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A Study of Hepatogenous Diabetes among Decompensated Chronic Liver Disease in a Tertiary Care Hospital of Tripura- A Cross-sectional Study

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ABSTRACT

Introduction: Hepatogenous Diabetes is a state of impaired glucose regulation caused by consequences of Liver Cirrhosis. Hepatogenous Diabetes (HD) is increases common complications of liver cirrhosis like Hepatic Encephalopathy, UGI bleeding, spontaneous peritonitis, ascites etc. Liver being a vital organ related to Glucose metabolism, Liver disease effects glucose metabolism due to several changes occurring in Chronic Liver Disease (CLD). There is a strong association between CLD and Diabetes risk & they co-exists too increasing the common complications. The management of diabetes in cirrhotic patients is also challenging because of physio-pathological changes in cirrhosis & altered pharmacokinetics of drugs used increasing the adverse events. Only few studies on Hepatogenous Diabetes has been done in India & it is the first study on this disease among population of Tripura.
Methodology: It is a Cross-sectional Study conducted by the Department of Biochemistry in collaboration with the Department of General Medicine at AGMC & GBP Hospital. Sample size was 190 & collected by Random Sampling method.
Results: Prevalence of Hepatogenous Diabetes (HD) among decompensated chronic liver disease is found to be 15.3 % & 84.7 % were CLD without HD. Among 190 samples analysed in this study, 76.3% were Male & 23.7% were Female. Among HD 89.7% Male & 10.3% Female & among Chronic Liver Disease without Hepatogenous Diabetes 73.9 % Male & 26.1% Female. In study population 54.7% were having ALD, 13.2% NAFLD, 19.4% HBV, 11.1% HCV & 1.6% both HBV&HCV. In HD & CLD without HD population, most cases were Alcoholic Liver Disease i.e. 65.5% & 52.8% respectively. In Receiver Operating Characteristic Analysis or ROC Analysis done among the different Biochemical parameters for the Hepatogenous Diabetes 2HrPG is having highest Area Under Curve (AUC) followed by HbA1c & FPG. Among the LFT parameters Direct Bilirubin having highest AUC, followed by ALP & AST & lowest AUC for Total Protein & Albumin. 2HrPG is expected to be the most efficient parameter among these to diagnose Hepatogenous Diabetes in this study. 2Hr PG shows Positive Correlation with FPG & HbA1c with p value <0.001 & showing Negative Correlation with Total & Indirect Bilirubin, AST, ALT, Tot. Protein & Albumin ratio but not significant. HbA1c shows Positive Correlation with FPG & 2HrPG with p value <0.001, Positive Correlation with ALP with p value <0.05 & Negative Correlation with Albumin with p value <0.05.
Conclusion: Prevalence of Hepatogenous Diabetes among decompensated chronic liver disease in this study is 15.3 %. This study is the first study on Hepatogenous Diabetes in Tripura. Studies on Hepatogenous Diabetes are done in very few & not done properly yet. This study will help in understanding the pathophysiology & dynamics of the disease; ultimately aiding to the better patient care.

Keywords: *Hepatogenous Diabetes, Chronic Liver Disease, NAFLD, ALD, HBV, HCV, Complications, Glucose Metabolism, HbA1c, Liver Function Test, Fasting Blood Glucose, Post prandial blood glucose, ROC analysis.*

INTRODUCTION

Hepatogenous Diabetes can be defined as a state of impaired glucose regulation caused by loss of liver function as a consequence of Liver Cirrhosis, implying that Diabetes Mellitus (DM) developed after the onset of Cirrhosis. [1] Liver diseases may exert a direct diabetogenic effect resulting in insulin resistance, impaired β-cell function [1] & impaired insulin clearance.[2] Association between Diabetes Mellitus & Liver Cirrhosis was first described by Bohan in 1947 [3] and named as Hepatogenous Diabetes by Megyesi et al. in 1967.[4] Hepatogenous Diabetes (HD) is linked to increase the risk of common complications of liver cirrhosis, such as hepatic encephalopathy, upper gastrointestinal bleeding, spontaneous peritonitis, ascites, infection and risk of progression to liver cancer. [1] Chronic Liver Disease (CLD), characterised by worsening liver function with a wide spectrum of complications estimated to be around 1.5 billion worldwide, having common aetiologies like Non Alcoholic Fatty Liver Disease (NAFLD, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Alcoholic Liver Disease (ALD) etc. [5] Liver diseases are fast being recognized as public health priorities in India, with a burden contributed to 18.3% of the 2 million global liver disease–related deaths in 2015. [6] The prevalence of Diabetes is increasing worldwide and is expected to affect around 300 million adults all over the world and around 57 million in India by the year 2025.[7] Since liver is a pivotal organ regulating plasma glucose level, glucose metabolic abnormalities occur frequently in patients with chronic liver diseases (CLD). These two common conditions co-exist & there is a strong association between NAFLD and diabetes risk [8] and improving NAFLD has been linked to modify the risk of developing diabetes. [9] Co-existent NAFLD increases the risk of microvascular complications of diabetes including chronic kidney disease, retinopathy, [10] increased insulin requirement [11] & risk factor for fibrosis. [12] The management of Diabetes in Cirrhotic patients is also challenging because of pathophysiological changes in cirrhosis, altered pharmacokinetics of oral hypoglycemic agents & lack of standard treatment guidelines, ultimately increasing the adverse events. [13] In India, studies on Hepatogenous Diabetes has not been undertaken intensively, few studies have been done till now. Moreover, it is the first study on Hepatogenous Diabetes among population of Tripura giving an insight to the disease which may help in managing these patients well. With this view, this Study is planned.

