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ORIGINAL ARTICLE

Complications associated with HCV-related liver cirrhosis and their relationship with diabetic control. A tertiary care center study in Peshawar, Pakistan.

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ABSTRACT… Objective: To determine the frequencies of liver cirrhosis-associated complications in patients with HCV+ diabetic patients and its association with HbA1C. **Study Design:** Observational Cross-sectional study. **Setting:** Medical Wards of Khyber Teaching Hospital. **Period:** October 2019 to November 2020. **Methods:** After approval from the hospital ethical committee, all HCV positive diabetic patients were enrolled in the study. Informed consent was obtained and relevant examination was performed. Hematemesis was diagnosed clinically, while venous blood was sent for all routine and relevant specialized investigations. Twenty-four-hour urinary output was calculated. Abdominal ultrasounds and Triphasic CT abdomen were done where required. Data were collected on structurally designed proforma. All data were entered into SPSS version 22. **Results:** A total of 62 patients were enrolled. The mean age was 49. 23 years ± 11.72 SD. Twenty-three patients (37.1%) were males, while 39 patients (62.9%) were females. Forty-nine patients (79%) were PCR-positive for HCV. Most patients (58.1%) had less than five years duration of HCV. Frequency of SBP was 16.1%, hepatic encephalopathy was 22.6%, ascites was 40.3%, hematemesis was 11.3%, portal vein hypertension was 45.2%, and HCC 3.2%. On post-stratification, significant associations emerged with age, where SBP ($p < 0.01$), hepatic encephalopathy ($p<0.001$), and ascites ($p<0.0001$), increased with advancing age, while hematemesis ($p<0.04$) and portal vein hypertension ($p<0.04$) were more pronounced in younger patients. **Conclusion:** In conclusion, individuals with both chronic HCV and diabetes mellitus exhibit an increased risk of cirrhosis-related complications. The most common complication was portal vein hypertension followed by ascites and hepatic encephalopathy. The complications like SBP, Hepatic encephalopathy and ascites associated with increasing age.

Keys words: Cirrhosis-related Complications, Glycemic Control, HCV, HbA1c.

INTRODUCTION

Hepatitis C and Type 2 diabetes (T2D) are widely distributed across the globe. Among the etiologies of chronic liver disease, the hepatitis C virus (HCV) is one of the most important causes of serious complications, including cirrhosis and cancer of the liver. Current statistics indicate that hepatitis C infects more than 185 million people around the globe, while 347 million people have diabetes mellitus (DM).[1-3]

Diabetes mellitus is a chronic disease characterized by either a relative or complete deficiency of insulin, resulting in type 2 DM or type 1 DM, respectively.[4] There is a 4–6-fold higher prevalence of DM in South Asians compared to European individuals.[5] The burden of DM in Pakistan ranges from 3% to 7.2% in the general population, according to a systemic review and meta-analysis from South Asia by Jayawardena et al.[6]

Cirrhosis is a chronic liver injury resulting in the histological development of regenerative nodules, causing portal hypertension and end-stage liver disease.[7] Chronic hepatitis C and its complications are significant public health issues, particularly cirrhosis and hepatocellular carcinoma, which are important causes of mortality.[8] The most frequent complications of

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cirrhosis are hepatic encephalopathy, gastro-oesophageal variceal bleeding (GEVB), spontaneous bacterial peritonitis (SBP), and ascites related to portal hypertension.[9] There is a 4% rate of decompensation annually for HCV-related cirrhosis.[7]

