Esophageal varices; non-endoscopic prediction of presence

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ABSTRACT…..Bleeding from esophageal varices is associated with high morbidity and mortality. It is currently recommended that all patients with liver cirrhosis undergo upper gastrointestinal endoscopy to identify those who have esophageal varices. This approach leads to unnecessary endoscopies. There is need to evaluate clinical, laboratory and imaging parameters that may predict the presence of esophageal varices and help select patients for endoscopy. Objective: Identify hematological, biochemical and ultrasonographic predictors of esophageal varices in patients of cirrhosis. Study design: Cross sectional Descriptive study. Setting: Department of General Medicine and Gastroenterology unit 1, Services Hospital, Lahore. Duration of study: 6 months (April 01, 2007 – September 30, 2007). Sample size: Study was done on One hundred patients who had established cirrhosis with oesophageal varices. Results: Majority (77%) were male who had evidence of esophageal varices. Hematemesis was the presenting complaint in 75% of patients and majority (83%) had clinically palpable spleen. Esophageal varices were present in 75% of patients who had platelet count <100,000. In patients who had portal vein diameter of >20mm 41% had evidence of esophageal varices. Splenic measurement of >13cm was associated with maximum number of cases of esophageal varices i.e 82%. Conclusion: It is concluded from the study that male gender, clinically palpable spleen, low platelet count, portal vein diameter and splenic measurement can be used as non invasive parameters to predict esophageal varices reducing the need of unnecessary endoscopies.

Key words: Esophageal varices, cirrhosis, non endoscopic predictors.

INTRODUCTION
Cirrhosis is defined as the presence of fibrous septa that diffusely involve the liver and subdivide the parenchyma into nodules. Cirrhosis results from the necrosis of liver cells followed by fibrosis and nodule formation. The liver architecture is diffusely abnormal and this interferes with liver blood flow and function. The derangement produces the clinical features of portal hypertension and impaired liver cell functions.

Following are the main complications: portal hypertension, ascites, renal failure, encephalopathy, hepatocellular carcinoma, coagulopathy. Portal hypertension is the consequence of an increase in splanchnic blood flow secondary to vasodilatation and increased resistance to the passage of blood through the cirrhotic liver.

Development of esophageal varices is one of the major complications of portal hypertension. Its prevalence varies from 20-30% in patients with cirrhosis. After varices have developed one third of all patients die of bleeding gastro- esophageal varices. One third cirrhotic patients develop esophageal varices during their lifetime. About 30% - 40% of cirrhotic patients develop intestinal bleeding as a complication of esophageal varices.

Despite significant improvements in the early diagnosis and treatment of esophagogastric variceal hemorrhage, the mortality rate of first variceal hemorrhage remains high (20%-35%). The reported mortality from first episode of variceal bleeding in western studies ranges from 17% to 57%as compared to 5-10% mortality reported in our population.

In 1996, the American association for the study of liver disease stated that cirrhotic patients should be screened for the presence of oesophageal varices when portal hypertension is diagnosed. Recently The Baveno 3 consensus conference on portal hypertension recommended that all cirrhotic patients...
should be screened by endoscopy for the presence of esophageal varices when liver cirrhosis is diagnosed.

Endoscopy has two limitations.
1. Endoscopy is an invasive procedure and
2. The cost effectiveness of this approach is also questionable as only 9-36% patients with cirrhosis are found to have varices on screening endoscopy. It may be more cost effective to screen patients at high risk for the presence of varices so as to reduce the increasing burden and procedure cost of endoscopy units.

There are factors that predict risk of first variceal hemorrhage. Certain biochemical, clinical and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the risk of bleeding from varices. Identification of non-invasive predictors of esophageal varices will enable us to carry out upper gastrointestinal (GI) endoscopy in selected patients thus avoiding unnecessary intervention and at the same time not missing the patients at risk of bleeding.

The study objective was to identify hematological, biochemical and ultrasonographic parameters associated with presence of esophageal varices in patients with cirrhosis without past history of upper gastrointestinal bleeding so that burden on endoscopic units is minimized and cost is reduced.

**OBJECTIVE**
The objective of the study is to identify hematological, biochemical and ultrasonographic predictors of oesophageal varices in patients of cirrhosis.

**Operational definition:**
**Cirrhosis:** Cases having pallor, spider nevi, jaundice, pedal, oedema, ascites, gynecomastia and splenomegaly on physical examination.

**Esophageal varices:** Endoscopy showing hyperaemic, red and engorged vessels in oesophagus.

**Esophageal varices predictors:** I will take hematological parameters as platelets below 150,000, bilirubin above 1mg/dl, asparate aminotransaminase above 40, alanine aminotransferase above 35, prothrombin time 4 sec above normal and serum albumin below 3.5mg/dl. On ultrasound, portal vein diameter above 11 mm will be considered as predictors of oesophageal varices.

