Original Article

Child Pug Class

# Frequency of Different Child Pug Class Presentation in Patients of Chronic Hepatitis-C and Diabetes Mellitus Based on HBA1c

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## ABSTRACT

**Objective**: To determine the frequency of different Child Pugh class presentations among patients with chronic hepatitis C and diabetes mellitus and to compare different child pugh class presentations among patients with chronic hepatitis C and diabetes mellitus based on HbA1c.

**Study Design:** Descriptive case series study

**Place and Duration of Study:** The study was conducted at the Department of Medicine, Shifa International Hospital, Islamabad in a period of 01 year i.e. from June, 2011 to June, 2012.

**Materials and Methods:** In this study a total of 500 patients with hepatitis C and diabetes mellitus were enrolled. Male and female adult patients, diagnosed with diabetes mellitus and chronic hepatitis C, at least six month history of both diabetes and chronic hepatitis C infection were included in the study. Patients with other causes of chronic hepatitis, like chronic alcoholism, chronic hepatitis B, hemochromatosis, autoimmune hepatitis were excluded from the study.

**Results:** Average age of patients was 59.5 $\pm$ 14.8 years. Majority of the patients were above 40 years of age. There were 245 (49.0%) males and 255 (51.0%) females. Of the 500 study patients, 189 (37.8%) had child pugh class A, 148 (29.6%) patients had child pugh class B. While 163 (32.6%) patients had child pugh class C. In group 1 (HbA1c $\leq$ 7%), of the total 307 cases, 107 (37.8%) were in class A, 89 (28.9%) were in class B while 111 (36.2%) were in class C. Similarly, in group 2 (HbA1c > 7%), of the total 193 cases, 82 (42.4%) were in class A, 59 (30.5%) were in class B and 52 (26.9%) were in class C. There was a significant association between child class C and group 1 (HbA1c $\leq$ 7%) (p-value = 0.04).

**Conclusion:** Based on our results it is concluded that strict glycemic control i.e HbA1c of $\leq$ 7% has a significant association with adverse outcome i.e child pugh class C in patients with chronic hepatitis C and diabetes mellitus.

**Key Words:** Hepatitis C, Diabetes mellitus, HbA1c

## INTRODUCTION

Chronic liver disease and its complications are a common problem in Pakistan[1]. Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. Milder forms are non-progressive or only slowly progressive, while more severe forms may be associated with scarring and architectural reorganization, which, when advanced, lead ultimately to cirrhosis. The prevalence of hepatitis C virus (HCV) infection in general population of Pakistan, estimated at 5.3%, is one of the highest rates in the world[2]. Hepatitis C accounts for about 53.2% of the newly diagnosed viral hepatitis in Pakistan[2].

Of patients exposed to the hepatitis C virus (HCV), approximately 80% develop chronic hepatitis C, and of those, about 20–30% will develop cirrhosis over 20–30 years. Nonetheless, this represents a significant number of patients[3].

It is expected that an even higher percentage will go on to develop cirrhosis over longer periods of time. HCV is a non-cytopathic virus, and liver damage is probably immune-mediated. Progression of liver disease due to chronic hepatitis C is characterized by portal-based fibrosis with bridging fibrosis and nodularity developing, ultimately culminating in the development of cirrhosis. In cirrhosis due to chronic hepatitis C, the liver is small and shrunken with characteristic features of a mixed micro- and macronodular cirrhosis seen on liver biopsy[3].

Diabetes mellitus (DM) is a metabolic syndrome of disordered glucose metabolism and its complications due to insulin deficiency or insulin resistance. Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system[4].

About 32% of patients with chronic hepatitis C are also suffering from diabetes mellitus[1]. Diabetes mellitus by itself is a morbid disease but when it is present along with hepatitis C, may be more harmful because insulin resistance is associated with impaired virologic response to interferon and early onset of liver cirrhosis[5]. Insulin resistance is often present in patients with

chronic hepatitis C, and this parameter is associated with more advanced HCV-related hepatic fibrosis[6].

HCV is able to induce insulin resistance (IR) directly and the role of specific viral genotypes responsible for such effect is disputed[7]. Diabetic patients are twice as likely to have severe fibrosis (60%) than those with IR but no diabetes (30%)[8].

In one study of about 41 months of follow up of chronic liver disease patients, 34% of non-diabetics were found in stage A, 22% in stage B and 4% in stage C, while 40% of diabetics were found in stage A, 22% in stage B and 8% in stage C according to child pugh score system[9].

So far from a search through the literature no significant data was found to figure out whether glycemic control in chronic hepatitis C patients with diabetes, can affect the outcome of the disease. A pilot study was carried out to find the frequency of different child pugh class presentations of chronic hepatitis C patients with diabetes mellitus based on HbA1c.

