Objective
To evaluate Serum albumin as a marker of Esophageal Varices (EV) in chronic liver disease (CLD) due to hepatitis B and C.

Method
In this prospective, cross-sectional study, patients with CLD due to HBV and HCV were assessed as per Child-Pugh class. All patients had full blood count, HBsAg, Anti-HCV antibodies by ELISA, abdominal ultrasound and Esophagogastrroduodenoscopy (EGD). Patients were divided into Group A (serum albumin <3.5 gm %) and Group B (normal serum albumin).

Results
Ninety-seven male (49.2%) and 100 female patients (50.8%) with age range of 15 to 80 years were evaluated. Mean Serum albumin was 3.8 gm%, (range 2.4-4.9). EV were present in 63 patients (32%) and absent in 134 patients (68%). Group A had 57 patients (28.9% of the total) with 35 patients having EV. Group B had 140 patients (71.1% of the total) with 28 patients having EV. Sensitivity of hypoalbuminemia as a marker of EV was 53.2% and specificity 91%, positive predictive value 73.3% and negative predictive value 80.8% and odds ratio was 11.57. Spearman's rank correlation showed a significant negative correlation of '-0.494' between serum albumin and EV. ROC curve showed 70.7% area under the curve for albuminemia of <3.5 gm%.

Conclusions

Keywords
Chronic liver disease, hypoalbuminemia, esophageal varices.

Abbreviations
HBV=Hepatitis B virus, HCV=Hepatitis C virus, HBsAg=Hepatitis B surface Antigen, Anti-HCV=Anti-Hepatitis C virus antibodies, EV=esophageal varices, EGD=Esophagogastrroduodenoscopy, PV=portal vein, ROC=Receiver Operating Characteristic

INTRODUCTION
HBV and HCV are the most important causes of CLD leading to cirrhosis. Patients with cirrhosis develop EV due to portal hypertension and although 90% of patients with cirrhosis develop varices, only 30% of them bleed and 30 – 50% die of the first episode. Two thirds of the survivors will rebleed within six months if not treated with prophylactic -blockers or endoscopic therapy. Those receiving such therapy are less likely to bleed and that is why screening such patients for EV is recommended. Periodic endoscopy can be expensive. Non-endoscopic surrogate markers directly or indirectly linked to portal hypertension have, therefore, been sought to identify patients at high risk of having varices. Hepatic venous pressure gradient is useful, but invasive and not widely available. Portal hypertension (portal pressure >12 mm Hg or >5 mm Hg gradient between the wedged hepatic venous pressure and the free hepatic venous pressure) has been shown in animal studies to induce hypoalbuminemia. Conversely, serum albumin is increased by 20% when portal pressure is reduced after Transjugular Intrahepatic Portosystemic Shunt Procedure suggesting a link between portal hypertension and hypoalbuminemia. Aim of this study was to evaluate relationship of serum albumin and EV in CLD.

METHOD
This prospective, cross-sectional study was carried out at Al-Ibrahimi Hospital and Khyber Teaching Hospital, Peshawar, from October 2006 to December 2007. Patients with CLD due to HBV/HCV (HBs Ag positive, Anti-HCV antibodies positive by ELISA) were assessed as per Child-
Sixty three (32%) patients had EV [F1 in 45 (22.8%), F2 in 12 (6.1%) and F3 in 06 (3%) patients] while 134 patients (68%) did not have EV. Mean serum albumin level was 3.8 gm%, (range, 2.4-4.9). Group A (serum albumin <3.5 gm%) had 57 patients (28.9%), with 35 patients (17.8% of the total, 61.4% within the group) having EV, while group B had 140 patients (71.1%) with 28 patients (14.2% of the total, 20% within the group) having EV. Hypoalbuminemia was seen only in three (1.5%) patients below the age of 30 years and in 54 (27.4%) patients above 30 years age (Table 3).

Table 3. Serum albumin and Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Serum Albumin &lt;3.5 gm%</th>
<th>Serum Albumin &gt;=3.5 gm%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>3 (1.5%)</td>
<td>50 (25.4%)</td>
<td>53 (27.9%)</td>
</tr>
<tr>
<td>&gt;= 30</td>
<td>54 (27.4%)</td>
<td>90 (45.7%)</td>
<td>144 (73.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>57 (28.9%)</td>
<td>140 (71.1%)</td>
<td>197 (100%)</td>
</tr>
</tbody>
</table>

Sensitivity of hypoalbuminemia as a predictor of EV was 53.2% and specificity was 91%. PPV was 73.3% and NPV was 80.8%. The odds ratio was ‘11.57’. Spearman’s rank correlation showed a significant negative correlation of ‘-0.494’ between serum albumin and presence of esophageal varices i.e. falling serum albumin associated with rising frequency of EV.

