Original Article

Serum uric acid level in chronic liver disease and its correlation with Child–Pugh score in a tertiary care hospital from South India

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Abstract

Background: Chronic liver disease (CLD) is one of the important causes of morbidity and mortality in our country, and since the damage to the liver is irreversible, we have to look for many severity markers or predictors for the prognosis of the patient. In this study, we have tried to correlate the level of serum uric acid (UA) with the severity of CLD presented as a Child-Pugh score. **Methods:** A cross-sectional observational study was conducted at Vijayanagar Institute of Medical Science (VIMS), Ballari, Karnataka, from October 2015 to June 2017 in the Department of General Medicine. Fifty patients diagnosed with CLD, aged between 18 and 65 years, of either gender, were enrolled in the study. Serum UA levels were measured, and liver function and coagulation parameters were assessed. A statistical analysis was performed to evaluate the association between serum UA levels, liver function test, and coagulation parameters. **Results:** In our study, the mean serum UA level was 6.52 mg/dl and was raised in patients with CLD in correlation to its severity. Alcoholic liver disease (ALD) was the most common etiology for CLD (80%) followed by hepatitis B (Hep B) virus infection (12%) and hepatitis C (Hep C) virus infection (6%). Serum UA levels increased as the Child-Turcotte-Pugh (CTP) score increased. The mean UA level in CTP class C was 8.29 mg/dl. Various parameters such as serum aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, total bilirubin, international normalized ratio (INR), calcium, and albumin were significantly associated with serum UA levels in CLD patients. **Conclusion:** The correlation between rising blood UA levels and the Child-Pugh score shows that UA estimate may be a valid and affordable indicator for assessing the extent of liver cirrhosis in CLD.

Keywords: Alanine transaminase (ALT), alcohol liver disease (ALD), aspartate aminotransferase (AST), Child-Turcotte-Pugh score (CTP), chronic liver disease (CLD), international normalized ratio (INR), uric acid (UA)

Introduction

Chronic liver disease (CLD) in the clinical context is a disease process of the liver that involves a process of progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis.[1] It is the 11th leading cause of death and the 15th leading cause of morbidity, accounting for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide in 2016.[2] In CLD, high uric acid (UA) levels are independently associated with severe disease and poor prognosis.[3] UA is not only a by-product of cell death and purine metabolism, but recent research has discovered that it is a mediator of inflammation and tissue damage.[4] In CLD, there is progressive liver damage

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eventually leading to loss of function.[5] In CLD of different etiologies, UA levels are found to be high.[6] High UA levels have been considered independent etiological risk factors in patients with nonalcoholic fatty liver disease (NAFLD).[5,7] In different studies, UA levels have been found to correlate directly with the level of tissue damage.[8,9]

However, studies regarding the relationship of UA levels with different parameters of liver dysfunction are rare in India.[3] We, therefore, undertook this pilot study to find the level of UA in patients of CLD and its correlation, if any, with the severity of the disease and other parameters.

Methodology

Study design and setting

This cross-sectional observational study was conducted from October 2015 to June 2017 among CLD presenting to the Department of General Medicine at Vijayanagar Institute of Medical Science (VIMS), Ballari, Karnataka.

Inclusion criteria

All patients diagnosed with CLD and admitted to General Medicine, aged 18 to 65 years, either gender, will be enrolled in the study.

Exclusion criteria

Patients with malignancy (leukemias and lymphomas), gout, chronic kidney disease, on drugs (frusemide, thiazide, allopurinol, and febuxostat), undergoing chemotherapy, and with recent surgery and trauma were excluded.

Sample size

All patients approaching to the General Medicine Department and fulfilling the inclusion and exclusion criteria were selected for the study; however, a minimum number of 50 patients were to be enrolled in the study.

Sampling technique

All patients coming to the emergency department and general medicine out patient department were screened, and those fulfilling inclusion and exclusion criteria were enrolled in the study. Patients who left against medical advice were excluded from the study.

Ethical clearance

The Institutional Ethical Committee (IEC) of VIMS, Ballari, Karnataka, gave the ethical clearance with letter no. VIMS/PG/IEC/15/2015–16 dated October 28, 2015. Permission was sought from the medical superintendent's office to screen the patient in the emergency department.

