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Non-invasive parameters for the detection of variceal bleed in patients of liver cirrhosis, an experience of a tertiary care hospital in Pakistan

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ABSTRACT

Objective: Cirrhotic patients commonly undergo screening endoscopy for the existence of esophageal varices. The use of this invasive procedure which is expensive, poorly tolerable and generally not acceptable for the patients is increasing due to increasing number of patients with chronic liver disease and their enriched survival. In this study, our aim is to identify clinical, biochemical, and ultrasonography parameters which might non-invasively predict the presence of esophageal varices and risk of bleeding in patients with liver cirrhosis. **Material and Methods:** Total 150 Patients of chronic liver disease admitted in ward-5, JPMC (Sep 2011-Feb 2012) with a complaint of hematemesis or melena were included in the study. Platelet counts of 75,000 to 150,000/ μ L was defined as grade I thrombocytopenia, 50,000 to <75,000/ μ L as grade II, 25,000 to <50,000/ μ L as grade III and below 25,000/ μ L as grade IV. The normal range for the INR is 0.8–1.2. Portal vein size of 1.2 cm or above was taken as dilated. Spleen of >13 cm was considered as enlarged in our study. **Results:** Out of 72 patients of variceal bleed 69 (46%) were males and 81 (54%) were females. Thrombocytopenia was present in 64 (88%) patients with mean platelet count of 85.86/ μ L (\pm 69.79). Deranged coagulation profile was present in 56 (77%) cases with mean INR of 1.63 (\pm 0.5). Portal vein diameter (PVD) of >1.2 cm was found in 46 (63.8%) of patients with mean PVD of 1.22 (\pm 0.3023) and splenic size of >13 cm was reported in 54 (75%) cases with mean splenic diameter of 14.5 cm (\pm 2.39). **Conclusion:** Thrombocytopenia, deranged coagulation profile, large splenic size, and dilated portal vein strongly predict the risk of variceal bleeding.

Key words: Variceal Bleed, Precipitating factors, Cirrhosis of the liver, Outcome

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INTRODUCTION

In underdeveloped countries, liver cirrhosis is a major cause of morbidity and mortality owing to unawareness of the patients, inadequate facilities and financial implications associated with the disease. In western world chronic alcohol consumption account for majority of the cases but in our part of the world infections by hepatotropic viruses (Hepatitis B & C) are most likely responsible. Liver cirrhosis follows an indolent course and eventually patients succumb to the complications of liver decompensation characterized by variceal bleeding from portal hypertension, ascites, hepatorenal syndrome,

hepatic encephalopathy and spontaneous bacterial peritonitis.¹ Esophageal varices are generally the most common clinical manifestation of portal hypertension and ruptured esophageal varices are a dreaded complication of portal hypertension, accounting for approximately 3200 deaths annually attributed to cirrhosis.² Varices usually form when hepatic vein pressure gradient (determinant of portal pressure) exceeds 10 mmHg and bleeds when it exceeds 12 mmHg. In cirrhosis, there is compression of hepatic veins by regenerating nodules along with collagen deposition in sinusoids and venules, factors responsible for increased intrahepatic resistance. The increase in blood flow is incompletely understood but is

