Original Article

Serum-ascites albumin gradient: an independent predictor of esophageal variceal bleeding in cirrhosis patients with ascites

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Abstract: Aim: The current study aimed to analyze the correlation between serum-ascites albumin gradient (SAAG) and esophageal variceal bleeding (EVB) in patients with cirrhosis. Methodology: This was a retrospective study, including 546 patients hospitalized for cirrhosis ascites at the Beijing Ditan Hospital, between January 2008 and January 2016. Patients were divided into the bleeding group and non-bleeding group, based on whether they had bled within the last year. Relationships between EVB and study variables were assessed using univariate and multivariate analyses, as well as receiver operator characteristic (ROC) curves. The prognostic value of SAAG was assessed by Kaplan-Meier analysis and by comparing log-rank test results. Results: Multivariate analysis revealed that SAAG and aspartate aminotransferase were significantly associated with EVB in patients with cirrhosis ascites. SAAG demonstrated the strongest prognostic value (area under ROC curve = 0.714). SAAG ≥ 25 g/L was a significant predictor of EVB at different degrees of esophageal varicosity and different etiologies. SAAG increased with increasing degrees of esophageal varicosity. Conclusion: SAAG is a useful predictive biomarker of EVB for patients with cirrhosis ascites. SAAG ≥ 25 g/L may identify patients at high risk of EVB.

Keywords: Liver cirrhosis, serum-ascites albumin gradient, esophageal variceal bleeding

Introduction

Liver cirrhosis is defined as chronic liver damage caused by repeated and long-term effects of multiple etiologies. When progression of liver cirrhosis enters the decompensation stage, various complications occur, including ascites, abdominal infections, hepatorenal syndrome, hypoproteinemia, and esophageal variceal bleeding (EVB) [1, 2]. Of these complications, EVB is the most common emergency medical admission, worldwide. It shows a high inpatient mortality rate of 10%, despite modern diagnosis and therapy. Many studies have recommended that cirrhotic patients be screened for presence of esophageal varices (EV) when liver cirrhosis is diagnosed [3, 4]. However, endoscopy procedures are invasive and unpleasant, carrying rare but serious complications [5, 6]. Mandating all patients with cirrhosis to a screening endoscopy may not be cost effective. Thus, some scholars have attempted to use other noninvasive indicators as alternatives to endoscopy, aiming to predict the degree of esophageal varicosity. These indicators include liver stiffness measurement, blood platelet count, platelet count/spleen size, and spleen stiffness [7-9]. However, no worldwide consensus has been reached regarding which variable is the best for predicting risk of EVB.

Serum ascites albumin gradient (SAAG), defined as serum albumin concentration minus the ascetic fluid albumin concentration, has been proposed as a reliable marker for differential diagnosis of ascites and predictor of EV in the past 20 years.

Over the past decade or so, multiple studies have shown that SAAG is associated with portal venous pressure, EV, and differential diagnosis of ascites [10-12]. Hoefs first introduced SAAG, reporting that SAAG can reflect portal vein pressure and improve the accuracy of asci-
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tes identification [13]. Thereafter, several other investigators demonstrated the superiority of SAAG (11 g/L) for distinguishing portal hypertensive ascites and non-portal hypertensive ascites [12, 14]. More recently, Rector et al. reported an excellent correlation between SAAG and portal pressure [15]. Demirel et al. also suggested that patients with alcoholic cirrhosis with SAAG > 20 g/L showed a significant increase in esophageal varicose veins [16]. Forhad Hossain Md Shahed et al. found a correlation between SAAG and esophageal varicose gastric varicose veins. A total of 50 patients with cirrhosis of various etiologies were included. The relationship between SAAG and portal hypertensive changes in the upper gastrointestinal tract were examined, including esophageal varices, gastric varices, and gastropathy [17]. Similarly, Forhad Hossain Md found a correlation between SAAG and ruptured bleeding of esophageal varicose gastric veins in children. However, the current study found that SAAG is correlated with esophageal varicose gastric veins only. No correlation was found with hemorrhaging [18]. To the best of our knowledge, no current studies have predicted the risk of EVB in patients with cirrhosis. Therefore, the current study was conducted to determine whether SAAG is associated with occurrence of EVB in patients with cirrhosis.