The results showed that 20% of the patients were in class A, 40% in class B and 40% in class C whose HbA1c was ≤ 7% and 27% in class A, 33% in class B and 40% in class C, in patients whose HbA1c was above 7%. Until now patients with chronic hepatitis C alone and patients with chronic hepatitis C and diabetes both, are treated on the same line of management. It was intended that a study would help to form the basis for reviewing the management guidelines of the patients with chronic hepatitis C and diabetes mellitus..

# MATERIALS AND METHODS

The study was completed over a period of one year. Patients were selected through non-probability consecutive sampling technique. Male and female adult patients, diagnosed with diabetes mellitus and chronic hepatitis C, at least six month history of both diabetes and chronic hepatitis C infection were included in the study. The treatment modality for glycemic control was not considered. Patients with other causes of chronic hepatitis, like chronic alcoholism, chronic hepatitis B, hemochromatosis, autoimmune hepatitis were excluded from the study, even if they have hepatitis C infection and diabetes or both. The data was analyzed by SPSS software version 16. Descriptive statistics was calculated for both qualitative and quantitative variables.

For qualitative variables like gender, glycemic control and child pugh score category, frequency and percentage were calculated. For quantitative variables like age, HbA1c level, bilirubin level, prothrombin time, mean ±SD were used. Frequency and percentage were calculated for patients in different child pugh score based on glycemic control. Chi square was used to determine the difference in child pugh score category in two groups. P-value < 0.05 was considered significant.

# RESULTS

In this study a total of 500 patients with hepatitis C and diabetes mellitus were enrolled. The overall average age of study patients was 59.5 ± 14.8 years. Majority of the patients were above 40 years of age with 102 (20.4%) between 41 and 50 years, 180 (36.0%) between 51 and 60 years and 104 (20.8%) of 61 or above age.

In our study out of the total 500 cases, 245 (49.0%) were males compared to slightly greater proportion 255 (51.0%) of females.

The distribution of study cases according to HbA1c was assessed. In our study 307 (61.4%) patients had HbA1c ≤ 7% while 193 (38.6%) patients had HbA1c of > 7%.

The current study patients were analyzed according to the child pugh class. Of the 500 study patients, 189 (37.8%) had child pugh class A, 148 (29.6%) patients had child pugh class B. While 163 (32.6%) patients had child pugh class C.

The baseline characteristics of patients were compared among study groups i.e. group 1 (HbA1c ≤ 7%) and group 2 (HbA1c > 7%). In group 1, of the total 307 patients 164 (53.4%) were male while 143 (46.6%) were females. Similarly, in group 2, of the total 193 patients 81 (42.0%) were male while 112 (58.0%) were females. This difference in proportions of gender among the two groups was found statistically significant (p-value = 0.02). The average ages in the two study groups were compared. In group 1 the average age was 58.0 ± 13.4 years compared to 61.0 ± 11.5 years in group 2. The difference in these two means was found statistically significant (p-value = 0.01). (Table 1)

As per study objective the child pugh class was compared among the two groups. In group 1 (HbA1c ≤ 7%), of the total 307 cases, 107 (37.8%) were in class A, 89 (28.9%) were in class B while 111 (36.2%) were in class C. Similarly, in group 2 (HbA1c > 7%), of the total 193 cases, 82 (42.4%) were in class A, 59 (30.5%) were in class B and 52 (26.9%) were in class C. the difference in the proportions of child pugh class was found equal in the A and B classes. However, there was an association between child class C and group 1 (HbA1c ≤ 7%). In group 1 (36.2%) were having child pugh class C while in group 2 (26.9%) were in class C and this difference in proportions among the groups was found statistically significant (p-value = 0.04).

**Table No.1: Comparison of baseline characteristics of patients in the two study groups**

| | HbA1c | | p-value |
|---|---|---|---|
| | **≤ 7%** (n = 307) | **> 7%** (n = 193) | |
| **Gender** | | | |
| Male | 164 (53.4%) | 81 (42.0%) | 0.02 |
| Female | 143 (46.6%) | 112 (58.0% | |
| **Age in years** (Mean ± SD) | 58.0 ± 13.4 | 61.0 ± 11.5 | 0.01 |

**Table No.2: Comparison of child pugh classes of patients in the two study groups**

| | HbA1c | | p-value |
|---|---|---|---|
| | ≤ 7% (n = 307) | > 7% (n = 193) | |
| **Child pugh class** | | | |
| A | 107 (34.8%) | 82 (42.4%) | 0.10 |
| B | 89 (28.9%) | 59 (30.5%) | 0.78 |
| C | 111 (36.2%) | 52 (26.9%) | 0.04 |