The co-existence of diabetes and cirrhosis is a much more threatening condition than any of these conditions individually, and studies across the globe have shown that this combination is associated with an increased incidence of cirrhosis complications, hospitalizations, and reduced survival.[10] The presence of DM can either enhance the fibrosis of the liver or accelerate the decline in liver functions, leading to liver failure.[11] The incidence of conditions characterizing decompensated cirrhosis like spontaneous bacterial peritonitis, ascites, hepatic encephalopathy, hepato-renal syndrome, hepatocellular carcinoma, bleeding from esophageal varices, and death is high in diabetic chronic hepatitis C patients.[12] In studies done by Saeed MJ et al., Gundling F et al., Arshad MF et al., Sigal SH et al., Butt Z et al., and Jepsen P et al., it was found that patients having diabetes and cirrhosis secondary to HCV have more frequent and severe hepatic encephalopathy than when compared with patients having only cirrhosis secondary to HCV but no diabetes.[12-17] In a study by Yang C-H et al., the presence of diabetes mellitus was associated with a higher class of Child-Pugh Class B/C than with patients with no diabetes.[9]

The transit time for the gastrointestinal tract is prolonged in diabetes, so it can be assumed that cirrhosis caused by HCV may precipitate and worsen hepatic encephalopathy.[15] The chances of infections such as bacterial peritonitis are raised by diabetes and cirrhosis, which are secondary to HCV.[18,19] Furthermore, mortality may be increased by infections such as SBP, which have a high incidence in DM.[20,21] The incidence of portal hypertensive upper gastrointestinal bleeds is increased in patients with both cirrhosis and diabetes when compared with patients who had cirrhosis due to HCV but no DM.[9,11] The incidence of portal hypertension and variceal bleeding has been shown to be positively correlated in patients with insulin resistance and diabetes.[22] Epidemiological data shows that DM2 increases the incidence of developing HCC.[23] Nadelson J et al. reported that the degree of glycemic control is related to complications of cirrhosis, and it was found that for the development of HCC, HBA1c was a strong independent factor. These findings can be extrapolated to show that good glycemic control can lead to a lower risk of HCC in patients with cirrhosis and DM.[24] Hepato-renal syndrome, acute tubular necrosis, and hypovolemia-induced pre-renal acute kidney injury are essential causes of renal diseases in cirrhosis patients.[25] Among them, hepatorenal syndrome is the most aggressive disease with a poor prognosis typically ranging from weeks to months.[26,27] It is a functional disease of the kidneys and is due to marked vasoconstriction of renal arteries caused by uncontrolled circulatory and neurohormonal changes due to underlying cirrhosis.[28] The aim of this study is to determine the frequency of hepatic decompensation in diabetic cirrhosis and its association with glycemic control.

METHODS

The study is an observational cross-sectional study. Study approval was taken from the Hospital Ethics Committee (Ref No: 969/ADR/KMC). After informed consent, data were collected from PCR or Elisa detected HCV+ patients having diabetes and cirrhosis admitted to the Medical Ward with any of the complications of cirrhosis. West Haven Criteria determined the presence of hepatic encephalopathy. Spontaneous bacterial peritonitis was diagnosed by a polymorph nuclear cell count of more than 250 per mm^{-3}. Laboratory investigations were carried out to look for complications like hepato-renal syndrome, deranged coagulation profile, and abnormal liver's abnormal synthetic and metabolic functions. Radiological examinations were carried out to look for portal hypertension using portal vein diameter as a marker. Hepatocellular carcinoma as a complication of cirrhosis was diagnosed either using a Triphasic CT Scan alone or a combination of ultrasound scan evidence of hepatocellular carcinoma and Alpha-fetoprotein levels. The variceal bleed in Hematemesis was

determined by taking an appropriate history from patients where possible or caretakers and upper gastrointestinal tract endoscopy. Also, data were collected regarding previous admissions for hepatic decompensation and the specific complications that triggered entry by looking at previous discharge cards or appropriate history. The duration of diabetes mellitus and the type of medicine used for glycemic control were also recorded.

Inclusion & Exclusion Criteria

Only those patients having both Hepatitis C and diabetes were included in the study. The lower age limit was 20, and the upper limit was 80. Both genders were included in the study. Patients having other coexistent liver pathologies like Hepatitis B, Alcoholic hepatitis, or Autoimmune hepatitis were excluded from the study. Patients having any malignancy other than hepatocellular carcinoma were also excluded to avoid any confusion regarding the presence of hepatocellular carcinoma as to whether it was a metastatic or primary liver malignancy.