Patients and methods

Study and patient characteristics

The current study included 546 patients with cirrhosis ascites, demonstrated by ultrasonography. SAAG was measured for all patients. These patients were selected from a pool of 2,779 patients, hospitalized at the Beijing Ditan Hospital, affiliated with Capital Medical University, in China, between January 2008 and January 2016. The remaining 2,233 patients were excluded because of comorbidities, including primary liver cancer, other malignancies, acute upper gastrointestinal bleeding, and renal insufficiency. Patients were also excluded if records were missing key clinical, laboratory, imaging, and follow-up data. Lastly, patients that had been treated with endoscopic sclerosis or endoscopic variceal ligation were also excluded.

This study was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. Since this study was retrospectively designed, informed consent of patients was not required. However, to protect patient privacy, patient records and information were anonymized and deidentified prior to analysis.

Data collection

Possible variables associated with the presence of EVB in cirrhosis were collected, including: 1) Patient demographics; 2) Serum indexes, including alanine aminotransferase, aspartate aminotransferase (AST), total bilirubin, total protein (TP), albumin (ALB), γ-glutamyl transpeptidase, total bile acid, cholinesterase (CHE), white blood cell count, absolute neutrophil count, absolute lymphocyte count (LC), absolute platelet count, serum potassium, serum sodium, prothrombin activity, and international normalized ratio (INR); 3) Related parameters of ascites, including ascites TP, ascites ALB, and SAAG; and 4) Abdominal ultrasound and upper gastrointestinal endoscopy findings. Rates of EVB at 1 year following enrollment were obtained from patient medical records or by direct contact with the patients and their families.

Definitions

Cirrhosis is mainly based on clinical diagnosis. Manifestations include hepatic function decompensation and portal hypertension. At least two imaging examinations are suggestive of typical cirrhosis (including ultrasonography, abdominal computed tomography, and magnetic resonance imaging) [19]. According to Child-Pugh grading standards, cirrhosis is divided into grades A, B, and C.

According to standard criteria published by the Japan Society for Portal Hypertension, EV staging is classified as none (no veins above the esophageal mucosal surface; F0), small (minimally elevated veins above the esophageal mucosal surface; F1), medium (large tortuous veins occupying < 1/3 of the lumen; F2), or large (large coil-shaped veins occupying ≥ 1/3 of lumen; F3) [20].

EVB is diagnosed based on one of the following endoscopic findings: 1) Active bleeding from a varix; 2) “White nipple” overlying a varix; 3) Clots overlying a varix; and 4) Varices with no others potential source of bleeding [21].
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Table 1. Single factor and multifactor analysis

<table>
<thead>
<tr>
<th>Patient’s Characteristics</th>
<th>Value</th>
<th>Univariate HR (95% CI)</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.5 ± 10.3</td>
<td>0.987 (0.975-1.002)</td>
<td></td>
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<tr>
<td>Male</td>
<td>412/546</td>
<td>0.928 (0.654-1.316)</td>
<td></td>
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</tbody>
</table>