OBJECTIVES

1. To estimate proportion of Hepatogenous Diabetes among patients of Decompensated Chronic Liver Disease in a Tertiary Care Hospital of Tripura
2. To determine any relation between various etiological factors with Hepatogenous Diabetes.

METHODOLOGY

It is a Cross-sectional Study conducted in the period from June 2023 to December 2024 by the Department of Biochemistry in collaboration with the Department of General Medicine at AGMC & GBP Hospital after obtaining the approval from the Institutional Ethics Committee for Clinical Studies by approval no. F.4(6-13)/AGMC/Medical Education/IEC Approval/2022/18834 dated 18.05.2023.

Sample size was calculated as 190 by using the standard formula $N= (Z_{1-\alpha/2})^2 pq / d^2$

with reference to the prevalence found in a similar study of the nearby geographic region of the country.[14] 190 samples were collected by Random Sampling method over aforementioned duration after taking consent from the participants.

Inclusion Criteria:

1. Any case of Decompensated Chronic Liver Disease patient admitted in Medicine ward of AGMC & GBPH willing to participate in the study.
2. Age more than 18 years.

Exclusion Criteria:

1. Known case of Diabetes Mellitus.
2. Patients on Anti-Diabetic medication.
3. Patients on immunosuppressive drug or drug likely to affect glucose metabolism.
4. Patients not willing to participate in this study.

Participants were selected based on the inclusion & exclusion criteria. Venous blood samples were obtained from participants in Red & EDTA vacutainers. Serum is separated by Centrifugation at 3000 rpm for 10 minutes. Serum is used for estimation of the Blood Biochemical parameters & EDTA samples were used for estimation of Glycated Hemoglobin on the same day of collection.

Biochemical tests were performed in Fully Automated Biochemical Analyzer XL-640 by Erba after satisfactory Quality check with adherence to Westgard Rules. Glycated Hemoglobin or HbA1c was estimated by High Performance Liquid Chromatography (HPLC) Autoanalyzer Biorad D-10 following strict Quality check. Both the Autoanalyzers were under Internal & External Quality Control (IQC & EQAS). Diagnosis of Diabetes is done by following ADA guidelines. [15] Data entry and analysis were performed using SPSS 27.0 in windows PC. Categorical data presented with the help of text, tables, charts etc. ANOVA testing done for the significance of difference between more than two means, ROC plots are made and *p-value* less than 0.05 is considered statistically significant.

RESULTS

Among 190 samples analysed in this study, 145 (76.3%) were Male & 45 (23.7%) were Female. 29 (15.3 %) were found to be having Hepatogenous Diabetes (HD) among whom 26 (89.7%) were Male & 3 (10.3%) were Female. Rest 161 (84.7%) were having Chronic Liver Disease (CLD) without Hepatogenous Diabetes (HD), among whom 119 (73.9 %) were Male & 42 (26.1%) were Female.

In the study population 88 were from Urban area & 102 from Rural area. Distribution among other Two Groups shown in **Fig no. 1.** Among study population, 126 were employed, 53 Unemployed & 11 retired. Among HD group 19 Employed, 6 Unemployed & 4 Retired. 107 Employed, 47 Unemployed & 7 retired among CLD without HD. **(Fig no. 2)**