Statistical Analysis

All the results were presented as tables and graphs. Every piece of information gathered from patients was entered into a SPSS. Frequency and percentage of all values was given. Chi square and Fisher exact test were used for association of hepatitis complication with age, gender, duration of diabetes and HCV. A p-value of lesser than 0.05 was considered significant. The analysis of the data was done with SPSS 22.

RESULTS

A total of 62 HCV+ diabetic patients were included. Among these 62 HCV+ diabetic patients, 23 (37.1%) were males, while 39 (62.9%) were females. The mean age of the patients was 49.23 years ± 11.72 SD. Based on age, patients were divided into three groups, 13 (21%) of them aged less than 40, 38 (61.3%) of them aged between 40 and 60 years, and 11 (17.7%) of them aged greater than 60 [Table-I]. 24-hour urinary output of 9 patients (14.5%) ranged from 450 - 1500ml, with 2 patients (3.2%) having a lower output and 51 patients (82.3%) having a higher output. 29 patients (46.8%) had no history of hospitalization, 20 patients (32.3%) had previously been hospitalized 1 - 2 times, 7 patients (11.3%) 2 - 4 times, and 6 patients (9.7%) greater than 4 times. [Table-I]. The reasons for hospitalization varied from SBP (17.7%), Ascites (19.4%), Hepatic Encephalopathy (6.5%), and Hematemesis (9.7%) [Table-I].

Parameters		f	%
Age (years)	18-30	5	8.1
	30-50	34	54.8
	50-70	23	37.1
Gender	Male	23	37.1
	Female	39	62.9
Duration of HCV	Newly diagnosed	2	3.2
	1-5 years	36	58.1
	5-10 years	21	33.9
	10-20 years	3	4.8
Duration of diabetes	Newly diagnosed	5	8.1
	5 years	25	40.3
	5-10 years	23	37.1
	10-20 years	7	11.3
	More than 20 years	2	3.2
Antidiabetic	Oral	37	59.7
	Insulin	25	40.3
No of previous admission for cirrhosis complication	No previous admission	29	46.8
	1-2 admissions	20	32.3
	2-4 admissions	7	11.3
	More than 4 admissions	6	9.7
Urine output in 24 hours at 1st day	Less than 450 ml	2	3.2
	450-1500ml	9	14.5
	More than 1500ml	51	82.3
Urine output in 24 hours in 48 hours	450-1500ml	8	12.9
	More than 1500ml	54	87.1
Reason for admission	No previous admission	29	46.8
	SBP	11	17.7
	Ascites	12	19.4
	Hepatic encephalopathy	4	6.5
	Hematemesis	6	9.7

Table-I. Demographics of subjects with BMI, HbA1c and lipid profile

HCV, Hepatitis-C Virus

Only 4 patients (6.5%) had a serum creatinine level ranging from 2 - 4 mg/dl, while 50 patients (90.3%) had a value lower and only 2 patients (3.2%) with a value higher. Serum Albumin of 25 patients (40.3%) was less than 2.5 mg/dl, ranged