Laboratory data

<p>| | | | |</p>
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Alanine aminotransferase, UL⁻¹</td>
<td>33.4 (19.7, 56.63)</td>
<td>0.998 (0.995-1.001)</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase, UL⁻¹</td>
<td>53.2 (34.5, 93.5)</td>
<td>0.996 (0.993-1.000)*</td>
<td>0.992 (0.995-0.999)*</td>
</tr>
<tr>
<td>Total bilirubin, μmol·L⁻¹</td>
<td>42.5 (26.3, 91.2)</td>
<td>1.000 (0.998-1.001)</td>
<td></td>
</tr>
<tr>
<td>Total protein, g·L⁻¹</td>
<td>62.4 ± 8.5</td>
<td>1.013 (0.992-1.035)</td>
<td></td>
</tr>
<tr>
<td>Albumin, g·L⁻¹</td>
<td>27.8 ± 5.0</td>
<td>1.076 (1.045-1.109)*</td>
<td></td>
</tr>
<tr>
<td>γ-Glutamyltransferase, UL⁻¹</td>
<td>44.6 (23.5, 90.7)</td>
<td>1.000 (0.999-1.002)</td>
<td></td>
</tr>
<tr>
<td>Total bile acid, UL⁻¹</td>
<td>50.8 (25.5, 111.2)</td>
<td>1.002 (1.000-1.004)</td>
<td></td>
</tr>
<tr>
<td>Cholinesterase, UL⁻¹</td>
<td>2238.2 ± 1190.7</td>
<td>1.000 (1.000-1.000)*</td>
<td></td>
</tr>
<tr>
<td>White blood cell, ×10⁹·L⁻¹</td>
<td>4.2 (3.0, 5.9)</td>
<td>0.959 (0.904-1.017)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count, ×10⁹·L⁻¹</td>
<td>2.7 (1.8, 4.1)</td>
<td>0.963 (0.902-1.029)</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count, ×10⁹·L⁻¹</td>
<td>1.1 ± 0.7</td>
<td>0.674 (0.477-0.954)*</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10⁹·L⁻¹</td>
<td>70.5 (46.4, 106.1)</td>
<td>0.997 (0.994-1.001)</td>
<td></td>
</tr>
<tr>
<td>Serum potassium, mmoL⁻¹</td>
<td>3.7 ± 0.6</td>
<td>0.859 (0.638-1.158)</td>
<td></td>
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<tr>
<td>Serum sodium, mmoL⁻¹</td>
<td>134.9 ± 12.5</td>
<td>1.001 (0.968-1.036)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin activity, %</td>
<td>54.5 ± 16.4</td>
<td>1.007 (0.997-1.018)</td>
<td></td>
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<tr>
<td>International normalized ratio</td>
<td>1.4 ± 0.5</td>
<td>0.466 (0.244-0.889)*</td>
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|                                |                |                          |                          |
| Ascites                        |                |                          |                          |
| Total protein, g·L⁻¹           | 12.5 ± 8.4     | 0.964 (0.939-0.989)*     |                          |
| Albumin, g·L⁻¹                 | 6.0 ± 4.7      | 0.949 (0.908-0.992)*     |                          |
| SAAG, g·L⁻¹                    | 21.4 ± 4.7     | 1.234 (1.178-1.293)*     | 1.225 (1.170-1.284)* |

Data are presented as n (%), mean ± standard deviation, or median (interquartile *P<0.05).

Statistics

Statistical analysis was performed using SPSS 20.0 statistical package (IBM, Armonk, NY, USA). The number of observations is reported to describe categorical variables. Mean ± standard deviation (SD) describes normally distributed continuous variables and medians with interquartile ranges describe continuous variables with skewed distributions. Univariate and multivariate analyses of the relationships between EVB and study variables were performed using Cox’s proportional hazard models. Variables shown to be associated with EVB in univariate analysis were evaluated in the multivariate Cox’s proportional hazard model. The likelihood ratio forward stepwise method was used for multivariate analysis.

Receiver operating characteristic (ROC) curves were constructed for each study variable shown to be significantly associated with EVB in multivariate analysis. Area under the curve (AUC) was calculated to evaluate the discriminatory capacity of each. Compared with Medcalc® software, out of the area under the ROC curve is statistically significant. Cut-off values for maximum sensitivity and specificity of SAAG were calculated and patients were divided into two groups, based on SAAG cut-off values. Kaplan-Meier survival analysis was performed to compare the presence of EVB of patients in different groups. The significance of the inter-group differences was evaluated using log-rank tests. Pearson’s correlation analysis was performed to determine the relationship between SAAG and degree of esophageal varicosity. All probability values calculated were 2-sided. P < 0.05 indicates statistical significance.

