JPSIM Journal of Pakistan Society of Internal Medicine QR

Original Article

Frequency of Gastroesophageal Variceal Bleeding in Cirrhotic Patients with and without Diabetes

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Abstract

Objective: The objectives were to establish the frequency of diabetes in cirrhotic patients presenting at Services Hospital Lahore and to compare the frequency of GEVB in cirrhotic patients with and without diabetes.

Methods: It was a cross-sectional study, conducted at Department of Medicine Unit-III, Services Hospital, Lahore from 22/12/2016 to 21/06/2017. This study involved 134 patients of both genders aged between 25-65 years diagnosed of cirrhosis at least a year ago. These patients were assessed for the presence of diabetes and gastroesophageal variceal bleed. Frequency of GEVB was compared among cirrhotic patients with and without diabetes.

Results: Mean age of the patients was 53.51±8.53 years, and majority were aged between 51-65 years (61.2%) and 35-50 years (38.8%). There were 80 (59.7%) male and 54 (40.3%) female patients in the study group with a male to female ratio of 1.5:1. The mean duration of cirrhosis was 23.73±10.24 months. 48 (35.8%) patients had Hepatitis B while 86 (64.2%) patients had Hepatitis C on viral serology. Diabetes was diagnosed in 46 (34.3%) patients with cirrhosis. We observed no significant difference in the frequency of diabetes according to age (p=0.751), gender (p=0.842), duration of disease (p=0.864) and serological (p=0.856) groups. Gastroesophageal variceal bleeding was seen in 20 (14.9%) patients with significantly high frequency with diabetes (28.3% vs. 8.0%; p=0.002) as compared to without. Similar significant difference was observed across all age, gender, duration of disease and serological groups.

Conclusion: The frequency of diabetes was 34.3% among cirrhotic patients and of gastroesophageal variceal bleeding was significantly higher among them with diabetes (28.3% vs. 8.0%; p=0.002) as compared to those without regardless of age, gender, duration of cirrhosis and viral serology.

Keywords: Cirrhosis, Diabetes, Gastroesophageal Variceal Bleeding.

How to cite this:

Mushtaq HI, Nadeem MA, Sarwar T, Afzal MN, Sarwar S. Frequency of Gastroesophageal Variceal Bleeding in Cirrhotic Patients with and without Diabetes. J Pak Soc Intern Med. 2020;1(1):60-66.

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Introduction

Cirrhosis is the end result of all chronic liver diseases. These patients are at high risk of developing many potential life-threatening complications. Patients with liver cirrhosis are at risk of developing many potential life-threatening complications.[1-3] Ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE),

and gastroesophageal variceal bleeding (GEVB) are related to portal hypertension. Of these complications, gastroesophageal variceal bleeding (GEVB) is most critical event leading to highest risk of mortality.[1,3] Various factors may predict outcome of variceal bleed. Gastro-esophageal varices are present in about 60% of patients with cirrhosis; bleeding occurs in >30% of patients and account for 85% of bleeding episodes in them.[2-5] Hepatic venous pressure gradient (HVPG) >20 mmHg is associated with early re-bleed and failure to control bleeding (83%) with high mortality (64%).[1-3] Various factors may predict outcome of variceal bleed like age, sex, stage of cirrhosis, etiology of the disease, associated conditions of renal disease, hepatocellular carcinoma, and diabetes mellitus (DM). Diabetes with insulin resistance is common happening in cirrhosis and prevalence of diabetes is up to 30% in these patients.[1-3] This resistance increases with the severity of liver disease and degree of fibrosis. The Verona Diabetes Study in patients with type 2 DM, found higher risk of death in cirrhotic patients as compared to general population not only due diabetic complications of but also to an increased risk of hepatocellular failure.[1,2] Recently, insulin resistance, has been established as a strong predictor of portal hypertension and varices.[1-3] Hyperglycemia leads to splanchnic hyperemia, increases portal pressure, and thus increase the risk of variceal bleeding.[1-6] There is lack of data related to effect of diabetes mellitus on complications of liver cirrhosis locally and internationally with only 3 international studies available.[1-6] Majid et al. found association of diabetes mellitus with failure to control bleeding on multivariate logistic regression analysis.[3] It was also associated with in-hospital re-bleed. 65.3% patient with diabetes had GEVB compared to 34.8% patients without diabetes.[3] A Korean study revealed that patients with DM had significantly higher ratio of Child-Pugh Class B/C ($p = 0.043$), renal insufficiency ($p = 0.002$), and history of GEVB ($p = 0.006$) compared with non-DM patients.[4] However, in contrast to study by Majid et al. the frequency of GEVB in diabetic patients was 32% versus 12% in non-diabetics. Study by Jeon et al. calculated frequency of GEVB in diabetics and non-diabetics to be 25.6% and 10.8% respectively.[6] The studies report a wide range of results and the data is inconclusive. The study would be a valuable contribution to the limited data on implicating diabetes in pathogenesis of a specific complication both of which are a major public health burden in Pakistan with more than 10 million people having chronic liver disease and about 10 million diabetic patients. Given the issues with the cited studies as well as scarcity of data, this study was carried out at a large tertiary care center with adequate sample size thus reducing bias.

