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BIOCHEMICAL AND ENDOSCOPIC EVALUATION OF UPPER-GASTROINTESTINAL BLEED IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Objectives: Evaluating the causes of UGIB, their relation with Child-Turcotte-Pugh (CTP) score and biochemical markers and the predictors of varices.

Study Design: Prospective comparative study.

Place and Duration of Study: Fauji Foundation Hospital Rawalpindi, from Jan 2016 to Jul 2017.

Methodology: The study population consisted of 256 patients with chronic liver disease who underwent upper gastrointestinal endoscopy to evaluate the cause of UGIB. Both variceal and non-variceal causes were notified. The patients were classified into class A, B and C according to CTP score. The relationship of varices with CTP score and biochemical findings were studied. The predictors of varices were also found by regression analysis.

Results: Gastroesophageal varices were present in 73.6% patients and 26.3% patients had non-variceal bleeding. Portal hypertensive gastropathy was the most common cause of non-variceal bleeding (20.5%). The presence and grades of varices were associated with CTP score (p<0.05). Class C had more advanced varices compared to Class A. Low platelets and albumin while high bilirubin, PT, INR and CTP class were prognosticators of varices.

Conclusion: Although a substantial portion bleeds due to variceal haemorrhage, non-variceal causes of UGIB were also not uncommon. Both pathologies resulted in substantial mortality. The advanced liver cirrhosis was associated with higher grades of varices. Blood chemistry markers helped in differentiating the two causes and manage them accordingly.

Keywords: Esophageal and gastric varices, Gastrointestinal Haemorrhage, Liver disease, Portal hypertension.

INTRODUCTION

Liver cirrhosis is among the top-tier causes of morbidity and mortality worldwide due to portal hypertension or hepatocytes insufficiency. Upper gastrointestinal bleed due to portal hypertension mostly ends in life-threatening complication among these patients[1]. Cirrhosis related upper-gastrointestinal bleeding is broadly divided into variceal and non-variceal categories. Variceal bleeding is common, affecting 50% to 70% of these patients. Non-variceal bleeding is also not an uncommon entity as it affects nearly 30-40% of the cases[2]. Upper-gastrointestinal bleeding can present as hematemesis, melena or haematochezia[3]. Esophago-gastro-duodenoscopy is a facilitating modality which is not only used to diagnose and manage the bleeding but also to assess risk for rebleeding in these patients[4].

Various classifications are used to grade esophageal and gastric varices. Paquet classified them into four grades in 1980s depending on the appearance and location of varices in esophagus[5]. While Sarin proposed a classification for gastric varices, thus classifying them into gastro-esophageal and isolated gastric varices (type I & type II)[6]. Non-variceal bleeding is the bleeding occurring in the absence of gastro-esophageal or duodenal varices[3]. Like variceal, non-variceal bleeding is also related to increased mortality rates, but they have been less studied as compared to variceal causes[5-7]. Peptic ulcers, portal hypertensive and erosive gastropathy, Mallory-Weiss tears, gastrointestinal ulcers, Gastric antral vascular ectasia, polyps and tumors are among non-variceal causes of gastrointestinal bleed[8,9]. Although much conflicting data are present relating to either peptic ulcers or portal hypertensive gastropathy as the most common cause of non-

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variceal bleeding but still portal hypertensive gastropathy is a relatively common cause[10].

The presence of esophageal varices has positive correlation with the advancement of liver disease[11]. As the liver disease advances, the severity and grades of esophageal varices also increase[12]. In the last few decades, much emphasis is paid to study the diagnostic validity of various non-invasive markers in predicting the presence of varices. These non-invasive markers are easily obtainable, simple in interpretation, economical and above all they show good accuracy in detecting the presence of esophageal varices[13,14]. Many biochemical markers like thrombocytopenia, splenic index and portal vein diameter have found to be good prognosticators of the presence of esophageal varices[15-17].