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probably due to circulating vasodilators and alterations in fluid and electrolyte balance. All these interactions result in the development of increase portal pressure and Porto-systemic collateral formation. These collaterals decompress the portal circulation by shunting the blood to the heart via the systemic venous circulation and the major sites of these collaterals are the esophagus, rectum, umbilicus and retro peritoneum.^{3,4,5} Gastro esophageal varices are present in approximately 50% of patients with cirrhosis with a lifetime incidence of 90%. Their presence also correlate with the severity of disease, being more common in Child Pugh Class C patients as compared to Child Pugh Class A patients (85% versus 40%)^{6,7,8} (Table 1). Variceal hemorrhage is a medical emergency. Approximately one third of patients with esophageal varices experience variceal bleeding with a mortality rate of up to 20%. After an initial episode, there is 70% chance of re-bleeding within a year with a mortality rate of up to 33% in the absence of any treatment⁹ Due to this reason a screening endoscopy is indicated in all patients with newly diagnosed cirrhosis to minimize the complications and also to reduce mortality associated with acute variceal bleed.² It has also been suggested to repeat endoscopy at every 2-3 years interval in patients without varices and at 1-2 years interval in patients with small varices to evaluate for progression¹⁰ Current treatment modalities have substantially reduced the rate of first and recurrent bleeding and has also decreased the mortality associated with acute variceal bleed.¹¹ However screening all patients with endoscopy will significantly increase the cost and has also variable patient compliance. A number of other factors such as platelet count, coagulation profile, splenic size and portal vein diameter also correlate with the risk of variceal bleed and can be assessed by less invasive and routine tests carried out on the patients of cirrhosis. Due to cost effectiveness and to limit the number of endoscopic procedures, these parameters become more significant and carry paramount importance in making it possible for endoscopy to be carried out only in selected group of patients thus to avoid un-necessary intervention and at the same time not to miss patients at risk of bleeding. Therefore, the present study has been carried out to identify clinical, biochemical and ultrasonographic parameters which might non-invasively predict the existence and the risk of variceal bleed.

Table 1: Child pugh classification

	1	2	3
Bilirubin (mg/dl)	<2	2 - 3	>3
Serum albumin (g/dl)	>3.5	2.8 - 3.5	<2.8
Grade of encephalopathy	None	Mild	Moderate to severe
Grade of ascites	None	Mild	Moderate to severe
INR	<1.2	1.2 - 1.7	>1.7

Child A: 5-6, Child B: 7-9, Child C: 10-15

MATERIAL AND METHOD

A total of 150 patients with chronic liver disease, admitted to the department of medicine, ward 5, Jinnah Postgraduate Medical Centre from September 2011 to February 2012 were included in this study. All patients were categorized into two groups according to the presence or absence of upper GI bleed in the form of hematemesis or melena. Diagnosis of liver cirrhosis was based on combination of clinical signs & symptoms, laboratory findings (deranged coagulation profile, reversal of albumin/globulin ratio) and Ultrasonographic findings (size and echogenicity of the liver). Patients suffering from acute liver failure, non-cirrhotic portal hypertension, and tropical splenomegaly were excluded from the study.

A structured proforma was used for data collection. Detailed history was obtained and patients were examined with special attention to anemia, jaundice, palmarerythema, spider nevi, gynaecomastia, edema, splenomegaly and ascites. Relevant hematological, biochemical and radiological investigations were ordered including complete blood count, urea, creatinine and electrolytes, liver function tests, coagulation profile, serum proteins, serum albumin and globulin ratio, HBsAg, Anti HCV Antibody, urine D/R, ascetic fluid D/R, serum ammonia, chest X-Ray, ultrasound abdomen and upper GI endoscopy (as part of routine workup) (Table 2).

Upper gastrointestinal bleed was defined on the basis of hematemesis or melena. Thrombocytopenia as platelet count of $<150,000/\text{mm}^3$, deranged coagulation profile as INR of >1.2 , splenomegaly as splenic size of >13 cm and dilated portal vein diameter of >1.2 cm on ultrasound. Platelet counts of 75,000 to 150,000/ μL was defined as grade I thrombocytopenia, 50,000 to 75,000/ μL as grade II, 25,000 to 50,000/ μL as grade III, and below 25,000/ μL as grade IV thrombocytopenia.

Statistical analysis was done using SPSS version 19 and the results were obtained in the terms of frequencies and percentages for descriptive analysis. Chi-Square and student t tests were used to analyze the numerical data and p value of <0.05 was set to be statistically significant.