Materials and Methods

It was a prospective study, conducted in Gastro-enterology Unit, Services Hospital Lahore from 22/12/2016 to 21/06/2017. Patients were selected by Non-Probability, Consecutive Sampling, and sample size of 134 cases was calculated with 95% confidence interval and 8% margin of error while taking expected frequency of diabetes to be 30.0% in patients with cirrhosis.[2]

Inclusion Criteria:

Patients of both genders aged between 25-65 years having liver cirrhosis (as per operational definition) diagnosed at least 1 year ago.

Exclusion Criteria:

Patients with hepatocellular carcinoma, severe septicemia with compromised hemodynamic status (i.e., Lactic acidosis, SBP <90 SBP Drop >40, WBC > 12,000/mm^3, <4,000/mm^3, hepatorenal syndrome, acute superimposed liver injury, advanced cardiac or pulmonary disease and end stage renal failure i.e., GFR <15 assessed from clinical examination and previous medical record.

Data Collection Procedures

One hundred and thirty-four patients of liver cirrhosis who met the inclusion and exclusion criteria were enrolled after informed consent from outdoor, indoor, and emergency department. Five ml of venous blood was drawn after an overnight fast and fasting blood glucose level was acquired. Diabetes was labeled as per operational definition. Chronic hepatitis B and C

status was assessed from previous records if available or from fresh results of enzyme-linked immunosorbent assay (ELISA). Gastroesophageal variceal hemorrhage was confirmed on endoscopy on very next day after initial management of the patient. Patients were labeled as having GEVB if there was bleeding from an esophageal or gastric varix. Biodata was entered in a predesigned structured proforma.

Data Analysis Procedure:

All the collected data was entered and analyzed through SPSS version 20.

1. Numerical variables i-e age had been presented by mean ±SD.
2. Qualitative variables i-e gender, diabetes, and presence of GEVB presented as frequency and percentage.
3. Frequency of GEVB was compared in patients with and without diabetes using chi-square test taking $p \leq 0.05$ as significant
4. Data were stratified for age, gender, HBV/HCV and duration of cirrhosis to address effect modifiers. Post-stratification chi-square test was applied taking $p \leq 0.05$ as significant.

Results

The age of the patients was 35 - 65 years with a mean of 53.51±8.53 years. Most of the patients were between 51-65 years (61.2%) and 35-50 years (38.8%). There were 80 (59.7%) male and 54 (40.3%) female patients in the study group having male to female ratio of 1.5:1. The cirrhosis was diagnosed 12 - 48 months previously with a mean of 23.73±10.24 months, while 48 (35.8%) patients had Hepatitis B while 86 (64.2%) patients had Hepatitis C on viral serology. Diabetes was present in 46 (34.3%) patients with cirrhosis. There was no significant difference in the presence of diabetes according to age (p=0.751), gender (p=0.842), duration of disease (p=0.864) and serological (p=0.856) groups respectively **(Table-1)**. Gastroesophageal variceal bleeding was encountered in 20 (14.9%) patients. The frequency of GEVB was significantly higher in cirrhotic patients with diabetes (28.3% vs. 8.0%; p=0.002) as compared to without diabetes **(Table 2).** Similar significant difference was also observed according to age, gender, duration of disease and serological groups **(Tables 1-2)** respectively.

Table-1: Comparison of frequency of diabetes across age, gender, duration of diabetes and viral serology groups n=134.

