

Risk Factors and Predictors of Variceal Re-bleeding in Schistosomal Portal Hypertension Patients at the Bleeding Center in Ibn Sina Specialized Hospital

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Abstract

Original Research Article

Background: Bleeding varices is a common complication of portal hypertension. It occurs secondary to schistosomal portal hypertension in the majority of our patients. The aim of this study is to determine the factors possibly affecting risk of recurrent variceal bleeding. **Methods:** This study is a descriptive cross sectional hospital based study which was carried out in Ibn Sina Specialized Hospital Bleeding Center during the period from July 2019 to January 2020. A total of 201 (n= 201) patients suffering from bleeding varices due to schistosomal portal hypertension were included. Any patients bleeding from other causes were excluded. Baseline laboratory investigations were done (CBC, RFT, and INR). Patients underwent upper GI endoscopy. **Results:** Males were predominant (78.6 %, n= 158), while 21.4 % of patients were females (n=43). Male: Female ratio was 4:1. Age ranged from > 20 to < 70 years, mean age being (52.15 ± 15.7) years. At presentation 44.7% of patients (n= 90) had both hematemesis and melena, 28.8% of patients (n= 46) had only melena and 32.2% (n= 65) had only hematemesis. Forty three percent of patients (n= 87) had Hemoglobin of less than 8 g/dl. Comorbidities were present in 19.9 %. Previous attacks of hematemesis were found in (88.6%) of patients (n= 178) and previous attacks of melena were found in 56.7% (n= 114). Endoscopy showed grade 3 esophageal varices in 50.7% (n= 102). Band ligation was done to 48.9 % (n= 97), while 29.4 % (n= 59) received sclerotherapy. One hundred and twenty two patients (60.7%) recovered and discharged from the hospital after one day and 38.3% (n= 77) stayed for more than 2 days. Unfortunately 7 Patients expired (3.5%). The correlations between the occurrence of re-bleeding and the level of hemoglobin at presentation ($P= 0.014$), grade of the varices, chronicity of schistosomiasis ($P= 0.03$ for both) and hypertension ($P= 0.04$) were statistically significant. Smoking was significantly associated with risk of re-bleeding ($P=.05$). **Conclusion:** In patients with schistosomal portal hypertension, drop of hemoglobin at presentation, variceal grade, chronicity of schistosomiasis and hypertension, were predictors for the occurrence of variceal re-bleeding. Furthermore, smoking is a risk factor for re-bleeding.

Keywords: Schistosomal portal hypertension, variceal re-bleeding, predictors, risk factors.

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INTRODUCTION

Portal hypertension is a sustained elevation of portal pressure more than 12 mm Hg [1]. Schistosomiasis is a parasitic disease caused by blood flukes (trematode worms) of the genus *Schistosoma*. *Schistosoma mansoni* causes periportal fibrosis and it is the commonest cause of portal hypertension in Sudan. Variceal bleeding is the main complication of portal hypertension due to schistosomiasis occurring in about 30% to 40% of patients [2]. Outcomes are poor once variceal bleeding has occurred, therefore primary

prophylaxis is indicated. Because there is a high risk of recurrence after the initial hemorrhage preventive measurements are required.

Primary prophylaxis: Is the therapeutic intervention that aims at the prevention of first variceal hemorrhage. The recommended modalities are: beta blockers or endoscopic band ligation.

Secondary prophylaxis: Prevention of rebleeding from varices. It can be accomplished by: medical therapy (beta blockers), endoscopic therapy (band ligation,

sclerotherapy) or surgical treatment if the former measures failed (selective, non-selective shunts) [3].

PATIENTS AND METHODS

This is a descriptive, cross sectional, hospital based study, which was conducted in Ibn Sina Specialized hospital in Khartoum from July 2019 to January 2020. A number of 202 Patients diagnosed with variceal bleeding, due to schistosomal portal hypertension were included. An abstraction form was used for data collection. Analysis was done with SPSS version 21.

