

ORIGINAL RESEARCH

Serum uric acid levels in chronic liver disease and its relation to Child Turcotte Pugh (CTP) score

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ABSTRACT

INTRODUCTION: Chronic liver disease is a dynamic process of inflammation, destruction and regeneration of liver parenchyma, which leads to fibrosis and cirrhosis. Cirrhosis is the final stage of chronic liver disease. Hyperuricemia is a risk factor for the development of cirrhosis. Proposed mechanisms include induction of endothelial dysfunction, insulin resistance, oxidative stress, and systemic inflammation which are now known to be important risk factors for the development or progression of liver diseases.

AIMS AND OBJECTIVES: The present study was designed to estimate the serum uric acid levels in patients of chronic liver disease and to determine and study the correlation between serum uric acid levels and Child-Turcotte-Pugh (CTP) score in patients presenting with chronic liver disease.

MATERIALS AND METHOD: The present cross-sectional study was conducted on 50 patients of chronic liver disease that presented to Medicine Department (indoor/outdoor department) of Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar. A Detailed history and thorough physical examination were done after taking informed consent. Serum uric acid, liver function test and other appropriate investigations were performed. CTP score calculated and statistical analysis were done.

RESULTS: Among 50 patients in this study, majority of them were male constituting 82% (n = 41). Females were 18 % (n = 9). Male: Female was 4.5:1. Among 50 cirrhotic patients, most of the patients belonged to CTP class C (44%) followed by CTP class B (40%) and then by CTP class A (16%). The mean serum uric acid of study population was 6.45±2.25 mg/dl. CTP score was used to assess the severity and prognosis of cirrhosis of liver in this study. In CTP class A, the mean serum uric acid level was 4.42±1.18 mg/dl. In class B and class C, the mean serum uric acid levels were higher: 5.49±1.49 mg/dl and 8.07±2.04 mg/dl respectively. The difference was statistically significant (p value=0.001). Pearson's correlation coefficient was used to assess the relation between serum uric acid level and CTP score and there was a positive correlation between the two variables with r value of 0.7 and p value of 0.001.

CONCLUSION: This study established a statistically significant positive correlation between serum uric acid levels and CTP score.

KEYWORDS: Uric Acid (UA), Chronic Liver Disease (CLD), Child-Turcotte-Pugh (CTP) Score, Cirrhosis of Liver.

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INTRODUCTION

Chronic liver disease (CLD) is a dynamic process of inflammation, destruction and regeneration of liver parenchyma, which leads to fibrosis and cirrhosis. Cirrhosis is the final stage of chronic liver disease that results in disruption of liver architecture, formation of widespread nodules, vascular reorganization, neo angiogenesis and deposition of an extracellular matrix. CLD is a progressive deterioration of liver functions for more than six months

Chronic liver disease, at present, is the 11th most common cause of death globally and 10th most common cause of death in India. Liver disease accounts for roughly 2 million deaths per year worldwide out of which 1 million deaths are due to complications of cirrhosis and other 1 million deaths are due to viral hepatitis and other causes.

The various etiologies of CLD are Alcoholic liver disease, Viral Hepatitis-B, Viral Hepatitis-C, Non-alcoholic fatty liver disease (NAFLD),

Hemochromatosis, Wilson's disease, Autoimmune hepatitis, Primary biliary cirrhosis (PBC), Primary sclerosing cholangitis (PSC), Budd Chiari Syndrome, Cardiac Cirrhosis and Cryptogenic cirrhosis.³

The main pathogenic feature underlying liver fibrosis and cirrhosis is activation of hepatic stellate cells, also known as Ito cells or perisinusoidal cells. The stimuli for stellate cell activation are varied and include: inflammatory cytokines, (such as tumor necrosis factor alpha (TNF- α), TGF- β and interleukin-17 (IL-17), altered interactions with extracellular matrix (ECM), toxins and reactive oxygen species (ROS).⁴ Ito cells become activated and secrete extracellular matrix (collagen types 1 and 3, sulphated proteoglycans, inflammatory cytokines, growth factors and glycoproteins) in response to injury, thus, leading to fibrosis.

