ORIGINAL ARTICLE

Diagnostic Accuracy of AST/ALT for Diagnosis of Esophageal Variceal Bleeding Taking Endoscopy as Gold Standard

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ABSTRACT

Aim: To determine the diagnostic accuracy of AST / ALT at ≥ 1 for the diagnosis of esophageal varices taking endoscopy as gold standard.
Study design: Cross - sectional study
Place and duration of study: Department of Medicine, Mayo Hospital, Lahore from 22nd August, 2014 to 21st February, 2015.
Methodology: 220 patients of either sex between 20-60 years of age with the diagnosis of liver cirrhosis were selected using non- probability purposive sampling. AST/ALT Ratio was measured and esophageal varices were confirmed on endoscopy.
Results: Out of a total of 220 patients, 133(60.5%) were males and 87(39.5%) were females. Mean age of sampled population was 9.23±7.7 years. Duration of CLD ranged from 2 to 9 years with mean 5.38±2.034 years. For AST/ALT Ratio >1, sensitivity of 97.05%, Specificity 57.1%, Positive predictive value 78.5%, Negative predictive value 92.3%, false positive rate 42.8% and false negative rate of 7.6% were recorded taking endoscopy as gold standard.
Conclusion: AST/ALT Ratio > 1 is sensitive (97.05%) but not specific (57.1%) for the diagnosis of esophageal variceal bleeding
Keywords*:* Hepatic cirrhosis. Chronic Liver Disease. Esophageal varices. Endoscopy. Aspartate aminotransferase. Alanine aminotransferase. AST/ALT Ratio

INTRODUCTION

Bleeding from esophageal varices is a dramatic and common complication associated with liver cirrhosis[1] and is lethal in patients with signs of clinical decompensation (i.e., upper gastrointestinal bleeding, ascites, encephalopathy or jaundice) . The prevalence of esophageal varices in cirrhotic patients is between 60 to 80%, and a mortality rate of 17% to 57% with variceal bleeding. Bleeding recurrence may reach 60% of patients in two years[2,3,4].

Endoscopy is the diagnostic investigation of choice in patients with upper gastrointestinal bleeding secondary to esophageal varices. It aids diagnosis, yields information that helps in predicting outcome and most importantly allows treatment options that can stop bleeding and minimize the risk of re-bleeding[5]. With advancement, several non-invasive factors have been studied that have a clinical implication in diagnosing varices in cirrhotic patients. These factors include portal vein diameter, platelet counts, splenic size and aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ratio[6,7] and another non- invasive technique, transient elastography, which is effective in diagnosing portal hypertension and esophagel varices[8,9,10]. The AST/ALT ratio as a simple and non-invasive tool to predict the presence of esophageal varices and cirrhosis has been used in various studies[11,12,13]..

The commonest cause of cirrhosis in the developing countries is HCV infection. According to WHO, the prevalence of HCV infection estimated globally is 2 - 3%, representing 130 - 170 million people.(14) HCV is the major cause of liver transplantation in the developed countries and hospital admissions in the developing countries. In many developed countries like Australia and many Western European countries, the burden of HCV is <2% that equals the estimated prevalence in the United States.(15) In Latin America, Eastern Europe, some African, South Asian and Middle Eastern countries, the infection rates with HCV are higher(≥3%)[16,17].

Hepatitis C is the second most common infection in Pakistan with a prevalence rate of 4.5% - 8%. The prevalence approaches 40% in studies carried out on small groups of chronic liver disease patients, blood donors, intravenous drug abusers and also healthcare professionals. According to a survey undertaken by the Pakistan Medical Research Council in 2007-2008, the combined prevalence of hepatitis B and hepatitis C in the Pakistani population was 7.3%, i.e., 2.5% and 4.8% of hepatitis B and hepatitis C respectively. This amounts to about 13 million chronic carriers of hepatitis B and C[18]. The major risk factors that account for the transmission of HCV infection globally are injection drug use, blood transfusions from unscreened donors, unsafe therapeutic injections and certain other hospital related procedures.

In cirrhosis, which is a late stage of hepatic fibrosis and is generally irreversible in its advanced stages, there is distortion of the liver parenchyma and regenerative nodules formation. Liver transplantation is the only treatment option for such cases. Alcohol intake, infection, medications, bleeding, constipation, dehydration and obesity have been identified as major risk factors that predispose a cirrhotic patient to decompensation[19].