Data collection

All the patients and attendants were explained regarding this study, and those consenting were enrolled in the study. Blood samples were collected for all enrolled subjects and evaluated for hemoglobin, total leukocyte count, platelet count, prothrombin time, serum concentration of bilirubin (total and conjugated), serum albumin, serum aspartate aminotransferase (AST), and alanine transaminase (ALT), and a modified Child–Pugh Score was be calculated.[10]

Calculation of Child–Turcotte–Pugh (CTP) score

CTP score

The score employs five clinical measures of liver disease. Each measure is scored from 1 to 3, with 3 indicating the most severe derangement [Table 1].

CLD is classified into Child–Pugh classes A to C, employing the added score from above [Table 2].

Data analysis

The collected data were entered into a Microsoft Excel Sheet. Tables were generated using Microsoft Word and Microsoft Excel version 2010. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) IBM version 18.0. The categorical variables were expressed as percentages, frequency, and proportions and compared using Pearson's Chi-square test or Fisher's exact test, as appropriate. A $p \leq 0.05$ was considered statistically significant.

Results

In our study, patients belonged to age groups varying from 24 years to 65 years with a mean age of 44.54 years. Three patients (06%) belonged to the age group of 20–30 years. Among them, two patients (04%) had a UA value of 7. Fourteen patients (28%) belonged to the age group of 31–40 years. Among them, six patients (12%) had a UA value of 7. Twenty-one patients (42%) belonged to the age group of 41–50 years.

Table 1: 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)	<4.0	4.0–6.0	>6.0
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grades I–II	Grades III–IV

Table 2: Classification of Child–Pugh Score

Points	Class	One-year survival	Two-year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

Among them, 16 patients (32%) had a UA value of 7. Twelve patients (24%) belonged to the age group of > 50 years. Among them, six patients (12%) had a UA value of 7 as depicted in Table 3.

As depicted in Table 4, 42 patients (84%) were male, and eight patients (16%) were female. Among the 42 male patients, 28 (56%) patients had a UA value of < 7 and 14 (28%) patients had a value of UA > 7. Among the eight (16%) female patients, four (8%) patients had a UA value of < 7 and four (8%) patients had a value of UA > 7.

As seen in Table 5, out of 50 patients, 40 (80%) were taking significant alcohol. Among those taking alcohol, 38 were male and two were female. Six (12%) patients in the study population were found to have hepatitis B (Hep B). Hepatitis C (Hep C) was present in three patients (06%). In one patient (02%), autoimmune hepatitis was present.

The mean UA level among various classes of CTP as depicted in Table 6 are as follows: In class A, the mean value is 4.25 among eight patients; in class B, it is 5.42 for 20 patients; and in class C, it is 8.29 for 22 patients showing a direct correlation between higher CTP and UA levels.

Of the total 50 patients, 29 of them had a UA value of less than 7 of which 21 had signs of portal hypertension, whereas in eight of them, no signs of portal hypertension were present. The rest of 21 patients had a UA value of greater than 7, and in all of them, signs of portal hypertension were present [Figure 1].

In our study, we have looked for the correlation of serum AST with UA. We found both serum UA and AST were normal in 16 patients, while normal AST with high UA was seen only in two patients. In 12 patients, AST was high with normal UA, while in 20 patients AST and UA were both high, which showed a direct relation to each other. The *P* value calculated is 0.004, which is significant (<0.05) [Figure 2].

We have looked for the correlation of serum ALT with UA. Among 30 patients with normal ALT levels, serum UA was normal in 24 patients and higher in only six patients. In 10 patients, ALT was high with normal UA, while in 14 patients ALT and UA were both high, which showed a direct relation to each other. The *P* value calculated is 0.024, which is significant (<0.05) [Figure 3].

We have looked for the correlation of serum bilirubin with UA. We found that among 16 patients with normal bilirubin levels, both serum UA and bilirubin were normal in 14 patients, while normal bilirubin with high UA was seen only in two patients. Among 34 patients with high bilirubin levels, 19 patients were having high UA levels, while 15 patients were having normal UA levels. The *P* value calculated is 0.0378, which is significant (<0.05) [Figure 4].