As upper-gastrointestinal bleeding results in significant mortality among the patients with liver cirrhosis, the prime objective of this study was to elaborate the causes of upper-gastrointestinal bleeding in patients with liver cirrhosis. The association of esophageal varices with Child-Turcotte-Pugh class of liver cirrhosis, the predictors of their presence and their correlations with biochemical markers were studied as secondary objective of the study.

METHODOLOGY

It was prospective comparative study conducted at Fauji Foundation Hospital Rawalpindi from January 2016 to July 2017 to evaluate the causes of gastrointestinal bleeding in patients who had chronic liver disease. The predictors of esophageal varices and correlation of biochemical abnormalities to endoscopic findings were also studied as the secondary objective of the study.

This study involved the patients who had chronic liver disease and presented with upper gastrointestinal bleeding. An informed consent was taken from patients. If one or more than one of the following features were present, the patients were labelled with the diagnosis of chronic liver disease.

i. Ultrasonographic evidence of chronic liver disease like liver texture showing coarse and heterogeneous appearance, nodular texture of liver surface or atrophy or hypertrophy involving hepatic segments.
ii. Liver fibrosis proven on liver biopsy.
iii. Deranged liver function tests for more than 3 months with other biochemical abnormalities suggesting chronic liver disease (prolonged prothrombin time, low albumin levels, low platelet count)
iv. Presence of Previous hospital records pertaining to the particular diagnosis.

The patients who were hemodynamically unstable were excluded.

The study group constituted Two hundred and fifty-six (256) patients. Sample size was calculated by using WHO sample size calculator. Non probability consecutive prior to study, Ethical Approval was taken from the hospital ethical committee dated 17th December, 2015. Patients were informed about the study details before taking their consent.

Demographic descriptions of patients were noted. Comprehensive details such as aetiology of liver disease, symptoms of upper gastrointestinal bleeding like hematemesis and melena, biochemical profile (Complete blood picture, Liver function tests, Serum albumin, Prothrombin time, INR) were noted for individual patient.

Child- Turcotte-Pugh (CTP) score was also assessed for each patient. Criteria to group the patients into A, B and C classes was based on five variables. (Hepatic encephalopathy, Ascites, Bilirubin, Prothrombin time and Albumin)[18].

Upper gastrointestinal endoscopy was done in all the patients. Sterilization and sedation were done according to standard measures. A single endoscopist performed all the endoscopies (endoscope XP180; Olympus Company, Japan) to lessen the intra-observational and inter-observational variations. Varices were graded into four grades (Grade I to IV) according to Paquet classification of esophageal varices and gastric varices

were graded according to Sarin classification[5,6]. Findings of endoscopy were noted in detail.

After endoscopy, the study population was divided into two groups. Variceal group; in whom esophageal, fundal or both varices resulted in gastrointestinal bleeding and Non-variceal group; in whom the cause of gastrointestinal bleeding was other than esophageal varices. Both groups were compared in relation to their biochemical features. The relationship of CTP class with the presence and grades of varices was also noticed. In addition, predictors relating the presence of varices and correlation of endoscopic findings to biochemical abnormalities were also studied.

SPSS version 20 was used for analysis. Quantitative variables in terms of Mean, Standard deviation and qualitative variables in terms of frequencies, percentages were expressed. Chi-Square and t-test was applied to compare the variables between two groups; variceal vs non-variceal group. Contingency Coefficient was used to find the association between the presence of varices and CTP class of liver cirrhosis. The relationship of grades of esophageal varices with CTP class was also studied by Contingency Coefficient. The predictors of the presence of esophageal varices were determined by using univariate and binary logistic regression analysis. At the end, Pearson correlation was carried out between endoscopic findings and various biochemical labs.