Results

Patient characteristics

A total of 546 patients with liver cirrhosis were included in this study. Baseline characteristics of the study population are shown in Table 1. The mean age in the current series was 52.5 ± 10.3 years. Patients were predominantly men (n = 412, 75.5%), of which 23.3% patients (n =
SAAG is a useful predictive biomarker of EVB

Further evaluating the predictive value of SAAG and AST for incidence of EVB, this study compared ROC curves of these parameters. As shown in Figure 1, the AUC value for SAAG (0.714) was significantly higher than that of AST (0.580), PLT (0.526), and portal vein width (0.571). The area under ROC under the joint diagnosis of AST and SAAG (0.734) was larger than that in SAAG (0.714), but there were no statistical differences ($P = 0.1073$). Compared with the width of AST, PLT, and portal veins, SAAG showed statistical differences under ROC curve ($P < 0.05$). Results indicate that SAAG in cirrhosis patients is significantly predictive of EVB.

To further verify the prediction value of SAAG in EV for patients with cirrhosis ascites, Pearson’s correlation coefficient was used to describe the relationship between SAAG and EV. As Figure 3A shows, SAAG increased with increasing EV stage. SAAG values presented as $17.4 \pm 6.3$ g/L in stage none, $21.4 \pm 4.7$ g/L in stage small, $22.1 \pm 4.1$ g/L in stage medium, and $23.1 \pm 3.7$ in stage large (none vs small, $P = 0.0307$; small vs medium, $P = 0.1855$; medium vs large, $P = 0.0858$; small vs large, $P = 0.0019$; none vs medium, $P = 0.0101$; none vs large, $P = 0.0007$). Positive linear correlation was observed between SAAG and degree of EV ($r = 0.244$, $P < 0.001$).
SAAG is a useful predictive biomarker of EVB

Figure 2. Kaplan-Meier curves for cirrhosis patients with SAAG ≥ 25 g/L and those with SAAG < 25 g/L for the 1-year follow-up period in the total population (A), different degrees of EV (B-D), and different etiologies (E-I).

55.3% and a specificity of 82.4% as optimal conditions, the cut-off value for SAAG was determined to be 25 g/L. Kaplan-Meier analysis showed that rates of EVB of patients with SAAG ≥ 25 g/L were higher at 1 year than those of patients with SAAG < 25 g/L in the total population (52.5% vs 14.9%) (Figure 2A). Different degrees of EV (Figure 2B-D) were shown to have statistical significance ($P < 0.05$). Moreover, 1-year incidence rates of EVB in none, small, medium, and large degrees of EV were 0%, 15.0%, 22.0%, and 41.9%, respectively (Figure 4A). Specifically, for small staging of EV, the incidence rate of the SAAG ≥ 25 g/L group increased by 30.2%, compared with that of the SAAG < 25 g/L group (39.1% vs. 8.9%, $P < 0.05$).

Furthermore, the current study analyzed the capacity of SAAG in different etiologies, including hepatitis B, hepatitis C, alcohol, hepatitis B combined with alcohol, and autoimmune liver disease. As Figures 2E-I, 4B show, the group of patients with SAAG ≥ 25 g/L also had a significant increase in risk of EVB for different etiologies ($P < 0.05$). Levels of SAAG in different etiologies are listed in Figure 3B.

Discussion

Esophageal variceal bleeding is the most common complication of liver cirrhosis and the most common cause of death. Six-week mortality rates of acute esophageal variceal bleeding ranges between 15% and 25% [22-24]. Every year, about 5 percent of patients with cirrhosis have varicose veins. One year later, about 10 to 20 percent of the venule varicose develops to vena cava varicose. Thus, the risk of esophageal variceal bleeding within two years is 20% to 30% [25].