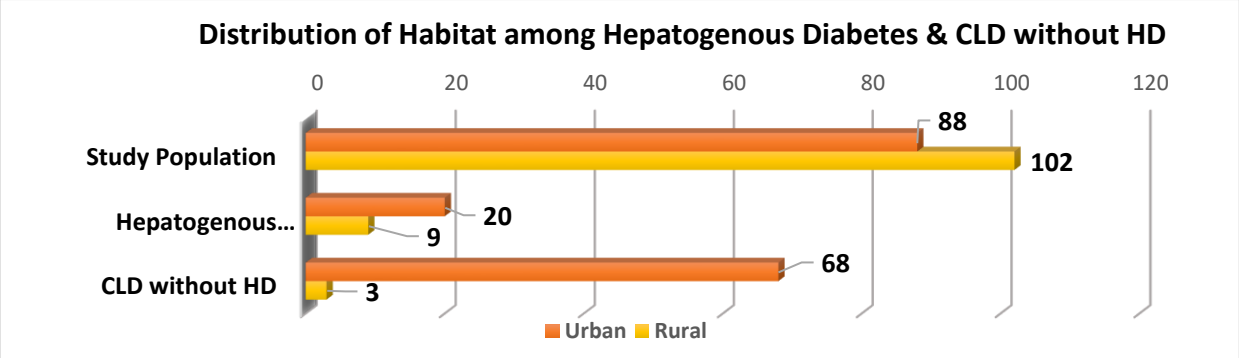


Fig. No. 1 -Distribution of Habitat among Hepatogenous Diabetes & CLD without HD

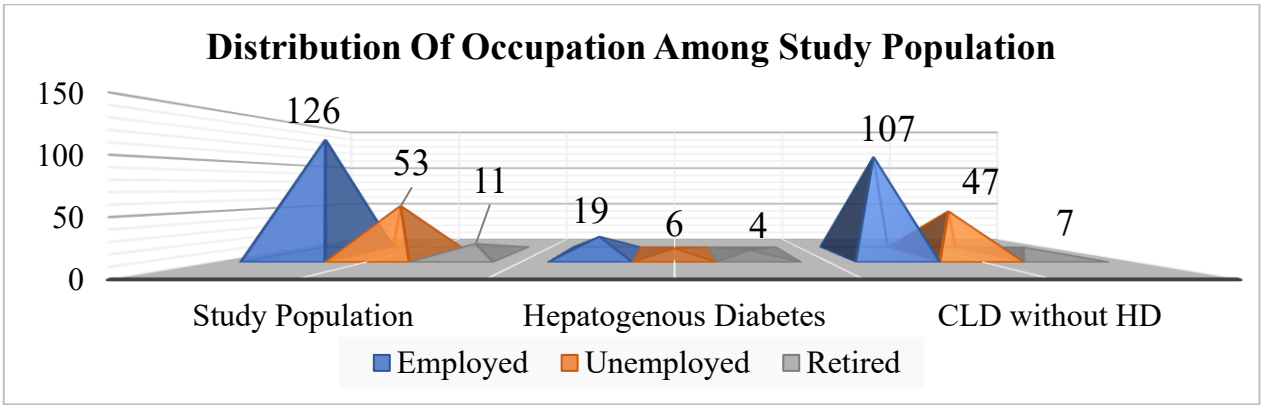


Fig. No. 2 - Distribution Of Occupation Among Study Population

Among study population, 134 (70.5%) were Hindu, 23 (12.1 %) were Muslim & 33 (17.4%) were Christian by Religion. In HD population 23 (79.3 %) Hindu, 2 (6.9 %) Muslim & 4 (13.8 %) Christian & CLD without HD 111 (68.9 %) Hindu, 21 (13 %) Muslim & 29 (18.1 %) Christian. Etiological cause distribution showed 104 (54.7%) were having Alcoholic Liver Disease (ALD), 25 (13.2%) Non Alcoholic Fatty Liver Disease (NAFLD), 37(19.4%) Hepatitis B Virus (HBV), 21(11.1%) Hepatitis C Virus (HCV) & 3 (1.6%) both HBV&HCV among study population **(Fig. no. 3)**. Among 29 Hepatogenous Diabetes & 161 CLD without HD, most cases were Alcoholic Liver Disease (ALD) i.e. 19 (65.5%) & 85 (52.8%) respectively. **(Fig. no. 4 & 5)**