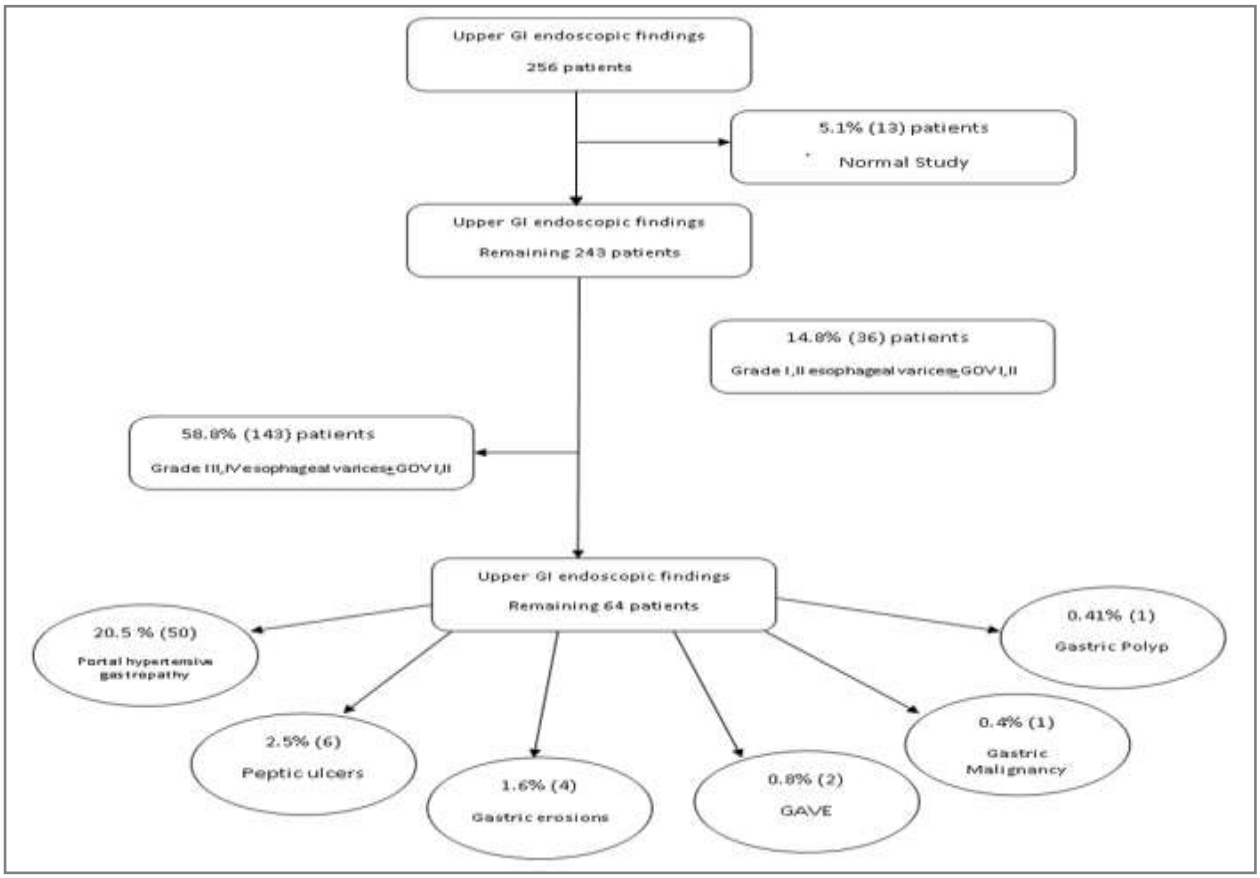

Figure: Flow-diagram of study population.

RESULTS

The mean age of the study group presenting with upper gastrointestinal bleeding (UGIB) was 54.22 ± 13.73 years ranging from 17-78 years. Among study population, 101 (39.5%) patients were males and 155 (60.5%) were females. Chronic hepatitis C infection resulted in chronic

liver disease in 236 (92.2%) patients, Chronic hepatitis B infection was the second common cause found in 14 (5.5%) patients, Wilson disease resulted in liver disease in 4 (1.6%) patients while Autoimmune hepatitis was found in 2 (0.8%) patients.