Cirrhosis has traditionally been classified as compensated or decompensated. The development of complications of Portal Hypertension, variceal hemorrhage, ascites, encephalopathy, jaundice, or HCC characterizes decompensated cirrhosis. Spontaneous bacterial peritonitis (SBP), Hepatorenal syndrome (HRS) and Hepatopulmonary syndrome (HPS) are other complications of decompensation. In compensated cirrhosis, these complications are absent. Clinical distinction of cirrhosis as compensated and decompensated has significant role in prognosis and treatment.⁵

Clinical, biochemical, imaging, and liver biopsy methods are used to make the diagnosis of chronic liver disease. The gold standard for diagnosis of cirrhosis is a liver biopsy, through a percutaneous, trans jugular, laparoscopic, or fine-needle approach. A biopsy is not necessary if the clinical, laboratory, and radiologic data suggests cirrhosis.

Child-Turcotte-Pugh (CTP) Score: CTP score has been widely used to assess the prognosis of cirrhotic patients in end-stage liver disease.⁶ Even though there are certain limitations, CTP score continues to be one of the robust predictors of prognosis of cirrhosis. Based on CTP score, CLD patients can be categorized into Class A to C according to severity of disease. CTP score includes 5 factors – ascites, encephalopathy, serum bilirubin, albumin, and prothrombin time. The score ranges from 5 to 15 points and is classified into 3 classes- Class A, B and C.⁷

Uric acid (UA) is an end product of purine metabolism. Approximately two thirds of total body uric acid is produced endogenously, the remaining one third is accounted for by dietary purines. Uric acid levels also increase with age.⁸ Normal reference level of serum uric acid is 3.5 to 7mg/dl (males) and 2.6 to 6.0mg/dl (females).⁹

Increased uric acid levels are independently associated with severity and prognosis of chronic liver disease and found to correlate directly with the level of tissue injury.^{10,11,12} Recent studies on serum uric acid have also shown an increased serum uric acid

level associated with the development of steatosis of liver in the patients who had Non-Alcoholic fatty Liver Disease (NAFLD) after adjustment for various features of metabolic syndrome. High uric acid level is a known sequelae of alcohol metabolism and therefore hyperuricemia may be found in alcoholic liver disease.^{13,14} Addition to this, hyperuricemia is also involved in the progressive development of hepatitis C virus related disease.¹⁵

Liver dysfunction can result directly through elevated uric acid level through multidimensional mechanisms. Interestingly, uric acid has the potential to cause oxidative stress and mitochondrial dysfunction directly.^{16,17} Uric acid activates inflammasomes and causes release of inflammatory cytokines which in turn causes induction of endothelial dysfunction, insulin resistance, oxidative stress and systemic inflammation which are important risk factors for CLD.^{18,19,20} These changes reduce the liver's functional capacity resulting in elevated levels of liver enzyme functions (ALT, AST, ALP).²¹

Hyperuricemia is involved in hepatic necro-inflammation. In fact, different studies across the world have found correlation between hyperuricemia and cirrhosis. Elevated uric acid levels in patients with liver disease have been found to be associated with a higher Child-Pugh score, indicating that the two may be related. Higher CTP scores correlate to more severe liver disease. Understanding the role of uric acid in liver disease progression may provide insight into potential treatment options and improve outcomes for patients with liver disease.

MATERIAL AND METHODS

The present study was conducted on 50 patients of chronic liver disease attending outdoor department or admitted in various medical wards of Medicine Department of Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar. This study was a Cross Sectional study. The nature of study was explained to each patient in their vernacular language, and informed written consent was taken from all patients.

After selection of patients for the study, detailed history was taken and thorough physical examination was conducted including measurements of vitals, other examinations relevant to the chronic liver disease. Diagnosis of chronic liver disease was established based on clinical features, hematological and biochemical investigations and imaging studies. Serum uric acid was measured by Uricase Peroxidase method.

Child Turcotte Pugh (CTP) score was calculated for each patient. The score employs five clinical measures of liver disease. Each measure is scored from 1-3, with 3 indicating most severe derangement.

CHILD TURCOTTE PUGH (CTP) SCORE

Measure	1 point	2 points	3 points
Total bilirubin, (mg/dl)	<2	2-3	>3
Serum albumin (g/dl)	>3.5	2.8-3.5	<2.8
PT prolongation (in secs.) Or INR	<4.0 <1.7	4.0-6.0 1.7-2.3	>6.0 >2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	Grade 0	Grade I-II	Grade III-IV

CLASS A: 5-6 points

CLASS B: 7-9 points

CLASS C: 10-15 points

In this study serum uric acid level of 50 patients aged above 18 years diagnosed with chronic liver disease was measured and its correlation with various classes of Child Turcotte Pugh Score (CTP score) was analyzed.