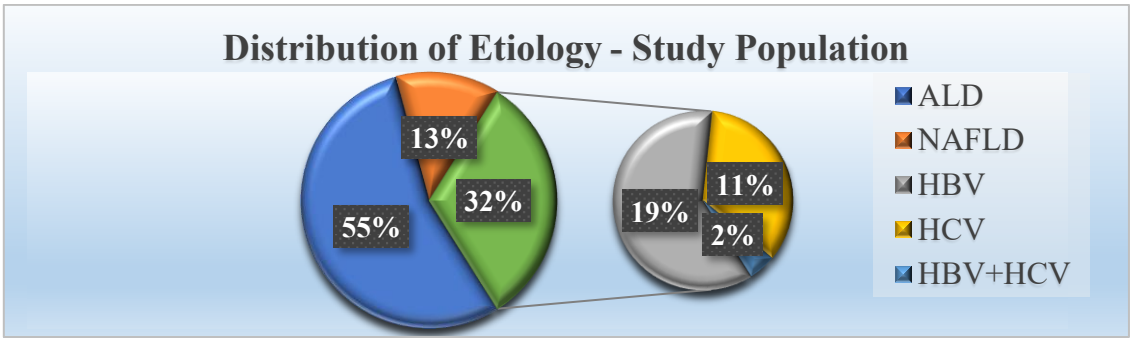
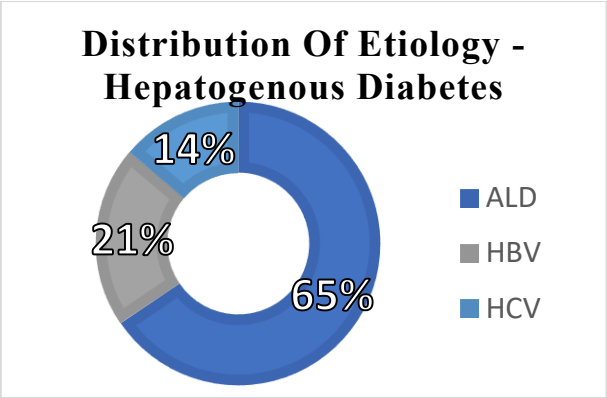


Fig. No. 3 - Distribution of Etiology - Study Population



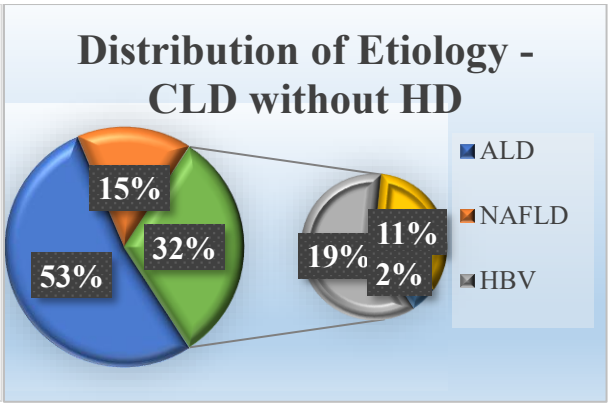


Fig. No. 4-Distribution of Etiology–Hepatogenous Diabetes **Fig. No.5-Distribution of Etiology – CLD without HD**

In Tripura we see a unique blend of Tribal & Non Tribal population, so in this study population also it is distributed likewise, 46 (24.2%) were Tribal & 144 (75.8%) were Non Tribal. Whereas among HD population 5 (17.2%) were Tribal & 24 (82.8%) were Non Tribal.

General Characteristics & Biochemical Parameters are presented in form of Mean ± Standard Deviation in overall Study Population & among the Hepatogenous Diabetes Group in **Table No. 1**.

Table 1 : General characteristics of Study Population & Hepatogenous Diabetes

Sl No.	Characteristic / Biochemical Parameter	Study Population	Hepatogenous Diabetes
1.	N	190	29
2.	Age	53.07 ± 6.2 years	54.6 ± 7.6
3.	FPG	102.76 ± 16.29	121.5 ± 16.7
4.	@2HrPG	159. 32 ± 40.56	226.9 ± 33.6
5.	HbA1c	5.6 ± 0.78	6.5 ± 0.4
6.	Total Bilirubin	1.6 ± 0.82	1.8 ± 0.9
7.	Direct Bilirubin	0.5 ± 0.4	0.67 ± 0.5
8.	Indirect Bilirubin	1.2 ± 0.5	1.2 ± 0.5
9.	AST	72.7 ± 69.7	76.7 ± 46.3
10.	ALT	82.3 ± 74.9	81.8 ± 49.2
11.	ALP	225 ± 51.92	241 ± 41.1
12.	Total Protein	4.9 ± 0.7	4.7 ± 0.7
13.	Albumin	2.7 ± 0.3	2.5 ± 0.3
14.	Globulin	2.2 ± 0.5	2.1 ± 0.5
15.	A:G	1.3 ± 0.3	1.2 ± 0.2

Prevalence of Hepatogenous Diabetes among decompensated chronic liver disease is found to be 15.3 % & 84.7 % were CLD without HD. (**Fig. No. 6**)