from 2.5 - 3.5 mg/dl in 28 patients (45.2%), and was greater than 3.5 mg/dl in 9 patients (14.5%) [Table-II]. These patients also had their serum bilirubin, PT, INR, RFTs, and 24 urinary output investigated. 58 patients (93.5%) had their serum bilirubin levels less than 2 mg/dl, 3 patients (4.8%) within 2-4 mg/dl, and only 1 patient (1.6%) with a higher value. The PT for 16 patients (25.8%) ranged within 16 - 25 seconds, with 44 (71%) having a lower value and 2 (3.2%) having a higher value than this range. INR values varied from up to 1.1 in 52 patients (83.9%), 2 - 3 in 6 patients (9.7%) and 3 - 5 in 4 patients (6.5%). HbA1c for these patients was also recorded, with 12 patients (19.4%) having a value of less than 6%, 29 patients (46.8%) within 6 - 8%, and 21 patients (33.9%) having greater than 8% [Table-II]. 13 (21%) of these patients tested positive for HCV on Elisa, while the remaining 49 tested positive on HCV and PCR. The ultrasound findings for liver, spleen and kidneys were also evaluated. 22 patients (35.5%) were normal, 29 patients (46.8%) had a shrunken liver only, 5 patients (8.1%) reported with shrunken liver and spleen, while 6 (9.7%) were found to have enlarged liver and spleen. 58 patients (93.5%) had normal kidneys, while 4 patients (6.5%) had small-sized kidneys. 34 patients (54.8%) had a portal vein diameter less than 12 mm, while the remaining 28 (45.2%) had a diameter greater than 12 mm. Serum alpha-fetoprotein was raised in 6 patients 9.7%. HCC was diagnosed in 2 patients (3.2%) on ultrasound and confirmed by triphasic CT abdomen [Table-II].

RFTs, Renal function tests; INR, International Normalized Ratio; USG, Ultrasound; HCC, Hepatocellular Carcinoma; HbA1c, Glycated haemoglobin

The most common complication was portal vein hypertension (54.8%), followed by ascites (40.3%), hepatic encephalopathy (22.6%), SBP (16.1%), hematemesis (11.3%) and HCC (3.2%) [Table-III].

These complications were stratified among age, gender, duration of diabetes, HbA1C level, and duration of HCV to see effect modification. Post-stratification chi-square test was applied, keeping p-value <0.05 as statistically significant. In our study, SBP (p = 0.01), hepatic encephalopathy (p=0.001), Ascites (p<0.001), have significant associations with advancing age whereas Hematemesis (p=0.02), and portal vein hypertension were more significant in lower age (p=0.046) [Table-IV and V].

Parameters		f	%
RFTs at Admission	Upto 2mg/dl	56	90.3
	2-4 mg/dl	4	6.5
	4-8 mg/dl	2	3.2
Serum Albumin	Less than 2.5	25	40.3
	2.5-3.5	28	45.2
	More than 3.5	9	14.5
Serum Bilirubin	Upto 2mg/dl	58	93.5
	2-5mg/dl	3	4.8
	More than 5mg/dl	1	1.6
Prothrombin time	Upto 16 sec	44	71.0
	16-25 sec	16	25.8
	More than 25 sec	2	3.2
INR	Upto 1.9	52	83.9
	2-3	6	9.7
	3-5	4	6.5
HbA1c	Upto 5.9%	12	19.4
	6-8 %	29	46.8
	Greater than 8%	21	33.9
Anti-HCV by ELISA	Yes	53	85.5
	No	2	3.2
	Not available	7	11.3
HCV PCR RNA	Yes	49	79.0
	No	5	8.1
	Not available	8	12.9
Alpha Fetoprotein	Raised	6	9.7
	Normal	56	90.3
USG evidence of HCC	Yes	2	3.2
	No	60	96.8
Triphasic CT evidence of HCC	Yes	2	3.2
	No	50	80.6
	Not available	10	16.1
Urine output in 24 hours at 1st day	Less than 450 ml	2	3.2
	450-1500ml	9	14.5
	More than 1500ml	51	82.3
Urine output in 24 hours in 48 hours	450-1500ml	8	12.9
	More than 1500ml	54	87.1
USG finding spleen and liver	Enlarge liver and spleen	6	9.7
	Shrunken liver and enlarge spleen	5	8.1
	Shrunken liver and normal spleen	29	46.8
	Normal	22	35.5
USG finding of kidney	Shrunken	4	6.5
	Normal	58	93.5

Table-II. Laboratory, Imaging findings of our study participant

In patients diagnosed with 5 to 20 years of diabetes duration, hepatic encephalopathy was frequently observed (p=0.019), whereas HCC associated with diabetes 10 to 20 years duration (p=0.030). Hepatic encephalopathy associated with HCV of 5 to 20 years duration (p = 0.009). Ascites and portal hypertension were linked to patients who received an HCV diagnosis five to ten years ago (P < 0.05) [Table-V].