RESULTS

Characteristics of the study population:

The study composed of 201 patients had upper GI bleeding, majority of them were 51-60 years old, with a mean age of 52.15 ± 15.7 . Male to female ratio was 4:1. Age and gender showed no statistical significant to the recurrence of bleeding ($P= 0.9$, $P= 0.5$ for age and gender respectively). Most of the patients were from Gezira the rest were distributed among the other states (Table1).

Presentation

Both melena and hematemesis were the presenting symptom of 44.7% (n= 90) patients. The rest has either hematemesis or melena (Table 2).

Laboratory Results

Hemoglobin level at presentation: Only 13.4% of patients (n= 27) had (12-10) mg/dl, 43.3% of patients (n= 87) were between (7.9 – 5) (Table 2). Level of hemoglobin on admission was significantly associated with re-bleeding ($P= 0.014$) INR levels were as shown in (Table 2).

Management

Glypressin was given to 70.1% of the patients (n=141), 78 % of them (n=110) received 2 injections and 14.9% (n= 21) received 1 injection. Only 5.5% (n= 11) needed Sengestaken tube.

Moreover, (82.6%, n=166) of the patients received blood. Ninety eight patients (59%) required (2-4) units (Figure 1).

The number of transfused units of blood was statistically significant to the rebleeding ($P= 0.03$) (Table 3).

Endoscopic findings:

Patients underwent “OGD” which revealed the following:

Site of the varices: majority of the patients (76.6% n=154) had (OV), four patients had either (JV) or (FV), (10.9% n= 22) diagnosed with OV+ FV, while (5.5% n=11) had OV+JV. Anatomical site of the varices wasn't significant ($P= 0.8$).

Signs of bleeding: 70.1% of patients (n= 141) showed red sign, 18.4% (n= 37) had active bleeding (spurting) and the rest (n= 23) had no sign.

Grade of the varices: grade 3 was observed in 50.7% of patients (n= 102). The relation of variceal grade with the re-bleeding was statistically significant. ($P= 0.03$) (Table 3).

Endoscopic intervention

Regarding the methods of endoscopic therapy used to treat the bleeding, 48.3% of patients (n= 97) were treated by band ligation, 29.4% (n= 59) by sclerotherapy (Figure 2). The endoscopic method correlates significantly with the recurrence of melena ($P= 0.05$), on the opposite side, it was found to be not significant with the recurrence of hematemesis ($P= 0.08$).

The amount of Ethanolamine injected among those who were treated with sclerotherapy as the following: 69.4% (n= 43) received 10-20 ml, while 19.4% (n= 12) and 11.3% of the patients (n= 7) received (>20, <10 ml) respectively.

Duration of hospital stay

About two thirds of the patients (n= 122) were admitted for 1 day at hospital (figure3). The relation between the duration of hospital stay and the level of hemoglobin at presentation was highly significant ($P= 0.000$), while age of the patient and the method of endoscopic intervention didn't affect the period of hospitalization ($P= 0.9$ $P= 0.8$ for age and endoscopic method respectively) (Table 4).

Outcome of management:

When assessing the outcome of the management, 90% of the patients were discharged home (n= 181). While 7 patients died (Figure 4)

Among the patients who died, 3 patients died within 6-12 hours of admission, 3 died within 13-24hrs and one patient died less than 6 hours from arrival. Age of the patient had no effect on the outcome of management ($P= 0.2$).

Past history of bilharzia

When reviewing the duration of bilharziasis among the patients, majority of them (82.1% n= 150) had bilharziasis for more than 2 years. Chronicity of schistosomiasis was statistically significant ($p= .03$) in relation to recurrence of bleeding (Table 5).

Viral screening

Sixty eight percent of the patients had a negative viral screening, 18.9% did not do the test before, while 8.5% (n= 17) and 4% (n= 8) had positive test results for HBV and HCV respectively.

Previous attacks of bleeding

Most of the patients had a previous attack of hematemesis (88.6%, n=178), while 56.7% of them (n=114) had a previous attack of melena. Almost half of the patients had about 2-5 previous attacks. About third of them had the first attack 1-2 years ago (Table 6).