**Hypothesis:**
Non endoscopic predictors can adequately help in diagnosis of oesophageal varices.

**MATERIAL AND METHODS**
It was a cross-sectional descriptive study conducted in Department of General Medicine and Gastroenterology unit 1, services hospital, Lahore. Study was completed in 6 months (April 01, 2007 – September 30, 2007). Study was done on 100 patients who have established cirrhosis with oesophageal varices. Purposive non-probability sampling technique was used. Inclusion criteria include patients of both sexes above 18 years and patients having established cirrhosis without past upper oesophageal varices documented on gastroscopy.

Patients who were not stable, had previously undergone sclerosis or band ligation of varices, taking medication for primary prophylaxis of variceal bleeding, active alcohol users and those who had comorbidity, such as chronic renal failure, malignancy or congestive cardiac failure were excluded from the study.

All patients with liver cirrhosis and esophageal varices due to any cause were considered. Careful history about present illness, severity and duration of symptoms, any past history relevant to cirrhosis, and signs like pallor, jaundice, clubbing, palmar erythema...
gynecomastia, spider nevi, ascite, pedal dema and splenomegaly was taken and relevant routine laboratory informations in form of haemoglobin percentage, TLC, platelets count, serum albumin, prothrombin time and portal vein diameter on ultrasound was done. Then gastroscopy of those patients was done to see whether esophageal varices were present or not. All the information was recorded in the proforma designed for purpose of study.

Data analysis was done on computer; SPSS 10 was used for analysis. Qualitative parameters like recovery was analyzed by chi square test, and quantitative terms like duration of stay, mortality will be measured by T test as needed other test will be applied.

RESULTS

Majority were of male patients (83) out of which 64(77%) had esophageal varices and only 17 patients were female and 05(29%) had evidence of esophageal varices.

69 patients were presented with combination of symptoms and 62% of which showed evidence of esophageal varices. The remaining 31 patients presented with symptoms like hematemesis(8), melena(3), abdominal distension(6), yellow discolourtion of eyes(11) and oedema(3).

29 patients had combination of clinical signs out of which 11(38%) had esophageal varices. 27 presented with ascites out of which 12(44%) had esophageal varices. 14 presented with jaundice, 12 with splenomegaly alone, 11 with spider naevi and 07 with palmer erythema.

46 patients had hemoglobin between 9-10.9g/dl, 41 had between 7-8.9g/dl and 13 had hemoglobin of less than 7g/dl out of which 06(46%) had esophageal varices.

More than 150,000 out of which 06(20%) had esophageal varices. 12 patients had count less than 100,000 out of which significant number i.e 09(75%) had esophageal varices. 58% had platelet count between 100,000-150,000 out of which 29(50%) had evidence of esophageal varices. 30 patients had platelets.

Majority i.e 78 patients had bilirubin of less than 2mg/dl, 16 had between 2-3mg/dl and only 06 had more than 3mg/dl.

83% had ALT between 40-100 out of which only 05(06%) had esophageal varices.

Major number of patients i.e 80 had AST between 40-100IU and out of which negligible number 04 had esophageal varices evidence.

Majority of patients i.e 57 had prothrombin time between 4-6 seconds above normal out of which 06 had esophageal varices, 29 had between 1-3 seconds in which 04 developed varices and 14 had more than 6 seconds and in this group only 01 had esophageal varice.

76% had albumin more than 3.5mg/dl out of which 03 had esophageal varices, 14% had between 2.8-3.5mg/dl out of which 01 had developed varices and 10% had less than 2.8mg/dl.

29 patients had portal vein diameter of more than 20mm and out of them 12(41%) had evidence of esophageal varices. 34 had diameter between 10-20mm out of which 08 developed varices and 37 had less than 10mm diameter of portal vein.

Majority of patients i.e 46% had splenic length of more than 13cm and out of this significant number i.e 38(82%) turned out to have esophageal varices. 26 had splenic length between 11-13cm out of which 12 had esophageal varices and 28 had less than 11cm out of which only 07 had esophageal varices.
### Table-I. Association of esophageal varices by sex distribution

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>Femal</td>
<td>17</td>
<td>05</td>
</tr>
</tbody>
</table>

Chi-Square Test = 15.0  
P-Value = 0.00 (Significant)

### Table-II. Distribution of cases by presenting complaints

<table>
<thead>
<tr>
<th>Presenting Complaint</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematemesis</td>
<td>08</td>
<td>06</td>
</tr>
<tr>
<td>Malena</td>
<td>03</td>
<td>02</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>06</td>
<td>04</td>
</tr>
<tr>
<td>Yellow discoulration of eyes</td>
<td>11</td>
<td>02</td>
</tr>
<tr>
<td>Oedema</td>
<td>03</td>
<td>Nil</td>
</tr>
<tr>
<td>Combination of symptoms</td>
<td>69</td>
<td>43</td>
</tr>
</tbody>
</table>