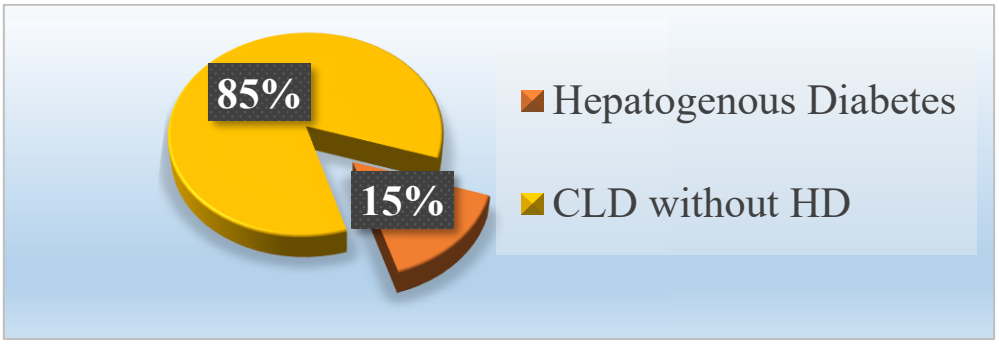


Fig. No. 6 – Prevalence of Hepatogenous Diabetes

Study Population based on their HbA1c values, is divided in Three groups i.e. Normal (<5.7%), Prediabetes (5.7 – 6.4%), Diabetes (≥6.5%) shown in Fig. No. 7.

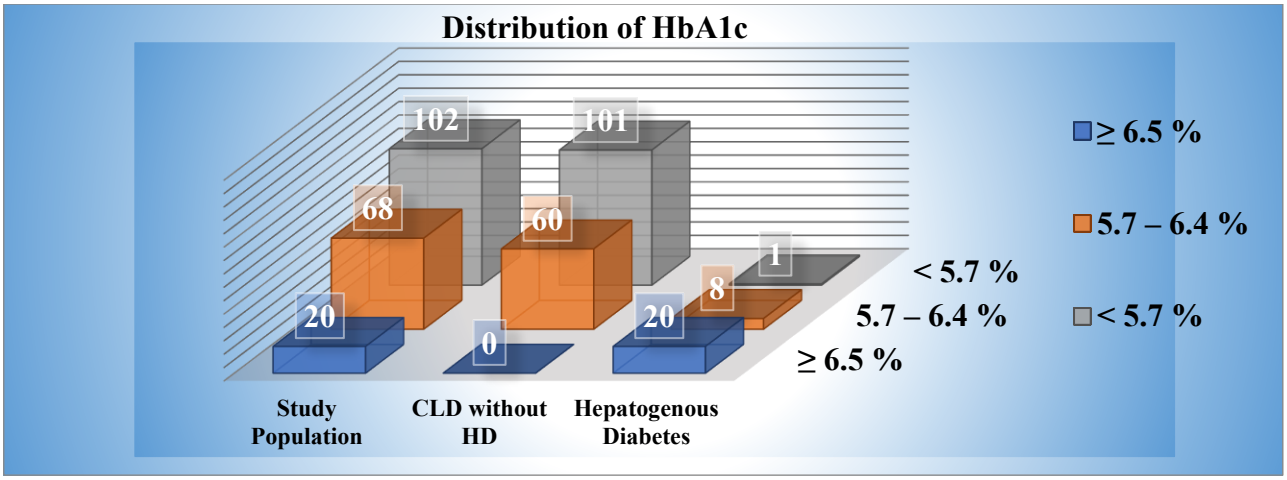


Fig. No. 7 – Distribution of Study Population among different HbA1c Groups

ANOVA test is done to compare between these three groups based on HbA1c values shown in **Table 2**.

Sl. No.	Parameter	HbA1c			*P value*
		Normal	Pre-Diabetes	Diabetes	
1.	Age	52 ± 5.7	54 ± 6.2	55 ± 8.2	0.147
2.	FPG	90 ± 8.8	113 ± 9.2	125 ± 15.2	0.000
3.	2Hr PG	130 ± 11.6	186 ± 31.6	222 ± 31	0.000
4.	Total Bilirubin	1.8 ± 0.9	1.4 ± 0.5	1.9 ± 1	0.000
5.	Direct Bilirubin	0.6 ± 0.4	0.4 ± 0.3	0.7 ± 0.5	0.001
6.	Indirect Bilirubin	1.3 ± 0.5	1 ± 0.3	1.2 ± 0.5	0.002
7.	AST	76 ± 79.1	68 ± 59.3	71 ± 49.5	0.001
8.	ALT	89 ± 85.3	74 ± 62.8	76 ± 51.5	0.777
9.	ALP	219 ± 58.6	231 ± 42.2	234 ± 43.6	0.435
10.	Total Protein	5 ± 0.7	4.8 ± 0.5	4.7 ± 0.8	0.253
11.	Albumin	2.7 ± 0.3	2.7 ± 0.2	2.6 ± 0.4	0.134
12.	Globulin	2.3 ± 0.5	2.2 ± 0.4	2.2 ± 0.5	0.133
13.	AG Ratio	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.2	0.605