Complications		f	%
SBP	Yes	10	16.1
	No	52	83.9
Hepatic encephalopathy	Yes	14	22.6
	No	48	77.4
Ascites	Yes	25	40.3
	No	37	59.7
Hematemesis	Yes	7	11.3
	No	55	88.7
Portal vein diameter	12 mm	34	54.8
	More than 12 mm	28	45.2
Hepatocellular carcinoma	Yes	2	3.2
	No	60	96.8

Table-III. Frequency of chronic complication of HCV

Complication		Age (years)				Gender		
		18-30	30-50	50-70	P-Value	Male	Female	P-Value
SBP	Yes	0 (0.0)	1 (10.0)	9 (90.0)	0.01	2 (20.0)	8 (80.0)	0.298
	No	5 (9.6)	33 (63.5)	14 (26.9)		21 (40.4)	31 (59.6)	
Hepatic encephalopathy	Yes	0 (0.0)	3 (21.4)	11 (78.6)	0.002	4 (28.6)	10 (71.4)	0.541
	No	5 (10.4)	31 (64.6)	12 (25.0)		19 (39.6)	29 (60.4)	
Ascites	Yes	2 (8.0)	5 (20.0)	18 (72.0)	<0.001	7 (28.0)	18 (72.0)	0.288
	No	3 (8.1)	29 (78.4)	5 (13.5)		16 (43.2)	21 (56.8)	
Hematemesis	Yes	2 (28.6)	0 (0.0)	5 (71.4)	0.02	3 (42.9)	4 (57.1)	1.00
	No	3 (5.5)	34 (61.8)	18 (32.7)		20 (36.4)	35 (63.6)	
Portal vein diameter	12mm	3 (8.8)	23 (67.6)	8 (23.5)	0.046	11 (32.4)	23 (67.6)	0.438
	> 12mm	2 (7.1)	11(39.3)	15 (53.6)		12 (42.9)	16 (57.1)	
HCC	Yes	0 (0.0)	2 (100.0)	0 (0.0)	0.586	2 (100.0)	0 (0.0)	0.134
	No	5 (8.3)	32 (53.3)	23 (38.3)		21 (37.1)	39 (62.9)	

Table-IV. Post Stratification of complications versus age category and gender

Complication		HbA1c level				Duration of HCV				
		up to 5.9%	6-8%	Greater Than 8%	P- Value	1-5	5-10	10-20	Newly Diagnose	P-Value
SBP	Yes	2 (20.0)	7 (70.0)	1 (10.0)	0.171	SBP	Yes	2 (20.0)	7 (70.0)	1 (10.0)
	No	10 (19.2)	22(42.3)	20 (38.5)		31(59.6)	17(32.7)	2 (3.8)	2 (3.8)	
Hepatic encephalopathy	Yes	4 (28.6)	5 (35.7)	5 (35.7)	0.527	5 (35.7)	6 (42.9)	3 (21.4)	0 (0.0)	0.009
	No	8 (16.7)	24(50.0)	16 (33.3)		31(64.6)	15(31.3)	0 (0.0)	2 (4.2)	
Ascites	Yes	2 (8.0)	11(44.0)	12 (48.0)	0.073	11(44.0)	11(44.0)	3 (12.0)	0 (0.0)	0.028
	No	10 (27.0)	18(48.6)	9 (24.3)		25(67.6)	10(27.0)	0 (0.0)	2 (5.4)	
Hematemesis	Yes	2 (28.6)	2 (28.6)	3 (42.9)	0.657	7(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.139
	No	10(18.2)	27(49.1)	18 (32.7)		29(52.7)	21(38.2)	3 (5.5)	2 (3.6)	
Portal vein diameter	12mm	8 (23.5)	15(44.1)	11 (32.4)	0.710	22(64.7)	7 (20.6)	3 (8.8)	2 (5.9)	0.021
	> 12mm	4 (14.3)	14(50.0)	10 (35.7)		14(50.0)	14(50.0)	0 (0.0)	0 (0.0)	
HCC	Yes	0 (0.0)	2(100.0)	0 (0.0)	0.678	0 (0.0)	2(100.0)	0 (0.0)	0 (0.0)	0.267
	No	12(20.0)	27(45.0)	21 (35.0)		26(60.0)	19(31.7)	3 (5.0)	2 (3.3)	