Beta blockers

Inderal was taken regularly only by 7 patients, their dose was 1 tab per day. The relation between taking a regular dose of Inderal and the re-bleeding was highly significant ($P=0.000$) (Table 5).

Splenectomy

Only 7.5% patients (n= 15) underwent splenectomy. The operation wasn't statistically significant ($P=0.5$).

Habits

Regarding social habits, 6.5% of patients (n =13) had history of alcohol consumption, while 7.5% (n= 15) were smokers. Smoking was significantly associated with risk of re-bleeding ($P=.05$).

Co-morbidities

On reviewing the co-morbidities, only 19.9% of patients (n= 48) had a co-morbid disease, 12.9% (n= 26) had HTN, 9% (n= 18) had DM. There was no recorded case of cancer. Diabetes, heart disease and renal disease were insignificant ($P= 0.7$ for each), while hypertensive patient had a significant risk of re-bleeding ($p=.04$) (Table 7).

Rockall score

Approximately, half of the patients (n= 94) scored 4, 21.4% (n= 43) their score was 5. A minority of 3% (n= 6) was observed to score either 8 or more (Figure 5).

Table 1: Demographic data of study population

		Number	Percentage%
Age "years"	<20-30	23	11.4
	31-40	27	13.4
	41-50	40	19.9
	51-60	48	23.9
	61-70	40	19.9
	>70	23	11.4
Gender	Males	158	78.6
	Females	43	21.4
Origin	Khartoum	32	15.9
	Jazeerah	85	42.3
	Kordofan	11	5.5
	White Nile	14	7.0
	Halfa	4	2.0
	Darfor	3	1.5
	Senar	7	3.5
	Others	45	22.4
N= 201			

Table 2: Clinical presentation and laboratory results of the study population

		Number	Percentage%	
Clinical Presentation	Hematemesis	65	32.2	
	Melena	46	22.8	
	Both	90	44.7	
Laboratory results	Hb % at presentation	>12	1	0.5
		12-10	27	13.4
		9.9-8	58	28.9
		7.9-5	87	43.3
		<5	28	13.9
	INR	<1	15	7.5
		1-2	178	88.6
		>2	8	4.0
	Serum creatinine	Normal	184	91.5
		High	17	8.5
N= 201				

Table 3: The relationship between rebleeding and study variables (endoscopic findings, duration of schistosomiasis and number of transfused units of blood)

Variable		Rebleeding		Number	R	P value
		Yes	NO			
Endoscopic findings	Oesophageal varices "OV"	85	69	154	1.404	0.844
	Junctional varices "JV"	4	3	7		
	Fundal varices "FV"	4	3	7		
	Both OV+FV	13	9	22		
	Both OV+JV	8	3	11		
Grade of oesophageal varices	Grade 1	0	2	2	4.390	0.036
	Grade 2	37	38	75		
	Grade 3	63	39	102		
	Grade 4	12	8	20		
	Not mention	2	0	2		
Number of units of blood transfused	< 2 unit	20	15	35	8.419	0.038
	2-4 units	54	44	98		
	5-7 units	22	7	29		
	>7 units	4	0	4		

*P value <0.05 is considered statistically significant.

Table 4: The relationship between duration of hospital stay and study variables (Hb at presentation, age and endoscopic interventions)

Variable		Duration of hospital stay			Number	R	P value
		1 day	2-3 days	>3 days			
Hb at presentation	>12	1	0	0	1	42.015	0.000
	12-10	25	2	0	27		
	9.9-8	42	14	2	58		
	7.9-5	46	38	1	85		
	<5	8	14	6	28		
Age	<20-30	14	8	1	23	3.369	0.992
	31-40	16	10	1	27		
	41-50	23	13	1	37		
	51-60	27	16	3	46		
	61-70	25	12	1	38		
	>70	12	8	2	22		
Endoscopic intervention	Sclerotherapy	41	15	2	58	11.959	0.063
	Band ligation	52	39	5	96		
	Both	0	3	0	3		
	None	29	11	2	42		

*P value <0.05 is considered statistically significant.