RESULTS

One hundred and ninety-seven patients [97 male (49.2%) and 100 female (50.8%)] were evaluated. Mean age was 41.57 years (range, 15-80). One hundred and fifty five patients (78.7%) were Anti-HCV positive, 38 (19.3%) were HBsAg positive and four (2%) were coinfected with HCV and HBV. Child-Pugh score is shown in Table 2.

Table 2. Child-Pugh Class

<table>
<thead>
<tr>
<th>Child - Pugh Class</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>138 (70.1%)</td>
</tr>
<tr>
<td>B</td>
<td>49 (24.9%)</td>
</tr>
<tr>
<td>C</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>197 (100.0%)</td>
</tr>
</tbody>
</table>

All patients had abdominal ultrasound and EGD the same day. Hypoalbuminemia was defined as serum albumin level <3.5 gm%. Patients with hypoalbuminemia were placed in group A and those with serum albumin level >3.5 gm% were placed in group B. Classification of EV was based on Japanese Research Society for Portal Hypertension. Sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV), odds ratio and correlations of serum albumin with presence or absence of EV (using Spearman’s rank correlation) were calculated to predict EV. SPSS 14 was used for data analysis.
ROC showed 70.7% area under the curve (Fig. 1) for albuminemia of <3.5 gm%. The area under curve increased to 94.1% for albuminemia of <=2.5 gm%.

**DISCUSSION**

Albumin (50%-60% of total plasma protein), globulin, and fibrinogen make up the major share of plasma proteins with 24%-56% increased risk of death per 2.5 g% fall in serum albumin. Child-Pugh score (serum albumin being integral part of the score) predicts advanced liver disease. Liver produces albumin at a rate of 130–200 mg/kg/day. Hypoalbuminemia in cirrhosis is multifactorial and may be due to reduced production (liver parenchyma replaced by fibrous tissue), increased removal by reticuloendothelial system (spleen) or increased loss through gut (portal gastropathy/enteropathy): all related to portal hypertension. Hypoalbuminemia with associated ultrasonographic features e.g. gall-bladder wall thickness and right liver lobe diameter have been cited as non-endoscopic predictors of esophageal varices. Similarly, Serum Ascitic Albumin Gradient (the difference between the serum and ascitic albumin concentration) i.e. SAAG, is thought to be an indirect marker of portal hypertension, with a high gradient (>1.1 g/dL) indicating portal hypertension and presence of EV. Torres E et al reported a SAAG value of >or=1.435±0.015 g/dl as an accurate indicator of the presence of EV with PPV of 87.5% and NPV of 66.7%.

We used albuminemia of <3.5 gm% while Schepis et al and Sarwar et al used level of <2.95 gm% to predict the presence of EV. Higher frequency of hypoalbuminemia above age 30 (27.4%) suggests worsening of albumin levels as the disease advances with growing age. Bressler et al found albuminemia of <4gm% as an independent risk factor for EV with odd ratio of 6.02. It was a retrospective analysis including 235 patients with CLD of diverse etiologies. Our odds ratio was 11.57 and the difference could be explained by <3.5 gm% albumin level we used and our study population with uniform etiology of the infective hepatitis. Zein et al in a study of 183 patients with primary sclerosing cholangitis, found 66% sensitivity, 80% specificity, 53.4% PPV, 87.2% NPV and odd ratio of 7.8 for albuminemia of <3.5 gm%; almost similar to our results. The minor differences in figures could be explained on the basis of difference in etiology of the study population.

Specificity of 91% and PPV of 73.3% suggests that hypoalbuminemia is a good indicator of EV. Negative correlation of -0.494 indicates that falling plasma proteins with 24%-56% increased risk of serum albumin level in CLD is associated with rising frequency of EV. The same is reconfirmed by the ROC curve: area under curve increased from 76.8% for albuminemia of <3.5 gm% to 94.1% for albuminemia of <2.5 gm%. However, low sensitivity of hypoalbuminemia (53.2%) and NPV of 80.8% indicates that absence of hypoalbuminemia does not rule out EV.

**CONCLUSION**

Hypoalbuminemia is a good non-endoscopic marker for the presence of esophageal varices; however the absence of hypoalbuminemia does not rule out the presence of esophageal varices as the NPV is <100% i.e. 80.8%, hence it can not be used as a single factor for the purpose.

**REFERENCES**

Hypoalbuminemia: a marker of esophageal varices in CLD