Whenever the pressure gradient between the hepatic and portal veins exceeds 12 mm Hg as a result of portal venous outflow obstruction, there is resultant formation of varices so as to decompress the portal vein. If the pressure

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in the portal veins is less than 12 mm Hg, there is no varices formation and, therefore, no bleeding. Varices can form in almost any part of the gastrointestinal tract extending from the esophagus to the rectum, but the commonest sites are the distal end of the esophagus, stomach and the rectum. Gastric fundal varices are more prone to bleeding.

The major complications of cirrhosis include the development of hepatic encephalopathy, hepatorenal and hepatopulmonary syndromes, spontaneous bacterial peritonitis, variceal hemorrhage and hepatocellular carcinoma. In the era prior to the use of current treatment options for bleeding varices, there was a 15- 20% mortality associated with a single episode of bleeding varices[20,21,22,23]. Mortality still remains high despite the use of modern therapeutic techniques for controlling variceal bleeding. If an early diagnosis of variceal bleed is made before the first bleeding episode, then there is a significant reduction in the risk of variceal hemorrhage, from 50% to 15% for large esophageal varices, as reported by Gludd LL et al[24].

Studies have shown that primary prophylaxis with either a nonselective beta blocker or the use of endoscopic variceal band ligation reduces the risk of first variceal hemorrhage and decreases the risk of bleeding-related mortality.

Typically, screening is done with an upper endoscopy, though wireless video capsule endoscopy has also been used. In addition, a platelet count to splenic size ratio (expressed as a standard deviation score) and other factors like splenic size, platelet count and albumin levels have been used as clinical predictors of varices in children. Screening with upper GI endoscopy is carried out 2-3 yearly in patients who have compensated cirrhosis(patients in whom no varices have been formed) and yearly for patients in whom decompensation has occurred.

METHODOLOGY

This Cross- sectional Study was conducted by the Department of Medicine, Mayo Hospital, Lahore from 22nd August, 2014 to 21st February, 2015. A sample size of 220 patients with liver cirrhosis was taken and was calculated using expected prevalence of esophageal varices in cirrhotic patients as 60% and expected sensitivity of 68%, specificity of 89% at cut off point of AST / ALT ≥ 1 for the diagnosis of esophageal varices[10]. Non- probability purposive sampling technique was applied.

The presence of liver cirrhosis was determined by deranged liver function tests, increased prothrombin time, portal vein diameter >15 mm, splenomegaly >14cm and the presence of ascites. Esophageal varices were seen as dilated sub-mucosal veins on endoscopy. AST/ALT Ratio was taken positive if this ratio was ≥ 1. Predictive accuracy of True positive was labeled if AST : ALT ≥ 1 with positive findings on endoscopy, True negative if AST : ALT < 1 and negative findings on endoscopy, False positive if AST: ALT ≥ 1 and negative findings on endoscopy and False negative was labeled if AST : ALT < 1 with positive findings on endoscopy.

Patients of either sex between the age group of 16-60 years, and diagnosed cases of liver cirrhosis based on Child Turcotte Pugh Class A, B or C were included in the study.

Patients who were clinically unfit for endoscopy, those with active variceal bleeding at the time of admission, or history of surgery for portal hypertension, endoscopic variceal band ligation or sclerotherapy, patients with tran-sjugular intrahepatic portosystemic shunt placement, or taking medication for the primary prophylaxis of bleeding varices and those with hepatic encephalopathy were excluded from the study. Also patients with gallbladder stones diagnosed on ultrasonography of the abdomen, those with renal disease (serum creatinine >1.2gm/dl) or undergoing hemodialysis, and those with thrombocytopenia (platelet count< 150,000/mm^3) were also excluded from the study.

After getting approval from the hospital Ethical Committee and taking informed consent from the patients, 220 patients with documented liver cirrhosis were enrolled in the study. Data was taken from all the four medical units of Mayo hospital, Lahore. After noting their basic demographic features like age, gender, a complete clinical examination was done. Blood samples were taken and were sent to the main hospital laboratory for analysis of AST and ALT. Then endoscopic evaluation of these patients was carried out by a Consultant Gastroenterologist to look for the presence or absence of esophageal varices. AST /ALT was compared with endoscopic findings to see the required diagnostic accuracy.

All the collected data was entered and analyzed by statistical software SPSS version 20.0. Qualitative variables like gender, Child Pugh class were presented in form of frequencies and percentages. Quantitative variables like age, AST and ALT were presented as Mean ± S.D. For predictive accuracy, sensitivity, specificity, predictive values for positive and negative were calculated using 2×2 table.