Table 5: The relationship between rebleeding and the study variables (duration of schistosomiasis and taking regular Inderal

Variable		Rebleeding		Number	R	P value
		Yes	NO			
Duration of schistosomiasis	< 6 months	4	1	5	4.720	0.030
	6-11 months	7	3	10		
	1-2 years	17	4	21		
	>2 years	150	15	165		
Inderal regularity	Yes	19	158	177	33.771	0.000
	No	15	7	22		

*P value <0.05 is considered statistically significant.

**r for Pearson chi square or likelihood ratio.

Table 6: History of previous attacks of hematemesis and melena

		Hematemesis		Melena	
		Number	Percentage %	Number	Percentage %
Patients who had previous attacks		178	88.6	114	56.7
Number of attacks	1	68	38.8	31	27.4
	2-5	87	43.3	65	57.5
	>5	23	12.9	17	15

N= 201

Table 7: The relationship between rebleeding and co-morbid diseases

Variable		Rebleeding		Number	R	P value
		Yes	NO			
Heart diseases	Yes	1	0	1	0.244	0.622
	No	177	23	200		
Liver diseases	Yes	2	0	2	0.489	0.485
	No	176	23	199		
Renal diseases	Yes	1	0	1	0.244	0.622
	No	177	23	200		
Diabetes mellitus	Yes	16	2	18	0.002	0.963
	No	162	21	183		
Hypertension	Yes	20	6	26	3.989	0.046
	No	158	17	175		

*P value <0.05 is considered statistically significant.

