

## ORIGINAL ARTICLE

## THE PREDICTORS OF RE-BLEEDING IN CHRONIC LIVER DISEASE PATIENTS AFTER ENDOSCOPIC VARICEAL BAND LIGATION

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**Background:** Variceal bleeding is a key and most fatal complication observed in chronic liver disease patients with portal hypertension and is a major contributor to the high morbidity and mortality seen in these patients. Exploring the predictors of rebleeding in chronic liver disease patients is of paramount importance to alter disease course and impact on morbidity and mortality.

**Methods:** About 50 patients with chronic liver disease who previously had evidence of varices on upper GI endoscopy and had at least one episode of rebleeding after EVBL were included in this study. Patients were assessed for the possible contributors to rebleeding through complete history, clinical examination, coagulation profile and platelet count, ultrasound features (splenic size and portal pressure), and upper GI endoscopic findings (site and grade of varices, red sign). Sample selection was done using non-probability purposive sampling technique and sample size calculated using the standard WHO formula. Data was entered and analyzed using SPSS version 20. **Results:** In this study, mean age of the patients was 51.34±6.34 years with male predominance (64%). Rebleeding was significantly associated with grade of varices, presence of red sign on upper GI endoscopy, site of varices, splenic size and coagulopathy. **Conclusion:** Rebleeding in chronic liver disease patients following EVBL is predicted by grade, extent and site of varices, red sign on upper GI endoscopy, splenic size and coagulation disturbances.

**Keywords:** Variceal bleed; Endoscopic variceal band ligation; Rebleeding

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### INTRODUCTION

Variceal bleeding is a key and most fatal complication observed in chronic liver disease patients with portal hypertension and is a major contributor to the high morbidity and mortality seen in these patients.<sup>1</sup> The precise mechanisms leading to the rupture of oesophageal varices are poorly understood. It has been observed that portal pressure is the primary determinant of oesophageal variceal bleeding and it is usually >10 mmHg in patients with oesophageal varices, and generally exceeds 12 mmHg in those with ruptured oesophageal varices. Management modalities for bleeding oesophageal varices include endoscopic band ligation or injection sclerotherapy, insertion of the Sengstaken–Blakemore tube, self-expandable metal stents (SEMS), radiological interventions like trans jugular intrahepatic shunting (TIPS), vasoactive drugs, and surgery.<sup>2,3</sup>

Once variceal bleed occurs, recurrent bleeding episodes are observed to take place over preceding months to years with several key factors contributing to its etiopathogenesis. Among several important factors are: grade and site of the

varices, splenic size, presence of coagulopathy, portal pressure, child Pugh score, red colour signs on varices, infection, and portal vein thrombosis (PVT).<sup>5-7</sup> Variceal rebleeding can be categorized into early rebleeding (within 6 weeks of acute bleeding), and delayed rebleeding.<sup>8</sup> Available literature reveals that rebleeding occurs at a frequency of 30–40% within the first 6 weeks, and is the primary contributor to the high risk of death during this time period.<sup>8</sup> Rebleeding rates in other studies are reported around 30% after one year follow-up and as high as 50% at five years.<sup>9,10</sup>

Correcting the hypovolemia due to acute variceal bleed, prevention of complications related to upper GI bleed and ensuring haemostasis are the one of the foremost aims of variceal bleed management. After attainment of airway, breathing and circulation in acute phase, patients with acute variceal bleed are started on vasoactive drugs. After the initial stability, endoscopic variceal band ligation (EVBL) is the next management step to prevent further bleeding episodes from the engorged oesophageal varices.<sup>11</sup> The success rate of endoscopic band ligation is around 80–90% in

experienced hands.<sup>12</sup> Rest of the 10–20% patients face refractory variceal bleeding and need more aggressive approach in the form of trans-jugular intrahepatic portosystemic shunting (TIPS).<sup>13</sup> Consideration of early TIPS procedure should be planned in treatment refractory cases.<sup>14</sup> TIPS procedure is effective in the control of oesophageal varices in majority of the cases but it carries a significant (25–60%) mortality rate in acute settings.<sup>15</sup> Another method of controlling variceal bleeding is direct compression of the varices by inserting a balloon, a procedure termed as balloon tamponade. Though effective in controlling acute variceal bleeding but balloon tamponade is not without complications and major complication is the recurrence of variceal bleeding soon after deflating the balloon.<sup>16</sup> About 25% of the patients with acute variceal bleeding managed with balloon tamponade suffer complications with 5% experiencing fatal ones. To avoid these complications, whenever balloon tamponade is performed, it must be undertaken by experienced personnel in ICU settings.<sup>17</sup>