Table no. 2: Comparison among HbA1c groups

Receiver Operating Characteristic Analysis or ROC Analysis is done among the different Biochemical parameters for the Hepatogenous Diabetes. Among all the parameters 2HrPG is having highest Area Under Curve (AUC) followed by HbA1c, FPG. Among the Liver Profile Test parameters Direct Bilirubin having highest AUC, followed by ALP & AST & lowest AUC for Total Protein & Albumin. 2HrPG is expected to be the most efficient parameter among these to diagnose Hepatogenous Diabetes in this study. (**Fig. no. 8**)

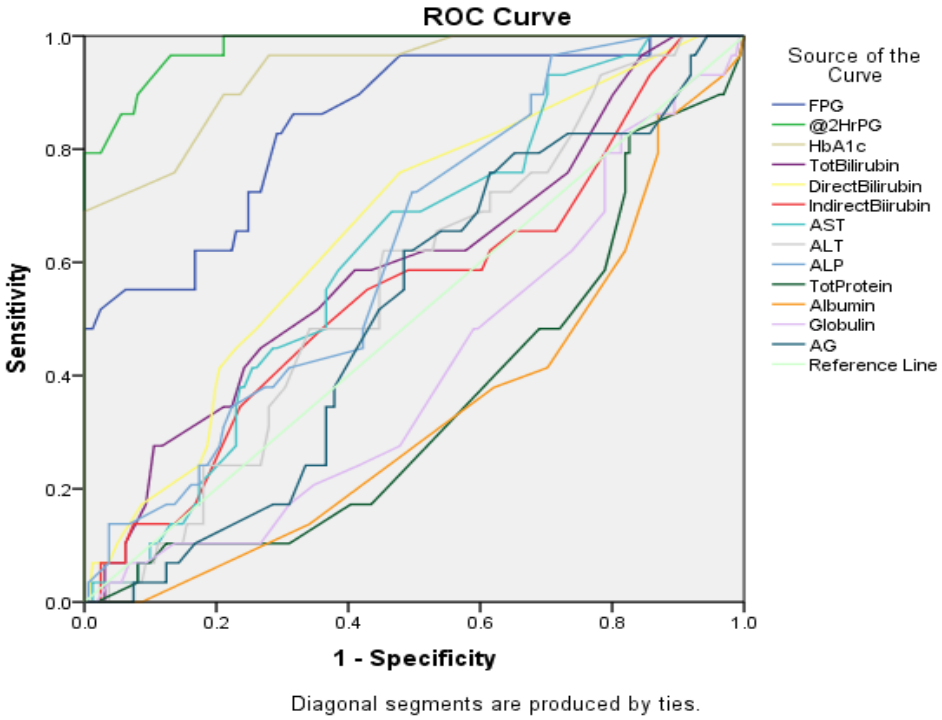


Fig. no. 8 : ROC Analysis

In ROC Analysis it is found that 2Hr PG & HbA1c are having the higher Area under curve (AUC). So, Correlation studies are done for these Two parameters with other Biochemical parameters involved.

Pearson Correlation Test is done. 2Hr PG shows Positive Correlation with FPG & HbA1c with p value <0.001. 2Hr PG showing shows Positive Correlation with Sr. Direct Bilirubin & Sr. ALP but not significant. 2Hr PG showing shows Negative Correlation with Total & Indirect Bilirubin, AST, ALT, Tot. Protein, Albumin, Globulin & A/G ratio but not significant.

HbA1c shows Positive Correlation with FPG & 2HrPG with p value <0.001, Positive Correlation with ALP with p value <0.05. HbA1c shows Negative Correlation with Albumin with p value <0.05.

HbA1c shows Negative Correlation with Total, Direct & Indirect Bilirubin, AST, ALT, Total Protein, Globulin, A/G ration but not significant. **(Fig. no. 9)**