		Diabetes			
		Yes (n=46)	No (n=88	Total	p-Value
Age Groups	35-50 Years (n=52)	17 (32.7%)	35 (67.3%)	52 (100.0%)	0.751
	51-65 Years (n=82)	29 (35.4%)	53 (64.6%)	82 (100.0%)	
Gender	Male	28 (35%)	52 (65%)	80	0.842
	Female	18 (33.3%)	36 (66.7%)	54	
Duration of Disease	<2 Years	27 (33.8%)	53 (66.7%)	80	0.864
	2-4 Years	19 (35.2%)	35 (64.8%)	54	
Viral Serology	Hepatitis B	16 (33.3%)	32 (66.7%)	48	0.856
	Hepatitis C	30 (34.9%)	56 (65.1%)	86	
	Total	46 (34.3%)	88 (67.7%)	134 (100%)	

Table-2: Comparison of frequency of GEVB across diabetic status, age groups and duration of diabetes n=134.

			Diabetes			
			Yes (n=46)	No (n=88	Total	p-Value
Age Groups	35-50 Years (n=52)	Yes	5 (29.4%)	2 (5.7%)	7 (13.7%)	

		No	12 (70.6%)	33 (94.3%)	45 (86.5%)	0.7019*
		Total	17 (100.0%)	35 (100.0%)	52 (100.0%)	
	51-65 Years (n=82)	Yes	8 (27.6%)	5 (9.8%)	13 (15.9%)	
		No	21 (72.4%)	48 (90.6%)	69 (84.1%)	0.031*
		Total	29 (100.0%)	53 (100.0%)	82 (100.0%)	
Gender	Male (n=80)	Yes	8 (28.5%)	5 (9.5%)	13 (16.3%)	
		No	20 (71.4%)	47 (9065.1%)	67 (83.7%)	0.028*
		Total	28 (100.0%)	52 (100.0%)	80 (100%)	
	Female (n=54)	Yes	5 (27.8%)	2 (5.6%)	7 (13%)	
		No	13 (72.2%)	34 (94.4%)	47 (87%)	0.022*
		Total	18 (100.0%)	36 (100.0%)	54 (100.0%)	
Duration of Diabetes	<2 years (n=80)	Yes	7 (25.9%)	4 (7.5%)	11 (13.8%)	
		No	20 (74.1%)	49 (92.5%)	69 (86.2%)	0.024*
		Total	27 (100.0%)	53 (100.0%)	80 (100.0%)	
	2.4 years (n=54)	Yes	6 (31.6%)	3 (8.6%)	89 (16.7%)	
		No	13 (68.4%)	32 (91.4%)	45 (83.3%)	0.030*
		Total	19 (100.0%)	35 (100.0%)	54 (100%)	

Table-3: Existing Literature on Association between DM and GEVB in Cirrhosis.

Author	Year	Population	GEVB		p-Value
			With DM	Without DM	
Kwon et al.[8]	2003	Korean	15.5%	208%	>0.05
Majid et al.[3]	2009	Pakistan	65.3%	34.8%	0.001
Quintana et al.[11]	2011	Mexican	15.0%	25.0%	0.48
Jeon et al.[5]	2013	korean	25.6%	10.8%	<.005
Ennaifer et al.[14]	2014	Tunisian	36.5%	33.3%	0.78
Yang et al.[4]	2014	Taiwanese	32.0%	12.0%	0.006
Khafaga et al.[19]	2015	Egyptian	46.4%	10.0%	0.003
Present Study	2017	Pakistan	28.3%	8.0%	0.002

Discussion

In cirrhosis various factors are predictors of outcome of variceal bleed. Recent literature claimed diabetes to be a frequent metabolic abnormality in cirrhotic patients and proposed it to be associated with increased frequency of variceal bleed in such patients.[3-6] However, the available evidence was limited and contained controversy, and also revealed prevalence of diabetes in these patients from 21% to 45% while we observed it as 34.3%).[2,4,7-18] Moreover, this is new collected data and was not available

previously in Pakistan and was aimed to determine the frequency of diabetes in cirrhotic patients to compare the frequency of GEVB in cirrhotic patients with and without diabetes. This study involved 134 patients of both genders aged between 25-65 years diagnosed of cirrhosis at least a year ago. These patients were assessed for the presence of diabetes and gastroesophageal variceal bleed. Frequency of GEVB was compared among cirrhotic patients with and without diabetes.