In addition, insertion of balloon is highly unpleasant experience for patients. With advancements in the field of gastroenterology in the form of endoscopic techniques and TIPS, Surgical intervention is less frequently employed in modern day practice because of the significant mortality observed in these procedures with most of the deaths occurring due to hepatic encephalopathy.<sup>18</sup> Because of these limitations, most of the physicians prefer other management strategies in treatment refractory cases. Therefore, exploring the predictors of rebleeding in chronic liver disease patients is of paramount importance to alter disease course and impact on morbidity and mortality. The aim of this case–control prospective study was to determine the key predictors of rebleeding in Pakistani cirrhotic patients after endoscopic variceal band ligation (EVBL) so that appropriate intervention can be taken to reduce the risk of rebleeding in cirrhotic patients.

## MATERIAL AND METHODS

This case control prospective study was conducted at department of medicine university of Lahore teaching hospital Lahore for a period of 6 months from October 2020 to April 2021. The study was performed in accordance with the principles of good clinical practice as laid down in the Helsinki declaration after receiving ethical approval letter from ethical review board of university of Lahore teaching hospital, Lahore. After written informed consent, fifty patients with chronic liver disease of any aetiology, both male and female, aged 25–65 years who previously had evidence of varices on upper GI endoscopy and had at least one episode of rebleeding after EVBL were included in this study. Patients were assessed for the possible contributors to rebleeding through complete history, clinical examination, coagulation profile and platelet count, ultrasound features (splenic size and portal pressure), and upper GI endoscopic findings (site and grade of varices, red sign). Sample selection was done using non-probability purposive sampling technique and sample size calculated using the standard WHO formula  $(n=Z^2P(I-P)/d^2)$ , where n indicates size of the sample, Z indicates confidence level taken as 95%, P indicates expected prevalence taken as 10 %, d indicates margin of error taken as 5%, and n (sample size) =150. Data was entered and analyzed using SPSS version 20 (IBM Statistics incorporated, Chicago, IL, USA). Qualitative variables were expressed as mean and standard deviation while quantitative variables were expressed as frequency and percentages. Chi square and t test were applied where appropriate.

## RESULTS

In this study, mean age of the patients was  $51.34 \pm 6.34$  years with male predominance (64%). Rebleeding was significantly associated with coagulopathy and splenic size (Table-1), grade of varices (Table-2), presence of red sign on upper GI endoscopy (Table-3), and site of varices (Table-4, 5).

**Table-1: Descriptive statistics**

	N	Minimum	Maximum	Mean	SD
Gastropathy	50	1.00	2.00	1.4200	0.49857
Duodenopathy	50	1.00	2.00	1.1800	0.38809
PT	50	1.00	2.00	1.2000	0.40406
APTT	50	1.00	2.00	1.0800	0.27405
Spleen	50	1.00	2.00	1.7400	0.44309
Valid N (listwise)	50				

**Table-2: Grade of varices**

	Frequency	Percent	Valid percent	Cumulative percent
VALID Grade 1				
Grade 2	22	44.0	44.0	44.0
Grade 3	19	38.0	38.0	82.0
Total	9	18.0	18.0	100.0
	50	100.0	100.0	

**Table-3: Red sign**

	Frequency	Percent	Valid percent	Cumulative percent
Valid positive	42	84.0	84.0	84.0
Negative	8	16.0	16.0	100.0
Total	50	100.0	100.0	

**Table-4: Gastropathy**

	Frequency	Percent	Valid percent	Cumulative percent
Valid mild	29	58.0	58.0	58.0
Severe	21	42.0	42.0	100.0
Total	50	100.0	100.0	