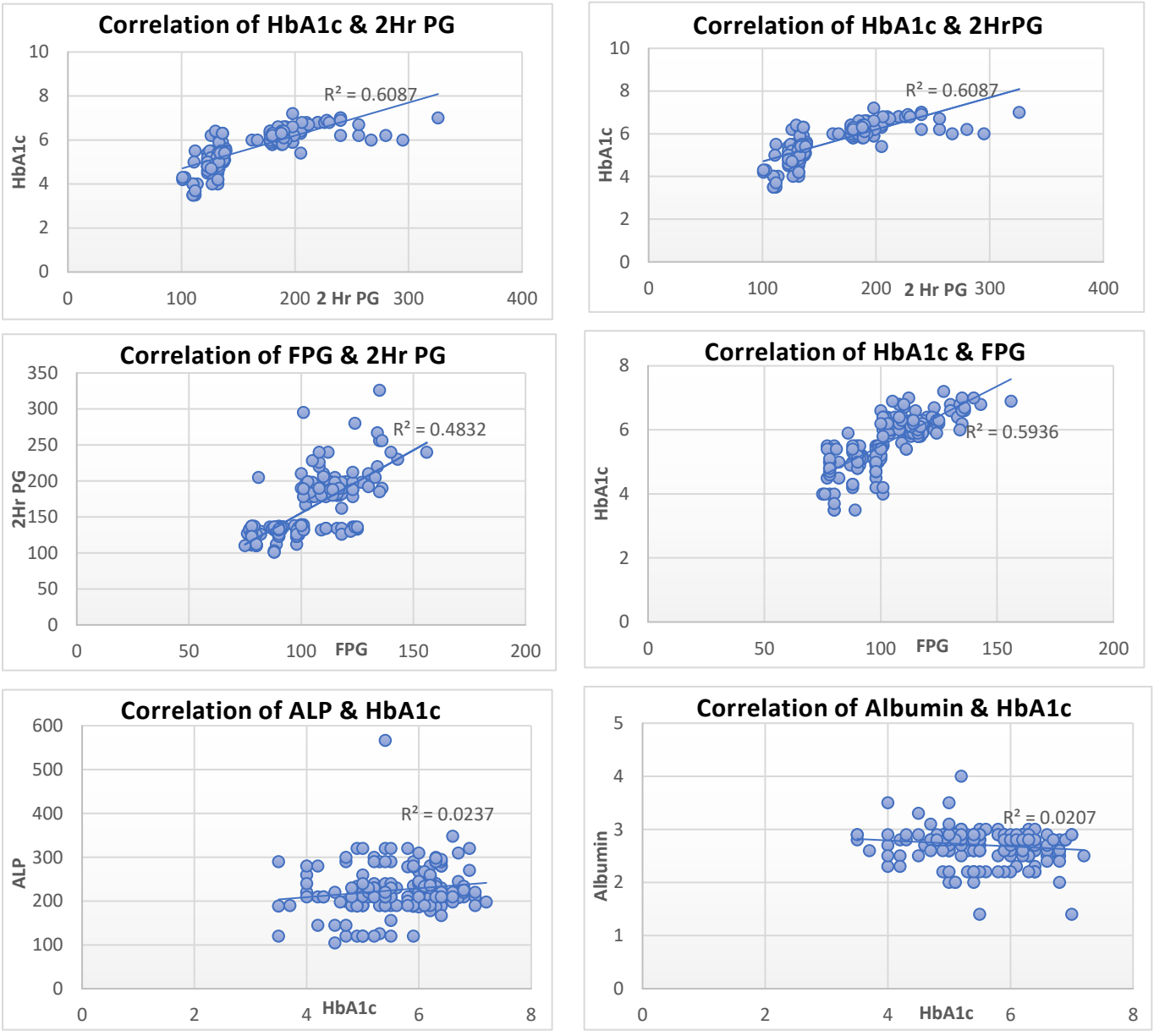


Fig. no. 9 : Correlation Analysis

DISCUSSION

This is the first study on Hepatogenous Diabetes in Tripura with prevalence of 15.3 %. Similar Prevalence of Hepatogenous Diabetes has been observed in a study conducted in North East India conducted by Perme O et al [14] in Manipur i.e. 12.9 %. Similarly in 2013 Mukherjee S et al [16] found prevalence of Diabetes was 14 % among Chronic Liver Disease patients. Study conducted by Ramachandran TM et al [17] prevalence was found to be 26.57 % whereas study conducted by García-Compeán D et al [18] Hepatogenous Diabetes had prevalence of 21.5%. Vasepalli P et al [19] found prevalence of Hepatogenous Diabetes to be 42.98% in 2020.

In a study conducted by Jeon HK et al [20] the Prevalence of Hepatogenous Diabetes was 55.4 %. A Study conducted by Mukherjee et al [21] in 2017, Data from North East India, suggests Diabetes was prevalent among 8.9 % & overall all India

data suggest that prevalence of Diabetes was 11.7 %. Singal AK et al [22] in Saudi Arabia found prevalence of Diabetes was 19.2 % among Chronic Liver Disease. In study conducted by Petit JM et al [23] prevalence was 13 % & study by Zein CO et al found prevalence of 14.5 %.
Whereas in studies by Grancini et al [24] the prevalence of Diabetes among Chronic liver disease was 48.6 %, Tietge UJ et al [25] found the prevalence was 35 %, Ortiz LC et al [26] found prevalence to be 30 %, Study by Alavian et al [27] found prevalence of 40 % & Rehmann UU et al [28] found prevalence of Diabetes of 61.8 % among Chronic Liver Disease.