RESULTS

Age & Gender

There were eighty one (n=81, 54%) females and sixty nine (n=69, 46%) males. The range of patient's age was 14-83 yrs. 58% (n=87) of the patients in our study belong to the age group of 40 – 60 years with mean age of 50.9 years and Standard deviation of ± 13.171 (Figures 1 & 2).

Table 2: Laboratory parameters of all patients with chronic liver disease

	Without bleed		With bleed		p-value
	Mean	Std. Deviation	Mean	Std. Deviation	
Hemoglobin (mg/dl)	8.429	2.2389	8.184	2.0675	0.492
Mean cell volume (fl)	88.421	14.1289	91.584	10.0995	0.142
TLC (x10 ⁹ /L)	8.790	6.1854	8.453	5.7380	0.739
Platelets/mm ³	113.96	67.188	86.10	69.645	0.012*
Random blood sugar (mg/dl)	137.58	84.530	137.64	68.215	0.997
Urea (mg/dl)	57.09	47.601	52.11	35.582	0.492
Creatinine (mg/dl)	1.4016	1.04940	1.1420	0.61934	0.084
Serum sodium (meq/l)	132.472	7.1617	133.277	9.3108	0.578
Serum potassium (meq/l)	4.2748	3.40198	3.9015	0.75980	0.400
Serum chloride (meq/l)	102.746	8.4363	103.127	6.2709	0.792
Total bilirubin (mg/dl)	4.2211	5.38458	3.3395	3.87788	0.300
Direct bilirubin (mg/dl)	1.9992	3.25431	1.6781	2.40724	0.540
Indirect bilirubin (mg/dl)	2.1063	2.44664	1.6953	1.72525	0.300
ALT (u/l)	44.81	53.126	51.90	39.677	0.428
AST (u/l)	85.15	64.431	99.00	109.509	0.439
ALP (u/l)	372.20	285.201	296.13	226.103	0.118
GGT (u/l)	58.13	74.675	47.33	35.865	0.358
Total proteins (mg/dl)	8.141	7.1363	8.202	9.6373	0.970
Serum albumin (mg/dl)	3.125	0.5835	3.623	4.1489	0.376
Globulin (mg/dl)	4.037	0.9202	3.677	0.8849	0.050
A/G ratio	0.810	0.1880	0.845	0.2007	0.390
INR	1.3731	0.45532	1.6385	0.50358	0.001*
Serum ammonia (µg/dl)	164.00	74.740	253.33	98.845	0.016*
Liver span (cm)	11.562	2.1332	12.029	3.3295	0.584
Portal vein diameter (cm)	1.092	0.2583	1.224	0.3023	0.007*
Spleen size (cm)	13.082	2.3503	14.565	2.3994	0.000*
Splenic vein diameter (cm)	1.167	0.2066	0.700	0.2828	0.041*

* Significant P-value

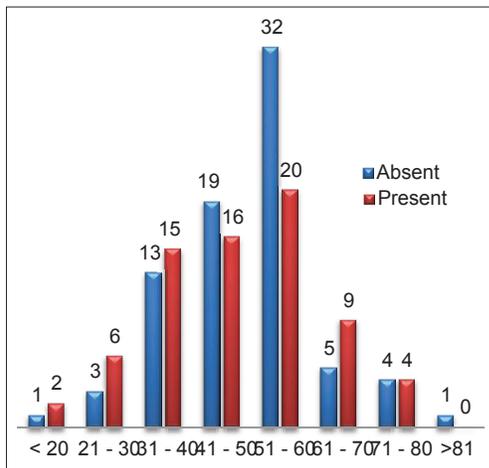


Figure 1: Age prevalence

Frequency of viral hepatitis

The most common cause of chronic liver disease was found to be HCV in our patients. Frequency of viral hepatitis as a cause of chronic liver disease is mentioned in Figure 3.