Among 256 patients, 133 (51.9%) patients presented with hematemesis, 75 (29.2%) patients presented with hematemesis, melena both and 48 (18.7%) patients presented with melena. The characteristic of study group is shown in flow chart (figure).

Upper gastrointestinal endoscopy reveals normal mucosa in 13 (5.1%) patients. Rest of the study group (n=243) was divided into two groups; variceal population and Non-variceal group. Esophageal varices were present in 179 (73.6%) patients. Fundal varices were found in 17 (6.9%) patient. The gastroesophageal varices (GOV) type II were in 16 (6.5%) while only one patient 0.4% had GOV type I. We didn't find any isolated fundal varices in our study.

Non-variceal upper gastrointestinal bleed was present in 64 (26.33%). Biochemical parameters like hemoglobin, platelets, bilirubin, albumin, prothrombin time, INR and Child-Turcotte-Pugh score were significantly different among these two groups (p<0.05). The biochemical characteristics of these two groups are shown in table-I

Table-I: The biochemical characteristics of two groups; Variceal and non-variceal group in relation to *p*-value.

	Variceal (Mean ± SD)	Non-Variceal (Mean ± SD)	*p*-value
Age (years)	53.91 ± 13.99	54.96 ± 13.11	0.57
Male vs Female	80 vs 90	21 vs 56	0.09
Hb (g/dl)	9.72 ± 2.22	8.90 ± 2.23	<0.001
WCC x10^3 cells/mcL	6.16 ± 3.04	6.45 ± 3.59	0.50
Platelets x 10^3 cells/mcL	94.80 ± 48.22	126.32 ± 90.40	0.00
Bilirubin (umol/L)	55.64 ± 49.01	40.80 ± 34.14	0.01
ALT (U/L)	57.56 ± 41.59	45.29 ± 38.98	0.96
ALP (U/L)	239.50 ± 90.69	231.32 ± 84.69	0.48
Albumin (g/L)	35.09 ± 4.24	36.52 ± 3.69	0.00
PT (sec)	5.02 ± 4.44	3.45 ± 2.33	0.00
INR (sec)	1.90 ± 0.35	1.50 ± 0.44	0.00
Child-Pugh score	8.84 ± 2.04	8.17 ± 2.33	0.03

SD: Standard Deviation; Hb: Hemoglobin; ALP: Alkaline Phosphatase; WCC: White Cell Count; PT: Prothrombin Time; ALT: Alanine Aminotransferase; INR: International Normalized Ratio.

Table-II: The distribution of variceal and non-variceal group according to Child- Turcotte-Pugh Class of patients with Liver cirrhosis.

	CTP Class A	CTP Class B	CTP Class C
Normal	7 (2.7%)	3 (1.1%)	3 (1.1%)
Non-variceal group	32 (12.5%)	15 (5.8%)	17 (6.6%)
Grade I, II esophageal varices + GOV Type I, II	16 (6.2%)	14 (5.4%)	6 (2.3%)
Grade III, IV esophageal varices + GOV Type I, II	19 (7.4%)	54 (21%)	70 (27.3%)

CTP Class: Child- Turcotte-Pugh; GOV: Gastroesophageal varices.

Among the study group, 74 (28.9%) were in CTP class A, 86 (33.6%) were in CTP class B while 96 (37.5%) were in CTP class C. It was found that the presence of varices was remarkably associated with CTP class of patients with liver cirrhosis. (Contingency Coefficient =0.445, p=0.001) (table-II).

The predictors showing the presence of varices were also determined by logistic regression analysis. Both univariate and binary regression analysis were carried out to find the predictors of varices. Only those variables which were found to be positive predictors on univariate analysis were checked by bivariate analysis. The binary regression model was statistically suitable to analyse the variables (Model Chi Square=48.64, *p*=0.001). The model covered 17% to 24% of variations in variables of study group (Cox and Snell R2 and Nagelkerke R2) and classified 68.8% of cases. Platelets, bilirubin, albumin, PT, INR, CTP class and score were found to be predictors of the varices. The univariate and binary logistic regression analysis showing the predictors of varices in patients who had liver cirrhosis is shown in table-III.