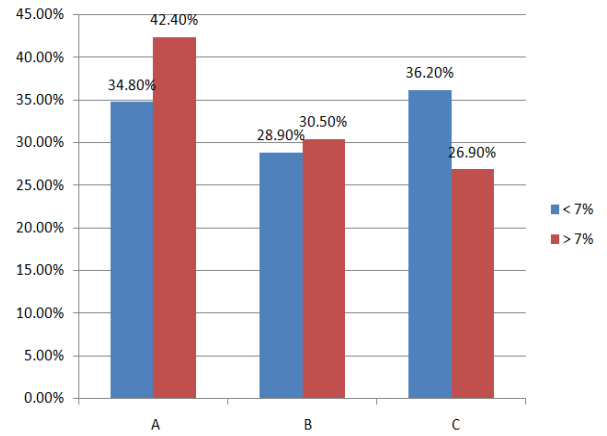


**Figure No.I: Distribution of HbA1c categories according to child pugh classes**

# DISCUSSION

Chronic hepatitis C is a common presentation in Pakistan with a prevalence of 5.3%. This complication is affecting huge general population and up to 50% of the viral hepatic pathologies are caused by it. About one third of chronic hepatitis C patients develop cirrhosis of the liver with the passage of time.

One of the co-morbidities of hepatitis C is diabetes mellitus. About 32% of patients with chronic hepatitis C also suffer from diabetes mellitus[1]. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system[4]. Diabetes mellitus as a co-morbidity of hepatitis C is more harmful because insulin resistance is associated with impaired virologic response to interferon thus, causing the early onset of liver cirrhosis[5].

Glycated hemoglobin measure as HbA1c in diabetic patients is used for the control of long term diabetes mellitus. Glycated hemoglobin most accurately reflects the previous 2-3 months of glycemic control. On the other hand diabetic patients could present with abnormal liver state such as benign hepatic stetosis or severe cirrhosis of liver[6,7]. Scientific data suggests that liver cirrhosis or chronic hepatitis promotes glucose intolerance and diabetes through various mechanisms including insulin resistance and impaired insulin secretion. Approximately up to 80% of patients with liver diseases also have glucose intolerance.

There has been a lot of scientific evidence on the relationship of glycated hemoglobin and diabetes mellitus. However, not much work has been found in literature regarding hepatitis C, diabetes mellitus and HbA1c. We conducted a study to determine the frequency of different child pugh classes of hepatitis C along with diabetes mellitus according to HbA1c. The study groups were divided into two as having HbA1c of ≤ 7% and > 7%. Adult patients of both genders, diagnosed with diabetes mellitus and chronic hepatitis C, with at least six month history of both diabetes and chronic hepatitis C infection were included in the study. Those with other causes of chronic hepatitis, like chronic alcoholism, chronic hepatitis B, hemochromatosis, autoimmune hepatitis were all excluded from the study. The study outcome was measured in terms of frequency of different child pugh class presentation among chronic hepatitis C and diabetes mellitus patients. Furthermore, the frequency of different child pugh class presentations among patients with chronic hepatitis C and diabetes mellitus were compared between the study groups based on HbA1c.

The average age of patients was 59.5 ± 14.8 years in the current study. Majority of the patients were above 40 years of age with almost 56.0% between 41 and 60 years and 20.0% of 61 years or above age. A Chinese study on the independent association of HbA1c and non-alcoholic fatty liver disease in an elderly population revealed mean age of 71.2 ± 4.3 years[8]. Another study by Luxmi S and colleagues from Karachi reported mean age of 50.0 ± 7.8 years[9]. These ages of presentation are comparable with our study findings and validate previous evidence on the topic where it has been witnessed that diabetes mellitus and chronic hepatitis C are more prevalent in elderly patients.

The gender distribution was found similar in our study, however, females were in slight dominance with 51.0% proportion. Previous literature has reported variable findings regarding gender of patients. A study by Ma H et al reported 62.6% males in their study with non alcoholic fatty liver diseases[8]. Another study by Luxmi et al reported female dominance with 65.8% proportion[9].

This is the first study ever done to determine the association of HbA1c with patients having hepatitis C and diabetes mellitus. It was observed that of the total 500 patients enrolled, most 307 (61.4%) had HbA1c ≤ 7% while 193 (38.6%) had it HbA1c > 7%. In this way it was again proven that glycated hemoglobin level decreases in patients having co-morbidities of hepatitis C and diabetes mellitus together.

When the demographic data of patients was associated with HbA1c groups, it was observed that males were more likely to have decreased HbA1c (≤ 7%) than females and similarly, females were more likely to have HbA1c level more than 7%.