Portal hypertension is a direct cause of esophageal varicose veins in patients with cirrhosis.
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There are many methods for detection of portal hypertension, including intraoperative esophageal manometry, pressure tests in portal angiography, testing the pressure of free dry veins during hepatic vein catheterizations, and hepatic venous pressure. It is believed that the clinical value of portal vein stress is highest by measuring the hepatic vein pressure gradient (HVPG), with HVPG > 10 mmHg the strongest predictor of varicose veins. Wall tension of varicose veins is the main factor that determines esophageal variceal bleeding. Intravenous pressure increases, varicose veins thicken and volume increases, and varicose veins become thin. Thus, wall tension of the varicose veins reaches its maximum, resulting in venous bleeding [6]. The above measurement techniques are invasive and have high requirements. They are difficult to apply in clinic. Therefore, to predict bleeding, endoscopic examinations, based on the degree of esophageal varicose veins and the ability to respond to the red sign of vascular wall tension, are an important clinical application. Gastroscopy also has restrictions of tolerance and contraindications. Therefore, it is important to find diagnostic indexes with non-invasive trauma, convenience, and economy in predicting esophageal variceal bleeding, avoiding repeated and unnecessary gastroscopy. In recent years, many scholars have carried out research. Of the many predictors, the ratio of plate counting to the length of the spleen has been considered to be the most valuable [27, 28], however, the accuracy of this measurement is influenced by the technique of ultrasound. Its predictive value has also been greatly questioned [29].

The current study is believed to be the first to address SAAG as a useful predictive biomarker of EVB for patients with cirrhosis ascites. According to subgroup analyses, it was found

Figure 3. Box plots of SAAG and the EV stage (A) and different etiologies (B) of patients with cirrhosis.

Figure 4. Risk for EVB of cirrhosis patients with SAAG ≥ 25 g/L and < 25 g/L group in the different degrees of EV (A) and different etiologies (B).
that elevated SAAG correlated with EV staging ($r = 0.244$, $P < 0.001$). Patients with a higher SAAG tended to have larger tortuous veins. SAAG of 25 g/L was determined as the best cutoff value for distinguishing between patients with poor prognosis and those with improved prognosis. Rates of EVB of patients with SAAG $\geq 25$ g/L were significantly higher at 1 year than those of patients with SAAG $< 25$ g/L in different degrees of EV and different etiologies [9].

This study examined different degrees of esophageal gastric varices in patients with cirrhosis, according to laboratory testing data, related laboratory evaluation parameters, the forecast model of liver cirrhosis, and SAAG esophageal gastric varices. Research results show that, in the detection of laboratory parameters, the width of portal veins and platelet counts associated with liver cirrhosis patients with esophageal gastric varices bleeding, in accord with previous reports [30-32]. According to ROC curve analysis, the correlation prediction model and SAAG values have the value of predicting hemorrhages of esophageal varices in the esophagus of patients with cirrhosis. This is consistent with the results of Berzigotti [33]. In comparison, sensitivity levels of SAAG values in predicting results are better than those in other prediction models. The prediction accuracy is relatively strong.

More remarkably, American Institute of Liver Disease and Gastroenterology guidelines recommend that incidence of the first variceal hemorrhage is only 7% for patients with cirrhosis and small varices that have not bled. Esophagogastroduodenoscopy (EGD) procedures should be repeated every 1-2 years [4]. The current investigation found that, for patients in the small staging of EV, the incidence rate of EVB was 15.0% in 1 year. However, if patients in the small staging of EV showed SAAG $\geq 25$ g/L, the risk of EVB in 1 year could increase to 39.1%. This is higher than that of patients in the medium staging of EV (22.0%). Thus, in patients with cirrhosis that have small varices and SAAG $\geq 25$ g/L, nonselective β-blockers can be used for prevention of the first variceal hemorrhage. EGD should be repeated every 6-12 months.

There were some limitations to the current study, however. First, this study was a retrospective study. Some patients were unable to trace their results, which may have reduced the statistical confidence of results. This also may have led to the inability to fully reflect patient clinical characteristics in baseline data. In addition, because ascites needs to be collected for calculation of SAAG, patients included in this study were only patients with a certain amount of ascites.

In conclusion, the current study suggests that SAAG can predict risk of EVB in patients with liver cirrhosis combined with ascites, along with SAAG $\geq 25$ g/L requiring clinical attention. Results of this study should be interpreted with caution. More studies with larger samples are required, especially prospective studies with improved results.

Acknowledgements

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Disclosure of conflict of interest

None.

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