DATA ANALYSIS:

The data was collected systematically and edited after collection. Then the data was entered into Microsoft excel sheet and statistical analysis of the results was done with Statistical Packages for Social Sciences (SPSS-22) (SPSS Inc, Chicago, IL, USA). The results were presented in tables and figures. Statistical significance was set at $p < 0.05$. Mean serum biochemical parameters were compared among patients according to uric acid (uric acid ≤ 7 mg/dl and >7 mg/dl). Unpaired student's test was used for data analysis. Relationship between uric acid and CTP class was assessed by ANOVA test. The correlation between uric acid and CTP was evaluated by means of Pearson's correlation test.

RESULTS

The present study was conducted in the Department of Medicine, Guru Nanak Dev Hospital Amritsar on 50 patients. The study reveals that most patients were in the age group of 41-50 years. The mean age of the study population was 47.66 ± 12.73 years. Majority of them were male constituting 82% (n = 41). Females were 18% (n = 9). Male: Female ratio was 4.5:1.

Table 1 shows causes of cirrhosis among the study subjects. Alcohol was the most common cause of CLD comprising of 28 patients (56%). Hepatitis C emerged as the second most common cause in 10 patients (24%). 4 (8%) patients had Nonalcoholic fatty liver disease (NAFLD). Autoimmune hepatitis was present in 3 female patients (6%).

TABLE 1: DISTRIBUTION OF PATIENTS BASED ON ETIOLOGY OF CIRRHOSIS

Etiology	Male	Female	Total	Percentage
Alcohol	28	0	28	56%
Hepatitis C virus	10	2	12	24%
NAFLD	2	2	4	8%
Autoimmune	0	3	3	6%
Others	1	2	3	6%

Among 50 cirrhotic patients, most of the patients belonged to CTP class C (44%) followed by CTP class B (40%) and then by CTP class A (16%).

TABLE 2: DISTRIBUTION OF URIC ACID LEVEL AMONG STUDY POPULATION

Uric acid	No. of patients	Percentage
≤ 7 mg/dl	28	56%
>7 mg/dl	22	44%
Total	50	100%
Mean \pm S.D	6.45 \pm 2.25	

Table 2 shows the distribution of uric acid levels among the study population. The mean serum uric acid of the study population was 6.45 ± 2.25 mg/dl. Among 50 patients, the largest percentage of patients (56%) belonged to uric acid ≤ 7 mg/dl. 22 individuals (44%) had hyperuricemia (>7 mg/dl).

TABLE 3: MEAN VALUE OF BASELINE BIOCHEMICAL PARAMETERS AMONG PATIENTS ACCORDING TO URIC ACID

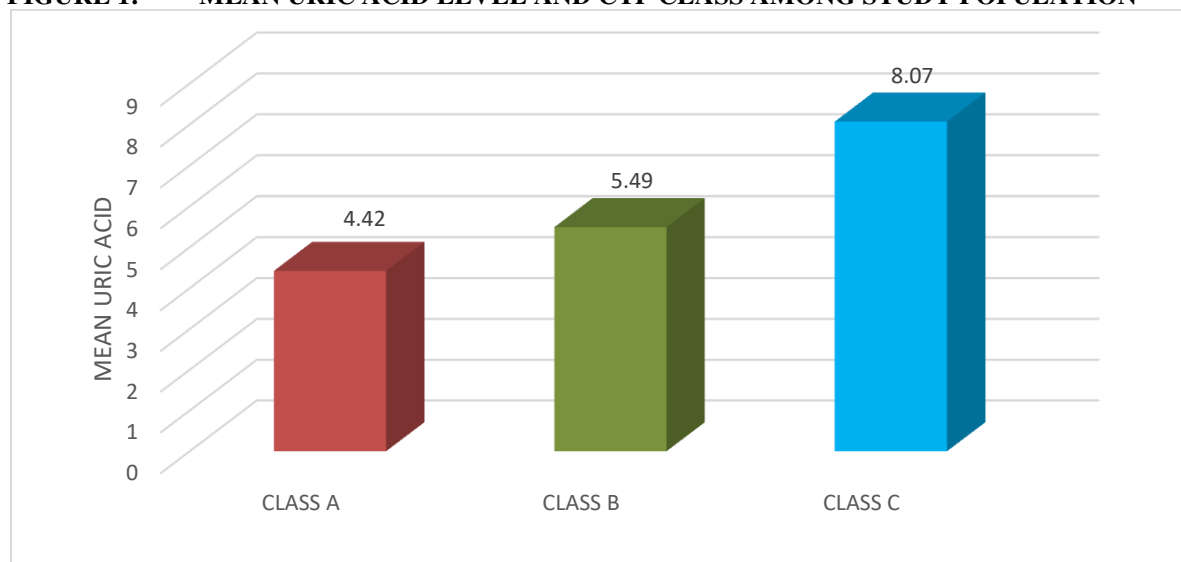
	Uric Acid ≤ 7	Uric Acid >7	'p' value
	Mean \pm SD	Mean \pm SD	
Bilirubin (mg/dl)	2.04 \pm 1.45	5.47 \pm 2.97	0.001
SGOT (U/L)	60.5 \pm 36.5	89.3 \pm 46.8	0.01
SGPT (U/L)	45.6 \pm 39.6	63.5 \pm 37.2	0.06
INR	1.23 \pm 0.17	1.40 \pm 0.21	0.001
Albumin (g/dl)	3.05 \pm 0.7	2.46 \pm 0.54	0.0004
ALP (IU/L)	103 \pm 37.7	111 \pm 45.7	0.34