Table-V. Post Stratification of complications versus HbA1c level and Duration of HCV

HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus

DISCUSSION

This study the complex interactions among age, duration of diabetes, and HCV infection that shape the range of complications in patients with HCV+ diabetes. The frequency of side effects like ascites and portal vein hypertension highlights how frequent these are. The age-stratified analysis showed different trends, with complications like SBP, Hepatic encephalopathy and ascites associated with increasing age. Furthermore, the complex correlations between diabetes and the duration of HCV and its particular complications underscore the necessity of tailored approaches in the treatment of this patient population. Notably, hepatic encephalopathy linked to HCV duration of 5-20 years ($p=0.009$), whereas ascites and portal hypertension were associated with an HCV diagnosis five to ten years ($p < 0.05$).

This study also concluded that poor glycemic control increases the risk of complications secondary to cirrhosis in HCV patients. A study conducted by Rosenblatt R et al. concluded that patients with uncontrolled diabetes mellitus were more prone to develop bacterial infections, including SBP, which is consistent with the results of our study. Rosenblatt R et al. also concluded that advancing age is a risk factor for complications in HCV patients. In our study, SBP ($p = 0.01$), hepatic encephalopathy ($p=0.002$), and Ascites ($p<0.001$) have significant associations with advancing age which is also in accord with Rosenblatt R et al.[29]

Our study concluded that poor glycemic control could worsen ascites in chronic HCV patients, which is one complication of liver cirrhosis. This statement is supported by Khan R et al, as the study concluded that diabetes mellitus has significant adverse effects on chronic liver diseases, which leads to earlier complications and premature mortality.[30]

Our study reports that the duration of diabetes mellitus is significantly associated with HCC ($p<0.030$). A study conducted by Hosokawa T et al. concluded that poor glycemic control was an independent predictor for HCC, its recurrence, and an independent predictor of lower survival as well.[31] Similar results were also reported by El-serag HB et al. that diabetes mellitus was significantly associated with HCC (HRR of 2.1, $p<0.0001$).[33]

In our study, we have concluded that hepatic encephalopathy (16%) in HCV patients was associated with the duration of diabetes mellitus ($p<0.05$) as well as the duration of HCV ($p<0.05$). A study conducted by Sigal SH et al. reported that hepatic encephalopathy was more significant in diabetic patients compared to non-diabetics ($p <0.007$), which also supports the results of our study.[32]

CONCLUSION

In conclusion, individuals with both chronic HCV and diabetes mellitus exhibit an increased risk of cirrhosis-related complications. The most common complication was portal vein hypertension followed by ascites and hepatic encephalopathy. The complications like SBP, Hepatic encephalopathy and ascites associated with increasing age. These patients are also prone to develop infections as they face a high risk of developing HCC. Co-existing diabetes and HCV can develop earlier complications. They should be regularly followed for proper glycemic control and checking of liver, spleen, kidney, and portal vein status.

RECOMMENDATION

There is limited local data on the topic. Further studies with larger sample sizes are recommended to properly evaluate the correlation of cirrhosis-related complications with appropriate glycemic control.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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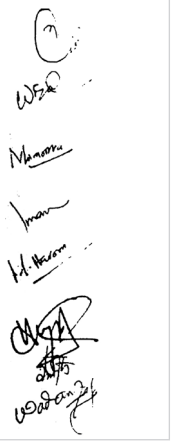
1	Zahidullah Khan	Conceptualization, Methodology, Supervusion.	
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4	Inamullah Khan	Methodology.	
5	Mohammad Haroon	Writing original visualization.	
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