RESULTS

Out of a total of 220 patients, 133 (60.5%) were males and 87 (39.5%) were females. Mean age of the patients was 9.23 + 7.7 years. Duration of Chronic Liver Disease ranged from 2 to 9 years with mean 5.38+ 2.034 years. AST/ALT Ratio >1 was seen in 168 (76.4%) patients, varices were found on Endoscopy in 136 (61.8%) patients and no varices in 84 (38.2%) patients. 206 (93.6%) patients were above the age of 40 years while 14(6.4%) patients were less than 40 years of age. Duration of CLD was more than 5 years in 98(44.5%) patients. Sensitivity was calculated to be 97.05%, Specificity 57.1%, Positive predictive value was calculated as 78.5%, while a Negative predictive value of 92.3%, false positive rate of 42.8% and false negative rate of 7.6% were recorded.

Cross tabulation between AST/ALT Ratio >1 & Varices on Endoscopy

AST/ALT Ratio >1	Varices on Endoscopy		Total
	Yes	No	
Yes	a=132	b=36	168
No	c=4	d=48	52
Total	136	84	220

Demographic characteristics of patients (n= 220)

Gender	
Male	133 (60.5%)
Female	87 (39.5%)
Age (years)	
Minimum	17
Maximum	60
Mean±SD	49.23 ± 7.7
Age Group distribution	
>40 years	206 (93.6%)
<40 years	14(6.4%)
Duration of CLD (years):	
Minimum	2
Maximum	9
Mean±SD	5.38±2.034
Frequency based on duration of disease:	
>5 years	98(44.5%)
<5 years	122 (55.5%)

Diagnostic yields of AST/ALT >1 taking endoscopy as gold standard

Outcome	**Formula x 100**	
Sensitivity	$\frac{a}{a+c}$	97.05%
Specificity	$\frac{d}{b+d}$	57.1%
Positive predictive value	$\frac{a}{a+b}$	78.5%
Negative predictive value	$\frac{d}{c+d}$	92.3%
False positive rate	$\frac{b}{b+d}$	42.8%
False negative rate	$\frac{c}{c+d}$	7.6%

DISCUSSION

With the advancement in endoscopic and radiological techniques combined with new pharmacological therapies, there has been a significant reduction in the episodes of variceal bleeding. Even then, a mortality rate of 15- 20% from bleeding esophageal varices has an important clinical significance[20,21,22,23]. Primary prophylaxis of esophageal varices before the first bleed has shown a significant reduction in the risk of hemorrhage from 50% to 15% in cases of large esophageal varices[24]. Therefore, current guidelines recommend screening for varices for all cirrhotic patients at the time of diagnosis, then follow-up every 2-3 years for patients without varices, 1-2 yearly for patients with small varices in order to assess any enlargement of varices and need for prophylactic treatment[25].

Upper GI Endoscopy still remains the gold standard for diagnosing variceal hemorrhage. However, several studies have been carried out to assess the usefulness of AST/ALT ratio as a non-invasive, yet simple, quick, reproducible and cost- effective tool to predict esophageal varices. These studies have shown marked variation the sensitivity and specificity of AST/ALT ratio owing primarily to the various etiologies of cirrhosis and also because of different cut off values for AST/ALT.

A study carried out by Treeprasertsuk S et al, showed an AST/ALT ratio > 1.12 to be significantly associated with the presence of varices at initial endoscopy (Odds Ratio = 3.9, p= 0.02, 95% CI 1.3–11.8). This cutoff gave a sensitivity of 47.8%, specificity of 87%, PPV 42.3%, and NPV 89.2%, and an AUROC of 0.69[9]

In another study, Castéra L et al, used a different cut-off of ≥1.0 and reported a sensitivity of 68%, specificity of 89%, PPV 77%, and NPV 83%, with an AUROC 0.83 (0.72–0.94) for predicting the presence of esophageal varices[10].

In this study, male sex (60.5%), age > 40 years (93.6%) were identified as major predictors of esophageal varices. Mean age of 49.23 years in this study is similar to other reported studies. Usually in the ongoing pattern of disease, Pakistani patients develop cirrhosis in fifth or sixth decade of their life.

CONCLUSION

AST/ALT Ratio > 1 is sensitive (97.05%) but not specific (57.1%). Limitations of this study include a smaller sample size from a tertiary care hospital which is not representative of the entire population. So the results need to be validated in a larger cohort of patients. Further studies need to be carried out in this regard keeping AST/ALT >1 as a simple, non- invasive tool for the diagnosis of variceal bleeding keeping endoscopy as gold standard.

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