The child pugh classes A and B were found to be similar among groups of HbA1c ≤ 7% and HbA1c >7%, however, child pugh class C was significantly associated with HbA1c ≤ 7%. This verifies that with severe morbidity of hepatitis C and diabetes mellitus, glycated hemoglobin diminishes. A previous study by Luxmi S and colleagues found a contrastable findings, where they found out mean HbA1c level significantly raised in patients with non-alcoholic fatty liver diseases compared to those without. Ma H and colleagues also reported from their study that patients with non-alcoholic fatty liver diseases had HbA1c level greater than those without non-alcoholic fatty liver disease[8].

There are reports comparable to our study results as well. A study by Lahousen T et al determined glycated hemoglobin in patients with advanced liver disease[10]. They reported that 40% of their patients with liver cirrhosis had HbA1c level below the non-diabetic reference range. Similarly, they also observed that 50% of patients with chronic hepatitis who were treated ribavirin had HbA1c level below the non-diabetic reference range[10]. These figures validate our findings of HbA1c < 7% significantly associated with chronic stage of hepatitis C.

The strengths of this study include a reasonable sample of 500 cases with hepatitis C and diabetes mellitus. This is the first study of its type as no previous literature could be found on the relationship of HbA1c and chronic hepatitis C along with diabetes mellitus. The study inferences of positive association between HbA1c < 7% and severe morbidity of hepatitis C in terms of child pugh class C have proven this study significant and impactful.

There were some limitations of the study as well which are related to research methods. This is a descriptive case series without any randomization of cases, which makes it weak. The study groups were not randomly selected so that there were equal number of subjects in both groups i.e. HbA1c ≤ 7% and HbA1c > 7%. The clinical and epidemiological data was not collected in the study which could be provided a greater sight of these patients.

It is known that HbA1c is used as a marker parameter in patients with chronic hepatitis C state with co-morbidity of diabetes mellitus. As the pathophysiologic reasons have not been well understood yet, it should be used with caution when evaluating the long term glucose control in chronic hepatitis patients[10].

# CONCLUSION

Based on our results it is concluded that strict glycemic control i.e HbA1c of ≤ 7% has a significant association with adverse outcome i.e child pugh class C in patients with chronic hepatitis C and diabetes mellitus.

Though our results have programmatic implications, we recommend that large scale randomized controlled trials on this topic should be done so that these findings can be generally acceptable and valid. Another way of validating our findings will be to look for independent risk factors associated with chronic hepatitis C in diabetic patients.

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# REFERENCES

1. Rathore R, Butt NF, Shoaib S, Iqbal A, Khan Z. Diabetes mellitus in patients with decompensated liver disease due to hepatitis C. Esculapio J Services Inst Med Sci 2008;3(4):6-9.
2. Bosan A, Qureshi H, Bile KM, Ahmad I, Hafiz R. A review of hepatitis viral infections in Pakistan. J Pak Med Assoc 2010; 60(12):1045-58.
3. Bacon BR. Cirrhosis and its complications. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jamson JL, editors. Harrison's principles of internal medicine. 17thed. New York: McGraw-Hill Medical; 2008.p.1971-80.
4. Alvin C. Powers: diabetes mellitus. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jamson JL, editors. Harrison's principles of internal medicine. 17thed. New York: McGraw-Hill Medical; 2008. p. 2275-2304.
5. Elgouhari HM, Zein CO, Hanouneh I, Feldstein AE, Zein NN. Diabetes mellitus is associated with impaired response to antiviral therapy in chronic hepatitis C infection. Dig Dis Sci 2009; 54(12): 2699-705.
6. Souza AF, Pace FH, Chebli JM, Ferreira LE. Insulin resistance in non-diabetic patients with chronic hepatitis C: what does it mean? Arq Bras Endocrinol Metabol 2011;55(6):412-8.
7. Lonardo A, Adinolfi LE, Petta S, Craxì A, Loria P. Hepatitis C and diabetes: the inevitable coincidence? Expert Rev Anti Infect Ther 2009; 7(3):293-308.
8. Ma H, Xu C, Xu L, Yu C, Miao M, Li Y. Independent association of HbA1c and non-alcoholic fatty liver disease in an elderly Chinese population. BMC Gastroenterol 2013;13:3.
9. Luxmi S, Sattar RA, Ara J. Association of non-alcoholic fatty liver with type 2 diabetes mellitus. JLUMHS 2008;1:188-93.
10. Lahousen T, hegenbarth K, Ille R, Lipp RW, Krause R, Little RR, Schnedl WJ. Determination of glycated hemoglobin in patients with advanced liver disease. World J Gastroenterol 2004;10: 2284-6.

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