Frequency of upper GI bleed

72 patients in our study presented with GI Bleed that makes 48% of total cases while 78 patients (52%) patients had no history of upper GI bleed. Out of 72 patients, 22 (15%) patients presented with hematemesis, 12 (8%) had melena

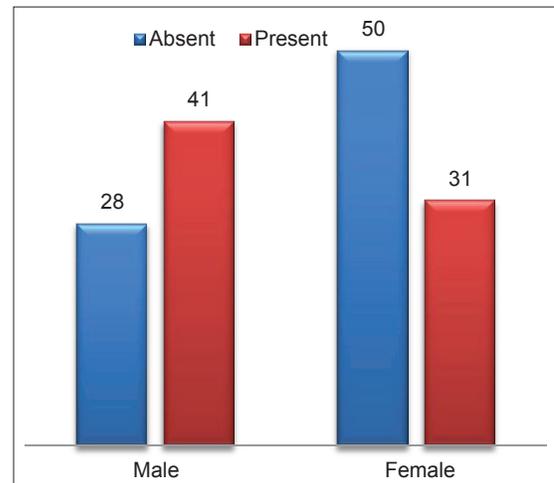


Figure 2: Gender prevalence

and 38 (25%) patients presented with both hematemesis and melena (Figure 4).

NON-INVASIVE PARAMETERS FOR ESOPHAGEAL VARICES

Thrombocytopenia

Thrombocytopenia was present in 64 (88%) patients, with mean platelet count of 85.86/µL (±69.79) in

patients with upper GI bleed. While 63 patients with no history of upper GI bleed had thrombocytopenia with mean platelet count of 113.96 (p-value 0.014). Statistically significant relationship was found between the severity of thrombocytopenia and risk of bleed in CLD patients (Figure 5) (Pearson's Chi Square: p value = 0.009).