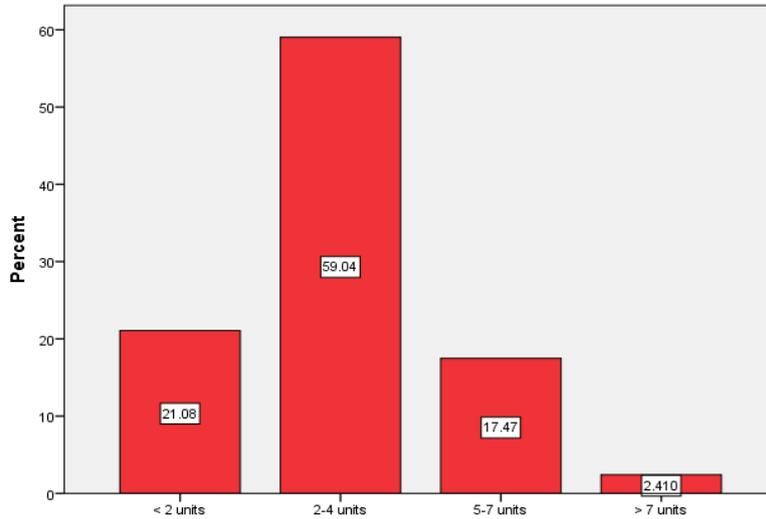


Figure 1: Number of transfused blood units on admission

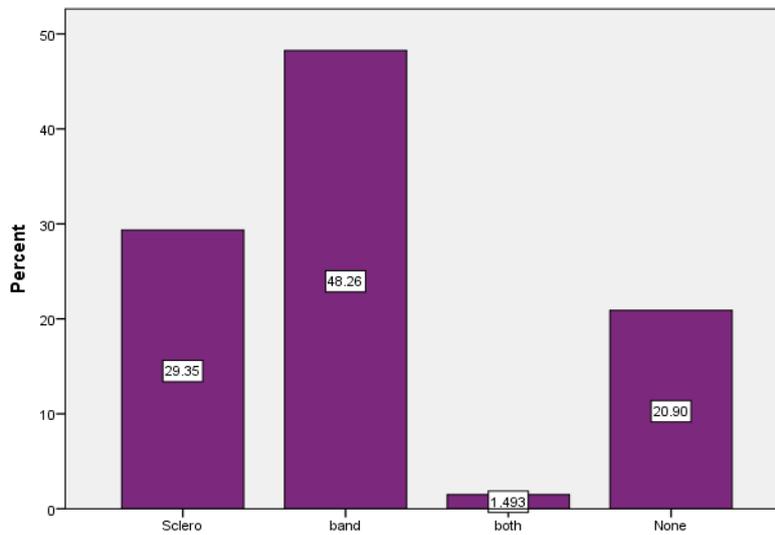


Figure 2: Methods of endoscopic intervention

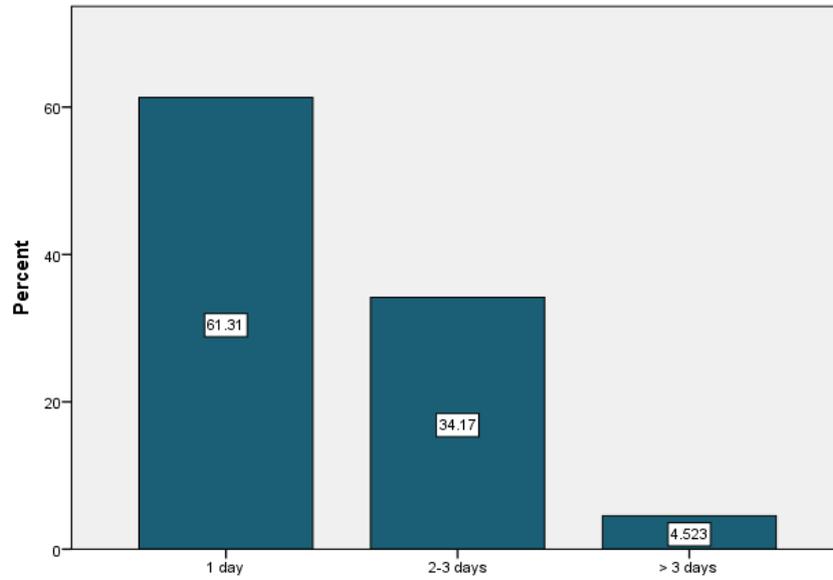


Figure 3: Duration of hospital stay

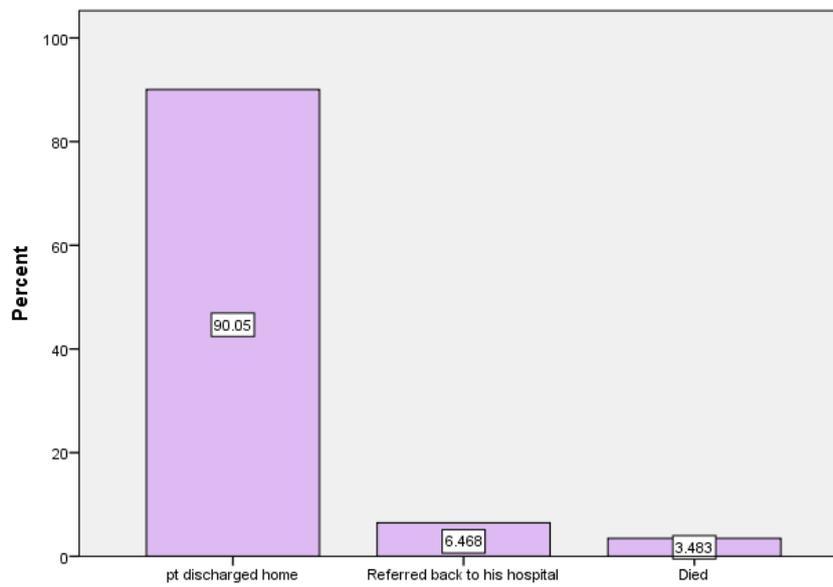


Figure 4: Outcome of management

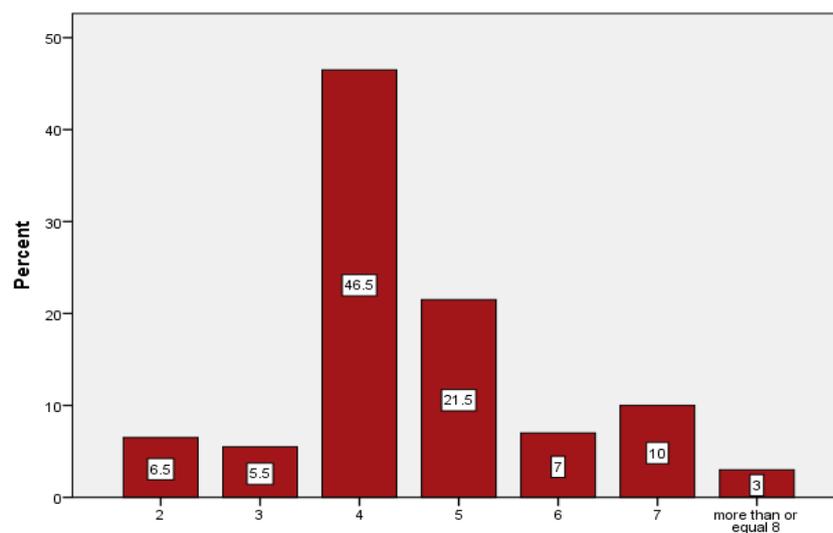


Figure 5: Rockall score of the patients

DISCUSSION

Bleeding varices is prevalent in Sudan where we have only one equipped center to receive emergency cases of GI bleeding. It is a life threatening condition which occurs secondary to schistosomal portal hypertension in the majority of our patients. There is a high risk of recurrence after the initial hemorrhage which carries a high mortality [4], therefore prognostic information to identify patients at risk who might be candidates for prophylactic treatment is of interest for these patients. A total of 201 patients were enrolled, the mean age was 52.15 ± 15.7 year. Male to female ratio was (4:1). Male predominance can be explained by their agricultural exposure. Age and sex weren't associated with a significant risk of re-bleeding ($p= 0.9$, $p= 0.5$ for age and gender respectively) these results build on existing evidence of Eltoun IA which showed that splenic longitudinal diameter of more than 11 cm, periportal fibrosis more than grade 1 were independently associated with a significant risk of bleeding. While age, sex, palpable liver and portal vein diameter were not associated with a significant risk of bleeding [5]. Most of the patients were from Gezira state accounting for 42% patients, which is an endemic area for schistosomiasis. Both hematemesis and melena were the presentation of 44.7% of them.