Table 3 shows the mean value of baseline biochemical parameters among patients according to uric acid.

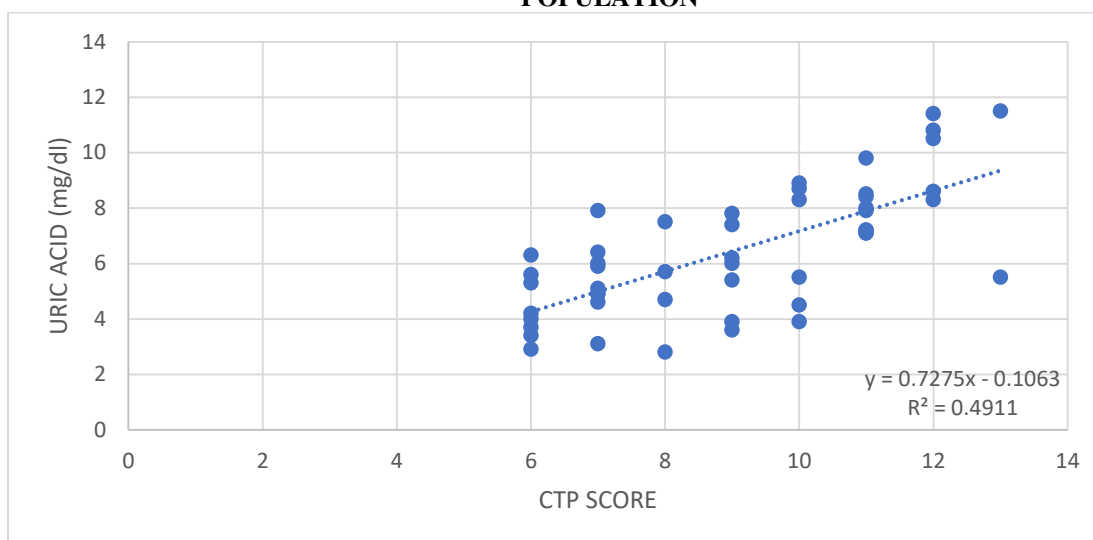
TABLE 4: MEAN URIC ACID LEVEL AND CTP CLASS AMONG STUDY POPULATION

CTP class	CTP score	n	Mean \pm S.D Uric acid	Range	Maximum value	Minimum value	'p' value
A	5-6	8	4.42 \pm 1.18	3.4	6.3	2.9	0.001
B	7-9	20	5.49 \pm 1.49	5.1	7.9	2.8	
C	10-15	22	8.07 \pm 2.04	7.6	11.5	3.9	
Total		50	6.45 \pm 2.25	8.7	11.5	2.8	

FIGURE 1: MEAN URIC ACID LEVEL AND CTP CLASS AMONG STUDY POPULATION



CTP score was used to assess the severity and prognosis of cirrhosis of liver in this study. Table 4 and Figure 1 show the mean uric acid level and CTP class among study population. In CTP class A, the mean serum uric acid level was 4.42 ± 1.18 mg/dl. In class B and class C, the mean serum uric acid levels were higher: 5.49 ± 1.49 mg/dl and 8.07 ± 2.04 mg/dl respectively. The difference was statistically significant (p value=0.001).