Chi-Square Test = 12.93  
P-Value = 0.024 (Significant)

### Table-III. Prediction of esophageal varices by physical sign on examination

<table>
<thead>
<tr>
<th>Physical sign</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>14</td>
<td>04</td>
</tr>
<tr>
<td>Palmer erythema</td>
<td>07</td>
<td>02</td>
</tr>
<tr>
<td>Spider naevi</td>
<td>11</td>
<td>02</td>
</tr>
<tr>
<td>Ascites</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Combination of signs</td>
<td>29</td>
<td>11</td>
</tr>
</tbody>
</table>

Chi-Square Test = 12.997, P-Value = 0.023 (Significant)

### Table-IV. Prediction of esophageal varices by haemoglobin

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 g/dl</td>
<td>13</td>
<td>06</td>
</tr>
<tr>
<td>7 - 8.9 g/dl</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>9 - 10.9 g/dl</td>
<td>46</td>
<td>09</td>
</tr>
</tbody>
</table>

Chi-Square Test = 3.74  
P-Value = 0.153 (Significant)

### Table-V. Prediction of esophageal varices by platelet count

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Number of cases</th>
<th>Esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100,000</td>
<td>12</td>
<td>09</td>
</tr>
<tr>
<td>100,000 - 150,000</td>
<td>58</td>
<td>29</td>
</tr>
<tr>
<td>&gt; 150,000</td>
<td>30</td>
<td>06</td>
</tr>
</tbody>
</table>

Chi-Square Test = 12.54  
P-Value = 0.002 (Significant)

### Table-VI. Prediction of esophageal varices by bilirubin

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mg/dl</td>
<td>78</td>
<td>09</td>
</tr>
<tr>
<td>2-3 mg/dl</td>
<td>16</td>
<td>02</td>
</tr>
<tr>
<td>&gt;3 mg/dl</td>
<td>06</td>
<td>01</td>
</tr>
</tbody>
</table>

Chi-Square Test = 0.143  
P-Value = 0.931 (Insignificant)

### Table-VII. Prediction of esophageal varices by alanine aminotransferase (ALT)

<table>
<thead>
<tr>
<th>ALT</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 iu/l</td>
<td>08</td>
<td>Nil</td>
</tr>
<tr>
<td>40-100 iu/l</td>
<td>83</td>
<td>05</td>
</tr>
<tr>
<td>&gt;100 iu/l</td>
<td>09</td>
<td>01</td>
</tr>
</tbody>
</table>

Chi-Square Test = 0.928, P-Value = 0.629 (Insignificant)

### Table-VIII. Prediction of esophageal varices by aspartate transaminase (AST)

<table>
<thead>
<tr>
<th>AST</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 iu/l</td>
<td>12</td>
<td>Nil</td>
</tr>
<tr>
<td>40-100 iu/l</td>
<td>80</td>
<td>04</td>
</tr>
<tr>
<td>&gt;100 iu/l</td>
<td>08</td>
<td>01</td>
</tr>
</tbody>
</table>

Chi-Square Test = 1.579, P-Value = 0.454 (Insignificant)

### Table-IX. Prediction of esophageal varices by prothrombin time

<table>
<thead>
<tr>
<th>Prothrombin time</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 seconds</td>
<td>29</td>
<td>04</td>
</tr>
<tr>
<td>4-6 seconds</td>
<td>57</td>
<td>06</td>
</tr>
<tr>
<td>&gt;6 seconds</td>
<td>14</td>
<td>01</td>
</tr>
</tbody>
</table>

Chi-Square Test = 0.457, P-Value = 0.796 (Insignificant)

### Table-X. Prediction of esophageal varices by Serum albumin

<table>
<thead>
<tr>
<th>Serum albumin</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3.5 mg/dl</td>
<td>76</td>
<td>03</td>
</tr>
<tr>
<td>2.8 - 3.5 mg/dl</td>
<td>14</td>
<td>01</td>
</tr>
<tr>
<td>&lt;2.8 mg/dl</td>
<td>10</td>
<td>01</td>
</tr>
</tbody>
</table>

Chi-Square Test = 0.839  
P-Value = 0.657 (Insignificant)

### Table-XI. Prediction of esophageal varices by portal vein diameter on ultrasonography

<table>
<thead>
<tr>
<th>Portal vein diameter</th>
<th>Number of cases</th>
<th>Cases of esophageal varices</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mm</td>
<td>37</td>
<td>03</td>
</tr>
<tr>
<td>10 - 20 mm</td>
<td>34</td>
<td>08</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>29</td>
<td>12</td>
</tr>
</tbody>
</table>

Chi-Square Test = 10.170, P-Value = 0.006 (Significant)
DISCUSSION

Development of esophageal varices and gastrointestinal bleeding represents a serious consequence in patients with cirrhosis of liver and portal hypertension. At the time of diagnosis of liver cirrhosis, esophageal varices are present in about 40% of patients with compensated disease and in 60% of those with decompensated disease and ascites. In patients with liver cirrhosis who do not have detectable esophageal varices, the later appear at a rate of nearly 5% per year. Also the size of varices tends to increase with the passage of time. It has been estimated that among those with small esophageal varices nearly 12% progress to large varices annually.