Based on the findings of a similar study by Fattahi E [6]. The data suggested that the requirement to transfuse more than 2 units of blood on admission and drop of hemoglobin at presentation were correlated to risk of re-bleeding which can be used as a prognostic indicator ($P= .04$, $P= .01$ respectively). Regarding transfusion strategy, Villanueva C study compared liberal strategy with a restrictive strategy, it was found that restrictive strategy is associated with a better outcome in patients with upper gastrointestinal bleeding. Therefore, current guidelines recommend initiating transfusion when Hb levels decrease to less than 7 g/dl, and the target level is 7 to 9 g/dl [7]. In our study, blood was provided to 82.6% of patients, 48.8% of them received more than 2 units which might be contributed to more mortality.

The anatomical site of the varices had no effect on the re-bleeding ($P= 0.8$) in contrast to the grade of varices ($P= 0.03$). Grade 3 was found in 50.7 % of the patients. The study demonstrated a correlation between grade of the varices and the risk of re-bleeding, patient who had a large varices were at higher risk. The pathogenesis is related to the high variceal pressure which is an attractive parameter to assess the risk of re-bleeding. According to D'Amico G and Luca A the risk can be reduced by decreasing variceal pressure [8]. Fortunately, a variceal hemorrhage is better tolerated in non-cirrhotic portal hypertensive patients than in cirrhotics, but measuring the variceal pressure is a major prognostic parameter in both categories as mentioned by EL Atti E [9].