**Table-5: Duodenopathy**

	Frequency	Percent	Valid percent	Cumulative percent
Valid mild	41	82.0	82.0	82.0
Severe	9	18.0	18.0	100.0
Total	50	100.0	100.0	

## DISCUSSION

In this study, patients with chronic liver disease in the fifth decade of life had the highest frequency of rebleeding after initial EVBL with a male predominance. The same trend was noted in a tertiary care hospital study from southern Nigeria, though lower mean age (51.5 years) was observed in that study.<sup>19</sup>

Endoscopic variceal band ligation (EVBL) is a time-tested modality to prevent variceal bleeding in chronic liver disease patients. However, recurrent bleeding is a major complication observed after EVBL and studies to determine the possible contributors are limited.<sup>20,21</sup> The present study enabled us to determine risk factors and predictors of rebleeding after EVBL in chronic liver disease patients. We found that extent, grade and site of varices is a primary determinant of recurrent bleeding. Varices that prevail along the entire length of oesophagus are much more fatal and prone to bleeding than varices only involving middle and lower part. Also, more extensive the varices, more rubber bands are required for band ligation further increasing chances of recurrent bleeding. Lee *et al* illustrated the same point in his study stressing that in cases of mild to moderate varices, it may not be reasonable to apply too many rubber bands, however it is unavoidable in severe cases.<sup>22</sup> Similarly, it was noted in our study that presence of red sign on upper GI endoscopy is significantly associated with recurrent bleeding. In a study by Lee FY *et al*, the type of endoscopic treatment (sclerotherapy, band ligation) and presence of red wale sign on endoscopy primarily determined the recurrent bleeding risk in varices. Rebleeding was more frequently observed in those patients with red wale sign on EGD. Also, rebleeding was more frequently observed in gastric varices previously treated with sclerotherapy in comparison with band ligation ( $p=0.085$ ).<sup>23</sup> However, in another study, no significant mortality benefit was observed between band ligation and sclerotherapy.<sup>24</sup>

Coagulation disturbances in advanced liver cirrhosis are known for years. A study by Krige JE and

colleagues<sup>25</sup> revealed that an INR (international normalized ratio) >2.3 was a predictor of rebleeding and death within the initial 6 weeks after EVBL. However, a study by D'Amico and co contradicted the positive correlation between coagulopathy and rebleeding risk.<sup>26</sup> Our study showed that post EVBL recurrent bleeding episodes were frequently observed in chronic liver disease patients with PT more than 18 seconds ( $p$ -value: 0.008). Prolongation of PT denotes inadequate synthesis of necessary clotting factors (I, II, VII or X) by the diseased liver and hence more bleeding tendency. Kayacetin *et al*<sup>27</sup> pointed out that sluggish portal venous flow due to poor liver function was associated with more liver damage and more risk of variceal rebleeding and hence a vicious cycle ensues. In the present study, Splenic size and stiffness were also observed to be important predictors of rebleeding in patients with cirrhotic liver disease. This observation was also validated by other studies.<sup>28</sup> In a study by Liang Li *et al*, splenic enlargement was not only associated with the development of portal hypertension but also associated with progression of liver cirrhosis and worsening splenic size with recurrent variceal bleeding.<sup>29</sup>

Strength of the present study was that several key contributors to recurrent variceal bleeding were assessed at the same time with important therapeutic implications in terms of monitoring these indices and devising a strategy accordingly. A limitation of our study was the small sample size which could alter the statistical proportions necessitating large sample study on the topic in future. In addition, some other important predictors like reduction of portal hypertension with beta blockers, hypovolemia and MELD scoring were not taken into account in this study.

## CONCLUSION

Rebleeding in chronic liver disease patients following EVBL is predicted by grade, extent and site of varices, red sign on upper GI endoscopy, splenic size and coagulation disturbances.

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### AUTHORS' CONTRIBUTION

Dr Khurram Saleem actively participated in data collection procedure. Dr Faisal Amin Baig contributed in literature review. Dr Tahir Ullah Khan wrote the article, designed it, did statistical analysis and correspondence. Dr Atif Masood contributed to data collection process. Dr Arsalan Nawaz did the proof reading and drafting. Dr Wali Khan did the final overview of the article.

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