Table-III: The univariate and multivariate binary logistic regression analysis indicating the statistically significant predictors of presence of esophageal varices.

	Univariate Analysis		Multivariate Binary Logistic Analysis	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Platelets	1.41 (1.32-1.51)	0.01	0.99 (0.98-0.99)	0.01
Bilirubin	1.24 (1.17-1.31)	0.01	1.007 (1.000-1.014)	0.04
Albumin	2.01 (1.49-2.53)	0.01	0.91 (0.85-0.97)	0.01
PT	1.21 (1.13-1.29)	0.01	1.10 (1.03-1.18)	0.01
INR	0.64 (0.45-0.54)	0.01	8.08 (4.04-16.15)	0.01
CTP score	1.07 (0.85-1.28)	0.03	1.14 (1.01-1.28)	0.03
CTP class	1.33 (1.24-1.42)	0.01	-	0.01

PT: Prothrombin time; CTP: Child- Turcotte-Pugh; INR: International normalized ratio; OR: Odd ratio.

Table-IV: Pearson correlation between biochemical and endoscopic findings.

	Pearson Correlation Coefficient	***p*-value**
Platelets x 10^3 cells/mcL	-0.17	0.01
Bilirubin (umol/L)	0.14	0.18
PT (sec)	0.18	0.01
INR (sec)	0.39	0.01
Albumin (g/L)	-0.16	0.01
CTP score	0.13	0.03

PT: prothrombin time; CTP: Child- Turcotte-Pugh; INR: international normalized ratio.

At the end, Pearson correlation was carried out to find the biochemical correlations with esophageal varices. Prothrombin time, INR, serum bilirubin, Child-Pugh score, low albumin and thrombocytopenia was found to be significantly correlated with presence of varices (table-IV).

DISCUSSION

Upper gastrointestinal bleeding (UGIB) following portal hypertension is the frequently observed complication of liver cirrhosis. Although esophageal or fundal varices account for many cases of UGIB in cirrhotic patients; non-variceal causes are also responsible for bleeding in a substantial portion of these patients. However, very few studies have been carried out to determine these non-variceal causes[9].

In our study, only 5.1% of patients had a normal endoscopic examination while the rest of the study group had bleeding either due to varices or non- varices sources. A substantial number of patients 73.6% had bleeding due to varices while only 31.68% had non-variceal causes of bleeding. Many studies had shown that among these patients, mostly UGIB results from gastroesophageal varices. Romcea *et al*[2] conducted study on more than 1000 patients and found that 73% had bleeding due to varices. This finding is same as our results. Similar findings are also described in the research article of Bieker *et al*[19] showing more than 60% of patients had variceal bleed

We found that 31% patients had non-variceal causes of bleeding. Romcea *et al*[2] also found that more than 25% patients had UGIB due to non-variceal causes showing that this group constitutes the major category among causes of UGIB.

It was reported in the large systemic review that the prevalence of Portal hypertensive gastropathy (PHG) was highly variable ranging from 20% to 60% in patients with liver cirrhosis[10]. In this study, 20.5% patients were affected by PHG resulting in the most common cause of non-variceal upper digestive hemorrhage. Similarly Bhattarai *et al*[9] also found that nearly 17% of patients had PHG leading to gastrointestinal bleeding. Hadayat *et al*[20] and Abbasi *et al*[21] found that PHG is the topmost cause of non-variceal digestive hemorrhage in liver cirrhotic patients although the frequency is higher than found in our study i.e. 40% and 60% respectively.