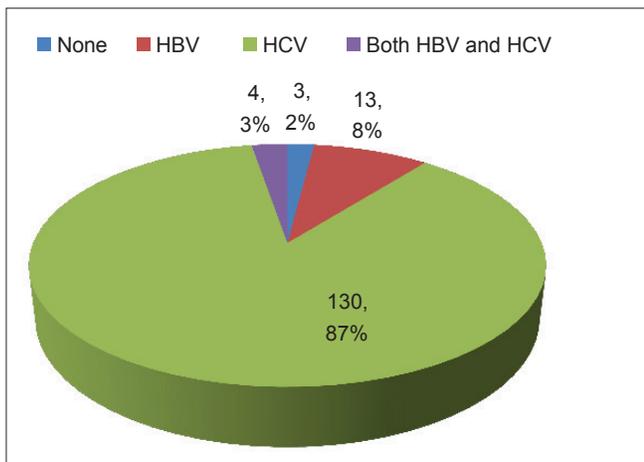


Figure 3: Frequency of viral hepatitis

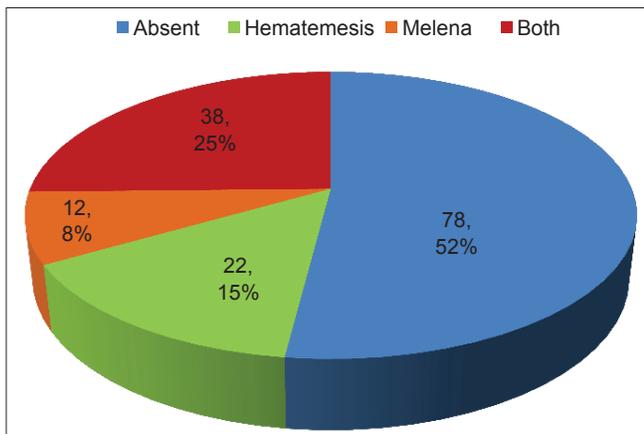


Figure 4: Frequency of upper GI bleed

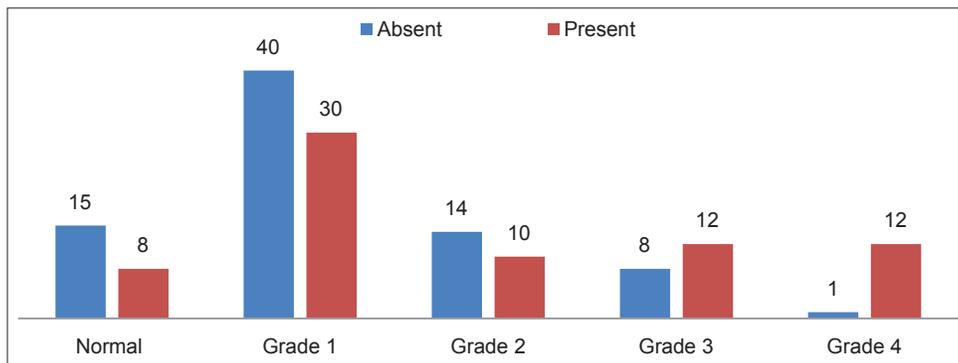


Figure 5: Grades of thrombocytopenia vs GI bleed (statistically significant difference was found between the groups by applying Pearson Chi Square (p-value 0.005))

Coagulation profile

Deranged coagulation profile was present in 56 (77%) cases with GI Bleed, with mean INR of 1.63 (± 0.5) in contrast to only 39 patients (50%) without upper GI Bleed had deranged coagulation profile with a mean INR of 1.37 (± 0.45) (p value = 0.001). Level of significance was determined by application of Pearson chi square (p-value 0.001) (Figure 6).

Portal vein diameter

Portal vein diameter of >1.2 cm was found in 46 (63.8%) patients who presented with GI Bleed with mean PVD of 1.22 cm (± 0.3023), (p value = 0.005) while 35 (44.8%) patients without bleed had dilated portal vein on ultrasound with mean PVD of 1.092 cm (± 0.02). Level of significance was determined by application of Pearson chi square (p-value 0.022) (Figure 7).

Splenic size

A splenic size of >13 cm was found in 54 (75%) cases having mean splenic diameter of 14.5 cm (± 2.39) (p value <0.001). On the other hand, 35 (44%) patients without GI Bleed had splenomegaly with mean splenic diameter of 13.08 cm (± 2.35). Level of significance was determined by application of Pearson chi square (p-value 0.000) (Figure 8).

DISCUSSION

Acute Upper GI hemorrhage is a medical emergency with high morbidity and mortality, numerous hospital admissions and a high burden on health care providers.^{12,13} Esophageal varices are the major cause of upper GI hemorrhage in our setting as compared to peptic ulcer in western population. Despite significant improvements in early diagnosis and advancements made in the treatment modalities, the mortality rate of first variceal hemorrhage is still 20%. Numerous studies have demonstrated the significance of pharmacologic therapy for primary prevention of