The annual incidence of first variceal bleeding has been estimated to be around 4% in patients with cirrhosis of the liver who have not bled previously. It has been shown that the risk of esophageal bleeding is related to the size of esophageal varices, with large esophageal varices being at greater risk. Thus, annual incidence of gastrointestinal bleeding is only 1-2% in patients without varices, 5% in those with small esophageal varices and 15-20% in patients with large esophageal varices.

Mortality rate of an episode esophageal bleeding is around 20-25%. It is currently recommended that patients with liver cirrhosis should undergo a screening endoscopy to look for the presence of large esophageal varices and if present be treated.

These recommendations imply a large workload on endoscopic units and a significant cost burden on patients with liver cirrhosis. As the prevalence of large esophageal varices is only 9-36% in patients with cirrhosis who have not bled, a large number of invasive endoscopic procedures turn out to be negative and therefore are not advisable. Thus, there is a need for non invasive means to diagnose or predict the presence or absence of large esophageal varices. Availability of such methods may help limit the number of endoscopic procedures performed for detection of large esophageal varices.

Several studies have evaluated possible non invasive markers of large esophageal varices in patients with cirrhosis and have found platelet count, splenomegaly, advanced Child status, serum albumin, high portal vein diameter at ultrasonography to be useful for this purpose.

In my study we used clinical, biochemical and ultrasonographic parameters to predict the presence of esophageal varices before they bleed so that morbidity and mortality due to esophageal variceal bleed could be reduced by early intervention and treatment.

In my study majority of patients were male in whom esophageal varices were diagnosed this was also supported in an article published in J Gastroenterol hepatol.

In this study maximum number of patients was diagnosed to have esophageal varices who presented with hematemesis followed by malena and abdominal distension.

In this study it was found that ascites and palpable spleen were the physical signs which predict the presence of esophageal varices de Franchis R et al which suggest that patients who had ascites and splenomegaly would have an increased risk of having
large esophageal varices.

Anemia found to be an important non invasive prediction of esophageal varices in this study which was also noted in the article published in J Gastroenterol Hepatol\textsuperscript{27}.

In my study it was noted that thrombocytopenia was an important non endoscopic predictor of esophageal varices which was also seen in studies conducted by Goh S et al\textsuperscript{30} and Sharara Al et al\textsuperscript{31}.

In this study it was seen that bilirubin, alanine aminotransferase and aspartate transaminase did not predict esophageal varices with insignificant P-value. Prothrombin time was also a poor predictor of presence of esophageal varices with insignificant P-value but it was found in the study by Schepis F et al\textsuperscript{32} that compensated cirrhotic patients should be screened by upper gastrointestinal endoscopy when prothrombin activity less than 70%.

In this study it was found that albumin did not predict the presence of esophageal varices which was in contrast to study conducted by Alempijevic T et al\textsuperscript{33} who concluded that right liver lobe diameter/albumin ratio is a non invasive parameter which provides an accurate information pertinent to the determination of esophageal varices presence and there grading in patients with liver cirrhosis.

In my study it was concluded that portal vein diameter of >20mm was a good predictor of esophageal varices with significant P-value. This was also seen by Prithatini J et al\textsuperscript{34} in his study, that portal vein diameter can be used as non invasive parameter to detect esophageal varices in cirrhotic patients.

In this study it was seen that splenic measurement of >13cm on ultrasonography can predict the presence of esophageal varices which was also seen by Sethar GH et al\textsuperscript{35} and Giannini E et al\textsuperscript{36} that platelet count/splenic diameter ratio is the parameter which is independently associated with the presence of esophageal varices, and its negative predictive value is reproducible.

**CONCLUSION**

It is concluded from the study that male gender, clinically palpable spleen, low platelet count, portal vein diameter and splenic measurement can be used as non invasive parameters to detect esophageal varices in cirrhotic patients.

These predictors can be used to calculate a predictor function, which showed moderate efficacy in predicting the esophageal varices. This predictor function needs further study in one or more prospective cohorts of patients with liver cirrhosis to validate its efficacy. If its efficacy is confirmed, it may permit institution of prophylactic measures like beta adrenergic antagonists for preventing primary variceal bleeding in patients with liver cirrhosis, without the need for costly and invasive investigations like gastrointestinal endoscopy.

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ESOPHAGEAL VARICES


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