We found that only 2.5% patients had peptic ulcers as a cause of upper gastrointestinal haemorrhage. Just like PHG, the prevalence of peptic ulcers is also greatly variable among cirrhotic patients as shown by various studies. Many studies have shown that peptic ulcer disease is the first most common cause of non-variceal haemorrhage among these patients[3,9,22]. But at the same time, the studies suggesting that lower frequency of peptic ulcers among cirrhotic patients as compared to PHG are also notable[8]. Demographic variations of Helicobacter pylori infection, greater tolerability of beta blockers for portal hypertension, use of alcohol, NSAIDs (non-steroidal anti-inflammatory drug) and ASA (acetyl-salicylic acid), over-prescribing of Proton pump inhibitors in some parts of world are reasonable causes explaining the variation of prevalence PHG and peptic ulcers as non-variceal digestive haemorrhage[4].

The distribution of gastroesophageal varices and their grades in relation to Child-Turcotte Pugh (CTP) Class of cirrhosis was also studied as the secondary objective of this study. We found that CTP class is not only statistically significant among variceal and non-variceal group, but grades of varices also increases as the CTP score advances. In CTP class C, only 2.3% had early varices as compared to 27.3% who had advance varices.

Zaman *et al*[11] also found that as the CTP class advances, the number of esophageal varices with higher grades also increases. These findings are like our results. Jijo V. Cherian *et al*[12] also found the advanced CTP Class as significant predictor of large esophageal varices. Similarly, Thierry *et al*[23] and Seo *et al*[24] established a high CTP score as a fundamental risk factor for variceal bleed.

The predictors of varices by logistic regression analysis were also studied as an additional objective of this study. Low Platelets and albumin while higher bilirubin, Prothrombin time, INR, CTP class and score were found to be the predictors of the existence of varices in these patients.

Platelet counts were significantly different among variceal and non-variceal group (Mean 94.80 and 126.32 respectively, p=0.000). They were found as the predictors of varices on both univariate and binary logistic regression analysis. Negative correlation was found between esophageal varices and platelet counts (pearson correlation=-0.178, p=0.004) showing thrombo-cytopenia is correlated with the presence of gastroesophageal varices. Many comprehensive studies have declared thrombocytopenia as an impartial predictor for detection of esophageal varices. Jamil *et al*[17] found thrombocytopenia as an effective tool for detecting gastroesophageal varices with sensitivity of 93% and specificity of 72%. Similar correlation are found by Zaman *et al*[11], Bressler *et al*[25] suggested in their study that patients with liver cirrhosis and platelet count $<140 \times 10^3/mm^3$ should be screened for gastroesophageal varices. Although their cohort was cirrhotic patients secondary to biliary cirrhosis.

Bilirubin, albumin, prothrombin time and INR were also significantly different among variceal and non-variceal group and they were

found to be predictors of varices. High bilirubin levels correlates with higher scores of Child-Pugh class thus indicating the presence of gastroesophageal varices[25]. Negative correlation is found between albumin levels and varices. Many studies have shown that hypoalbuminemia is not only predictor of portal hypertension and varices, but it is also an indicator of increased mortality rate in these patients. Prolong prothrombin time and INR are also noted to be associated with increased risk of bleeding varices.

LIMITATION OF STUDY

The main limitation of this study was follow up of the patients presenting with upper gastrointestinal bleeding was not done. The effects of variceal vs non-variceal bleed, liver disease advancement and biochemical predictors determining the survival of these patients can enhance the impact of this study.

CONCLUSION

The causes of upper gastrointestinal bleeding in patients suffering from diseases of chronic liver were variable. Bleeding resulting either from gastroesophageal varices or non-varices pathologies resulted in substantial mortality rates. The management of both ends were wholly different. Thus if patient presents with upper digestive haemorrhage, in addition to detailed history and examination, the resulted of their blood chemistry can also help the physicians a lot in differentiating variceal from non-variceal causes and manage them accordingly. Thrombocytopenia and worsening of Child-Turcotte-Pugh class indicates the presence of gastroesophageal varices as cause of digestive haemorrhage.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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