FIGURE 2: COORELATION BETWEEN URIC ACID LEVEL AND CTP SCORE AMONG STUDY POPULATION

Pearson's correlation coefficient was used to assess the relation between serum uric acid level and CTP score. Figure 2 shows that there was a positive correlation between the two variables with r value of 0.7 and p value of 0.001.

DISCUSSION

Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal regenerative nodule. CTP score has been widely used to assess the prognosis of cirrhotic patients in end-stage liver disease. Recent research has shown that uric acid is a mediator of inflammation and tissue damage. Hyperuricemia is now an established factor to cause oxidative stress, insulin resistance and systemic inflammation. So, it is likely that hyperuricemia might be involved in hepatic necro-inflammation and destruction which are the common underlying pathophysiology of cirrhosis.

Severity of cirrhosis of liver was assessed by CTP score in this study. Among 50 cirrhotic patients, most of the patients belonged to CTP class C (44%) followed by CTP class B (40%) and then by CTP class A (16%). In a study done by Das J et al²² showed that most of the patients belonged to CTP class C (50.71%) followed by CTP class B (40%) and then by CTP class A (9.29%). Hasan R et al²³ observed that 21.8% of study subjects had CTP Class A grade of prognosis, 25.9% had CTP Class B grade of prognosis and 52.3% had CTP Class C grade of prognosis.

The findings of present study were comparable with that of the above 2 studies as majority of the patients belonged to Class B and Class C. This shows that most patients seek medical care only during the later stages of the cirrhosis as well as due to the difficulty in diagnosing CLD in its early stages.

In present study, the focus of laboratory variable was serum uric acid. The mean serum uric acid was 6.45 ± 2.25 mg/dl. Among 50 patients, the largest percentage of patients (56%) belonged to the uric

acid ≤ 7 mg/dl. 22 individuals (44%) had hyperuricemia (>7 mg/dl). In a study done by Hasan R et al²³, 72.27% patients had normal level of uric acid (≤ 7 mg/dl) and the rest 27.73% patients had hyperuricemia (>7 mg/dl). The mean serum uric acid was 6.19 ± 3.25 mg/dl. In a prospective study conducted by Gupta PK et al²⁴, mean uric acid among the study subjects was 6.69 ± 2.92 mg/dl.

CTP score was used to assess the severity and prognosis of cirrhosis of liver in this study. In CTP class A, the mean serum uric acid level was 4.42 ± 1.18 mg/dl. In class B and class C, the mean serum uric acid levels were higher: 5.49 ± 1.49 mg/dl and 8.07 ± 2.04 mg/dl respectively. Analysis of variance (ANOVA) test was performed. There was a statistically significant difference between the mean serum uric acid levels of these three groups. (p value < 0.001). Pearson's correlation coefficient was used to assess the relationship between serum uric acid level and CTP score and there was a positive correlation between the two variables with r value of 0.7 and p value of 0.001.

A study done by Das J et al²² found that in CTP class A, the mean serum uric acid level was 4.57 ± 0.88 mg/dl. In class B and class C, the mean serum uric acid levels were higher: 6.42 ± 1.78 mg/dl and 7.97 ± 2.31 mg/dl respectively. This study linked serum uric acid level with CTP classes and uric acid levels were significantly higher in class B and C as compared to class A (p-value < 0.001). Serum uric acid levels also showed positive correlation with CTP score (r value: 0.3860; p value- 0.001). The findings of present study were in concordance with the above-mentioned study.

The findings were comparable to the study done by Hasan R et al²⁵ regarding the relationship of uric acid

with severity of liver cirrhosis according to CTP class. Mean serum uric acid level increased gradually as the patients progressed to higher CTP class. Mean serum uric acid level was maximum in CTP class C patients (6.98 ± 3.80) followed by class B (5.60 ± 1.83) and class A (4.30 ± 1.64). This increase of serum uric acid was statistically significant.

Hence, uric acid can be considered as marker of inflammation in patients of different classes of CTP with chronic liver disease patients. However large-scale studies are needed to confirm the same. Elevated uric acid levels in patients with liver disease have been found to be associated with a higher Child-Pugh score, indicating that the two may be related.

CONCLUSION

The present study established that there is a statistically significant positive correlation between serum uric acid levels and CTP score. It showed that higher uric acid levels in patients correlated with higher CTP grades which raises an important possibility that uric acid plays a causative and even a promotive role in hepatocyte inflammation and necrosis. Uric acid is easily available, cost effective and routinely done, hence can be considered as a novel marker for inflammation, severity and prognosis in patients with chronic liver disease.

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