In the present study, the mean age of the patients was 53.51±8.53 years. Almani et al. (2008) reported similar mean age of 53.09±8.86 years at Hyderabad while Ali et al. (2008) reported similarly mean age of 52±9 years Mirpurkhas. Achakzai et al. in 2016 (54±11 years) and Hussain et al. in 2014 (51.12±6.03 years) also reported similar mean age among cirrhotic patients in local population.[20-24] Penteado et al. reported similar mean age of 51.4±7.6 years among Brazilian such patients. Mansour-Ghanaei et al. (2012) also observed similar mean age of 55.03±12.05 years in Iranian such patients.[24-25] Tariq et al. in 2015 reported much younger mean age of 41.1±6.1 years among such patients presenting at Civil Hospital, Karachi. [26] Bhattacharyya et al. (2016) and Deepika et al. (2015) also reported similar younger mean age of 45.8±10.45 and 44±13.7 years in Indian patients of liver cirrhosis, respectively.[27-28] Mousa et al. (2016) reported similar younger mean age of 45.6±11.3 years among Sudanese such patients while Anastasiou et al. (2015) reported much lower mean age of 40.4±1.7 years among such patients in Germany.[29-30] There were 80 (59.7%) male and 54 (40.3%) female patients in our study with a male to female ratio of 1.5:1. A similar male predominance among has been reported previously by Ali et al. as 1.5:1 in local population.[21] Abdel-Fattah El-Feki et al. (2016) reported similar male to female ratio of 1.5:1 among Egyptian such patients. [31] Mansour-Ghanaei et al. (2012) reported male to female ratio of 1.9:1 among Iranian such patients.[25] Achakzai et al. (2016) however observed a female predominance among such patients presenting in Karachi with a ratio of 1:1.5. [22] We had 48 (35.8%) patients with Hepatitis B while 86 (64.2%) patients had Hepatitis C on viral serology. Bhattacharyya et al. (2016) observed similar frequency of Hepatitis B (32.1%) and Hepatitis C (67.9%) in Indian patients with liver cirrhosis while El-Kabbany et al. (2012) reported the frequency of Hepatitis B and Hepatitis C to be 25.06% and 74.94% in Egyptian such patients.[32]

Diabetes was diagnosed in 46 (34.3%) patients with cirrhosis. Our results are similar to those of Arshad et al. (2016) who reported similar frequency of 33.5% for diabetes among cirrhotic patients presenting at Medical Unit III, Services Hospital Lahore. Similar frequency of 31.5% and 36.1% has also been reported by Memon et al. (2013) and Saleem et al. (2013) respectively in local population.[12-13,18]

The frequency of GEVB was significantly higher in cirrhotic patients with diabetes (28.3% vs. 8.0%; p=0.002) as compared to without diabetes. Our results are in line with those of Jeon et al. (2013) who also reported similar increased frequency of GEVB among Korean cirrhotic patients with diabetes (25.6% vs. 10.8%; p<.005) as compared to without diabetes. [5] Yang et al. (2014) also observed similar significant difference in Taiwanese cirrhotic patients with and without (32.0% vs. 12.0%; p=0.006). [4] Our results also support the observation made by Majid et al. (2009) who reported significantly higher frequency of gastroesophageal variceal-rebleed in local cirrhotic population with and without diabetes (65.3% vs. 34.8%; p=0.001).[3]

The present study is first of its kind in local population and had found that presence of diabetes is associated with significantly higher frequency of gastroesophageal variceal bleeding in cirrhotic patients independent of patient's age, gender, duration of disease and viral serology. Thus, it can be advocated in the light of results of the present study that patients presenting with cirrhosis should be screened for diabetes and positive cases should be taken as high risk for GEVB in future practice. Anticipated management in such patients may decrease the morbidity and mortality related to gastroesophageal variceal bleeding **(Table -3)**.

A very important limitation was that we didn't consider the effect of diabetic control on GEVB among such patients. Such a study would further help in the management of such patients and is recommended in future.

Conclusion

The frequency of diabetes was 34.3% among cirrhotic patients and of gastroesophageal variceal bleeding was significantly higher among cirrhotic patients with diabetes (28.3% vs. 8.0%; p=0.002) as compared to those without diabetes regardless of patient's age, gender, duration of cirrhosis and viral serology.

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