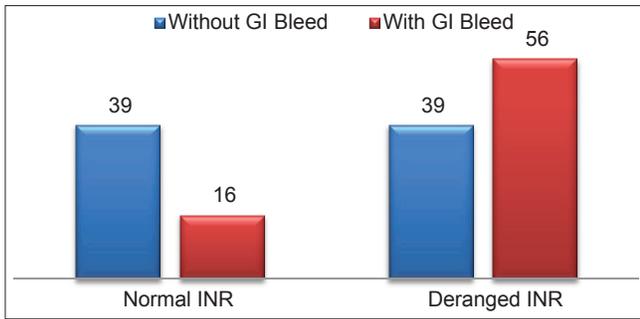


Figure 6: Coagulation profile vs GI bleed

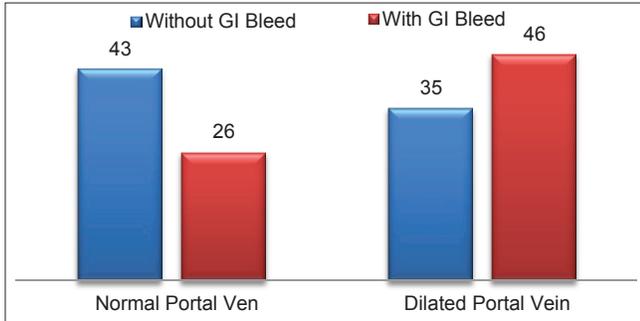


Figure 7: Portal vein size vs GI bleed

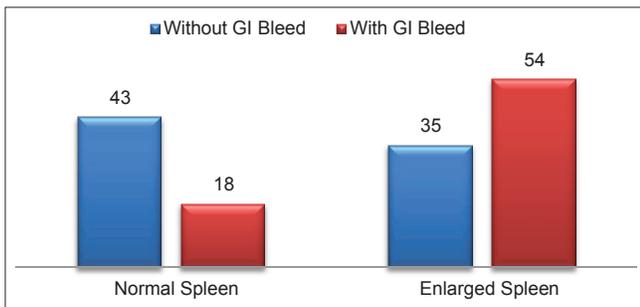


Figure 8: Splenomegaly vs GI bleed

variceal bleeding, emphasizing the importance of screening endoscopy in all newly diagnosed cirrhotic patients for the presence of varices.^{9,14} Therefore, there is a particular need for the identification of noninvasive parameters that strongly predict the presence of esophageal varices as that might decrease the medical, public and economic burden of the disease.

Our Study demonstrated that thrombocytopenia, deranged coagulation profile, presence of portal hypertension with splenomegaly and portal vein diameter are strong predictors of developing variceal bleed presenting clinically as upper GI hemorrhage.

Earlier, the pathophysiology of thrombocytopenia in liver disease was linked to the presence of hypersplenism, but now it has been discovered that thrombopoietin production is dependent on functioning liver cell mass

and is responsible for reduced thrombopoiesis and consequently peripheral thrombocytopenia in patients of advanced liver disease.^{15,16} Prolonged PT is also related to the severity of liver diseases and is also a simple, inexpensive and accurate marker of liver impairment and a predictor of upper gastrointestinal bleeding in chronic liver disease.¹⁷

Splenomegaly and portal vein diameter are also reliable predictors of variceal hemorrhage, in a study carried out by Mandal et al¹⁸ it has been shown that grading of esophageal varices also correlate with splenic size and portal vein diameter. In their study average portal vein diameter and splenic size in high grade varices were 14.43 ± 0.86 mm and 15.36 ± 2.14 cm. Sharma and Agarwal in their study had noted that clinically palpable spleen was associated with high grade varices however they did not measure the splenic size radiologically.¹⁹ The measurement of the splenic diameter using ultrasonography is easily obtainable, reproducible, non-invasive and is routinely performed on patients with cirrhosis. In another study carried it was demonstrated that the platelet count/spleen diameter ratio is also useful in the discrimination of large versus small varices and in their study a platelet spleen diameter ratio of less than 909 was statistically significant in predicting large varices.²⁰ Farooqi et al²¹ also found out that platelet count of $< 65 \times 10^3/\mu\text{L}$, serum albumin < 2.2 g/dl and portal vein diameter of > 13 mm are independent and significant predictors of esophageal varices on endoscopy.

Though, upper GI endoscopy remains the gold standard for the diagnosis of esophageal varices in cirrhotic patients, from the present study and a number of other studies it has been found that certain non-endoscopic parameters such as thrombocytopenia ($< 75,000/\text{mm}^3$), coagulation profile (PT > 1.3), spleen size (> 13 cm), and portal vein diameter (> 1.2 cm) are significant and reliable predictors of esophageal varices on endoscopy, therefore screening endoscopy could be safely limited to the group of cirrhotic patients with no history of upper GI bleed but in the presence of above deranged parameters.

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Authors Contribution:

AU and FAQ – designed the study, collected and analyzed the data and scripted the parts of manuscript; **BU** – scripted the manuscript and reviewed the results; **RAS** – reviewed the manuscript.

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