p <0.05$). The size of the esophageal varices had no association with the level of SAAG in patients with High SAAG ($p = 0.426$) [18].

One more study reported that from total 100 patients, males were 62 and females were 38. SAAG was 2.01 ±0.52 g/dl. Esophageal varices (EV) were found in 87 patients and were absent in 13 patients. Grades of the esophageal varices highlighted significant correlation with degree of SAAG

(p<0.001). With the use of ROC curve, a SAAG value i.e. ≥1.65 ± 0.014 g/dl was a correct marker of the occurrence of EV; cutoff points for the higher predictive value 98% were positive, and 96% were negative. Another study aimed to identify the mean SAAG "serum-ascites albumin gradient" value in DCLD patients, mean SAAG was found out to be 2.01 ±0.52 g/dl. Grades of the esophageal varices highlighted significant correlation with degree of SAAG, showing the mean value of SAAG in F1 Varices = 2.0 ±0.54, in F2 varices = 2.1 ±0.38 and in F3 varices = 2.3 ±0.44 [6].

We in this study found that according to variceal grades, grade 1 was seen in 21 (21%), grade 2 was seen in 38 (38%) and grade 3 was seen in 24 (24%) of the patients. Mean SAAG in age group 40-44 and 45-50 was 1.96 ±0.70 g/dl and 1.99 ±0.60 g/dl in this study, the mean SAAG was statistically same in both age groups, p-value > 0.05. We also found that the mean SAAG in grade-1 was 2.03 ±0.56 g/dl, in grade 2 was 2.13 ±0.44 g/dl and in grade 3 was 2.33 ±0.49 g/dl, the mean SAAG was significantly higher in grade 3, p-value < 0.001.

Lastly, the SAAG is minimally invasive method that is highly precise and allows for classification of ascitic fluids according to the absence or presence of portal hypertension. It is pointed out in the literature that the SAAG is an indicator of portal hypertension and that a direct relationship probably exists between SAAG and different PHTN measurements such as the portal pressure gradient, net portal pressure or corrected portal pressure. These measurements are obtained only by invasive methods, which are not feasible in most centers in the resource constrained countries [18,19].

Conclusion

SAAG is an oblique marker in approximating portal hypertension and its complications and may act as a helpful mean in forecasting the incidence of esophageal varices effectively eliminating undue invasive endoscopies.

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