Band ligation was the commonest endoscopic therapy used in 48.3% of the patients. A study conducted in Greece showed that the efficacy of band ligation was clearly increased by adding beta blockers. This combination was suggested as the first-line treatment for the prevention of rebleeding [10]. Although sclerotherapy is no longer recommended as standard treatment for acute bleeding as stated by Seo Y because of higher incidence of treatment failure, mortality, and adverse effects compared to band ligation [11], yet 29.4% of the patients in this study received sclerosing agents. Xue H suggested that early use of TIPS is more effective than endoscopic treatment in preventing variceal rebleeding and improving survival rate [12]. None of the studied patients was offered the procedure.

Another significant finding was most of the patients had bilharziasis for more than 2 years. In line with Ibrahim SZ [13] patients with longer duration of the disease were at higher risk of re-bleeding ($P= 0.03$). This emphasizes the importance of putting patients of bilharziasis on endoscopic surveillance, as these patients has difficulties in reaching the endoscopy center and many of them die before reaching the hospital. Unfortunately, in this study 3 patients died within hours of arrival.

HBsAg seroprevalance among our studied patients was 8.5%, which was higher than Mohammed S study results in patients with schistosomal portal hypertension (6%) [14] and the seroprevalance of HBsAg among the general population of central Sudan (6.8%) [15]. Moreover, Hepatitis C virus showed a seroprevalance of 4%, similar to the reported prevalence of the virus among the general population of Sudan [15]. The study pointed an increase of the hepatitis virus infection. Hence, viral screening and immunization program should be extended among patients with periportal fibrosis.

Most of the patients had multiple previous attacks of hematemesis or melena or both, their first attack was 1-2 years ago, during this period 57.5% had a number of two to five attacks which indicated short intervals between hospital admissions.

Beta blockers reduce portal pressure by causing splanchnic vasoconstriction, they are recommended for primary and secondary prophylaxis against variceal bleeding [11]. Our study indicated a significant decrease in risk of re-bleeding among patients who took the drug regularly ($P= 0.000$). In a study that compared the efficacy of beta blockers with that of endoscopic band ligation in preventing the recurrence of variceal bleeding in patients with non-cirrhotic portal hypertension, it was found that beta blockers are as effective as endoscopic variceal band ligation in the secondary prevention of variceal bleeding in these patients [16].

The study provided a new insight into the relation between risk of rebleeding and smoking ($P=0.05$). No study was found to compare the results.

The results contradicted the study of C Lacet [2] which concluded that combined surgical and endoscopic treatment was more effective for the prevention of recurrent variceal bleeding. Our study showed no difference between the patients who underwent splenectomy and the patients who didn't ($P=0.5$).

In this study, patients with comorbidities had a higher Rockall score. Dewan K concluded that there were significant correlations between high Rockall scores (>5) and the occurrence of rebleeding ($p=0.001$) [17], However, our study indicated that only hypertension significantly affected the re-bleeding ($P=0.04$), these results should be taken into account when considering secondary prophylaxis for hypertensive patients.

The data contributed a clearer understanding to Baveno criteria and definitions of a significant re-bleeding [18], the study demonstrated a correlation between the level of hemoglobin at presentation and the duration of hospital stay ($P=0.000$), patients with low levels of hemoglobin stayed for longer period than patients with a near normal levels. In contrary to age of the patient ($P=0.9$) and the modality of endoscopic therapy ($P=0.8$) had no significant difference on the hospitalization period.

CONCLUSION

- Age of the patient doesn't affect the risk of re-bleeding.
- Drop of hemoglobin on admission and the required number of blood units can predict re-bleeding.
- Chronicity of bilharziasis affects the occurrence of re-bleeding.
- Re-bleeding can be predicted endoscopically by: signs of bleeding and grade of the varix.
- Beta blockers play a major role in decreasing the risk of recurrent bleeding, patients should take the drug constantly.
- Smoking and hypertension are risk factors of re-bleeding.
- Hemodynamic stability at presentation provides information about the duration of hospital stay and the re-bleeding risk.

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