In our study the Male participants were more than the Female i.e. 76.3 % Male & 23.7 % Female, which is similar to most of the studies conducted on Hepatogenous Diabetes in India. [14, 19, 21, 22] But, around equal distribution of gender can be seen in some studies. [18] In our Study Etiological distribution was like, 54.7 % were Alcoholic Liver Disease (ALD), 13.2% were Non Alcoholic Fatty Liver Disease (NAFLD), 19.4 % were Hepatitis B Virus (HBV), 11.1 % were Hepatitis C Virus (HCV) & 1.6 % were both HBV + HCV ;

Perme O et al [14] found most of the cases i.e. 70.9% were alcoholic liver disease followed by 24.5% Chronic hepatitis C cases and 4.5 % chronic hepatitis B cases. In a Study conducted by Vasepalli P et al [19] distribution of etiologies of cirrhosis were alcohol in 50.41%, Hepatitis B virus in 19.83%, Hepatitis C virus (HCV) in 5.79%, Budd-Chiari syndrome in 5.79%, Autoimmune hepatitis in 1.6%, Wilson disease in 0.8% and cryptogenic in 15.70% patients. Mukherjee et al [21] found among Chronic liver disease , distribution of etiology among all India is about HBV 33.3 %, HCV 21.6 %, ALD 17.3 % NAFLD 12.8 % & Others 15.5 % ; In the same study among the North Eastern states data, distribution of etiology was about HBV 29.8 %, HCV 26 %, ALD 31.9 %, NAFLD 3.4 % & Others 9.7 %.

In our study, the IGT (Impaired Glucose Tolerance) is found to be 91 out of 190 (47.89 %); which is similar to the study conducted by Vasepalli P et al [19] i.e. 47.93 %. But, in a study conducted by García-Compeán D et al [18] found IGT as 38.5 %, & Jeon HK et al [20] found IGT as 31.3 %, whereas Tietge UJ et al [25] found prevalence of IGT was 38 %. But, prevalence as low as 11.4% was found by Alavian et al [27] for IGT among Chronic liver disease.

In our study, in ROC Analysis, 2 Hr Plasma Glucose having the Highest Area under curve (AUC) of 0.980, followed by HbA1c with AUC 0.936, which signifies, among the Biochemical tests done here, 2 Hr Plasma glucose followed by OGTT is the best test to diagnose Hepatogenous Diabetes which is similar to the findings of Vasepalli P et al. [19]

In our study 15 cases out of 29 cases (51.7 %) of Hepatogenous Diabetes were having normal to prediabetic range of Fasting Plasma Glucose; 9 cases out of 29 cases (31 %) of Hepatogenous Diabetes were having normal to prediabetic range of HbA1c levels & 6 cases out of 29 cases (20.7 %) of Hepatogenous Diabetes were having normal to prediabetic range of 2 Hr PG levels. These results are similar with the results found by Orsi E et al [1] as reduced lifespan of RBCs caused reduced levels of HbA1c. So all the Biochemical tests for screening of diabetes i.e. FBS, PPBS & HbA1c should be considered for diagnosis of Hepatogenous Diabetes, because some may be missed by single test.

Limitations:
Our study have some limitations too. It is a Cross sectional study in a single institute. Due to it's cross sectional design comparison with control or healthy group was not possible. Sample size is 190. Study with larger sample size with comparison group may have a better impact on the results.

CONCLUSION

In our study, we found that the prevalence of Hepatogenous Diabetes among decompensated chronic liver disease in this study is 15.3 %. This study is the first study on Hepatogenous Diabetes in Tripura. Population wise Tripura is an unique state, as it is having a perfect blend of Tribal & Non Tribal population. Many studies have been done on Chronic liver diseases in India, but overall studies on Hepatogenous Diabetes are done in very few & not done properly yet. This study will help in understanding the pathophysiology & dynamics of the disease; ultimately aiding to the better patient care.

In our study most sensitive parameter among all the Biochemical parameters was 2 Hr Plasma Glucose, as analysed by ROC Analysis; followed by HbA1c in respect to Area Under Curve.

Some cases of Hepatogenous Diabetes were having Fasting Plasma Glucose & HbA1c levels in Normal to Prediabetes range. So, all the Biochemical tests for screening of diabetes should be considered for diagnosis of Hepatogenous Diabetes.

Hepatogenous Diabetes is a special category of diabetes which is less explored having multiple complications & has special way of approach as treatment. So, all the patients of Chronic liver disease should be screened for Hepatogenous diabetes for early detection, timely intervention & minimising complication. Study planned with larger sample size involving multiple centres with comparison group may yield better understanding of the disease.

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