We have looked for the correlation of serum calcium with UA. We found that among 31 patients with normal to high calcium levels, both serum UA and calcium were normal in 23 patients, while normal calcium with high UA was seen only in eight patients. Among 19 patients with low calcium levels, 13 patients were having high UA levels, while only six patients were having normal UA levels. The *P* value calculated is 0.03, which is significant (<0.05) [Figure 5].

Table 3: Age distribution and its relationship with serum uric acid value

Age (years)	Uric acid<7 (n)	%	Uric acid>7 (n)	%	Total
20–30	02	04%	01	02%	03
31–40	06	12%	08	16%	14
41–50	16	32%	05	10%	21
>50	06	12%	06	12%	12
Total	30	60%	20	40%	50

Table 4: Sex distribution among study groups

Gender	Number of patients with uric acid<7	%	Number of patients with uric acid>7	%	Total
Male	28	56%	14	28%	42
Female	04	08%	04	08%	08
Total	31	62%	17	34%	50

Table 5: Etiology among study groups

Etiology	Male	Female	Total	%
Alcohol	38	02	40	80%
Hepatitis B	03	03	6	12%
Hepatitis C	01	02	03	06%
Autoimmune	00	01	01	02%
Total	42	08	50	100%

Table 6: CTP class and uric acid

CTP class	N	Mean	Range	Maximum value	Minimum value
A	08	4.25	2.4	5.3	2.4
B	20	5.42	5.1	7.8	2.8
C	22	8.29	7.7	11.2	3.7
Total	50	17.96	15.2	24.3	8.9

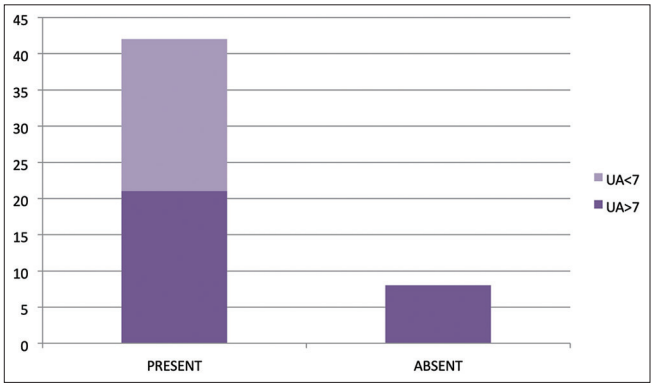

Figure 1: Presence of portal hypertension

We have looked for the correlation of serum albumin with UA. We found that among 19 patients with normal albumin levels, both serum UA and albumin were normal in 17 patients, while normal albumin with high UA was seen only in two patients. Among 31 patients with low albumin levels, 19 patients were having high UA levels, while only 12 patients were having normal UA levels. The *P* value calculated is 0.001, which is significant (<0.05) [Figure 6].

We have looked for the correlation of the international normalized ratio (INR) with serum UA. We found that among 23 patients with normal INR values, both serum UA and INR were normal in 19 patients, while normal INR with high UA was seen only in four patients. Among the 27 patients with increased INR values, 17 patients were having high UA levels, while only 10 patients were having normal UA levels. The *P* value calculated is 0.001, which is significant (<0.05) [Figure 7].

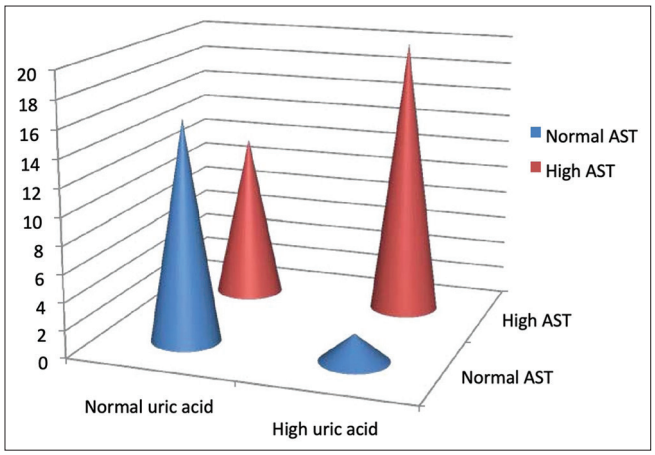

Figure 2: Association of serum AST level and uric acid level

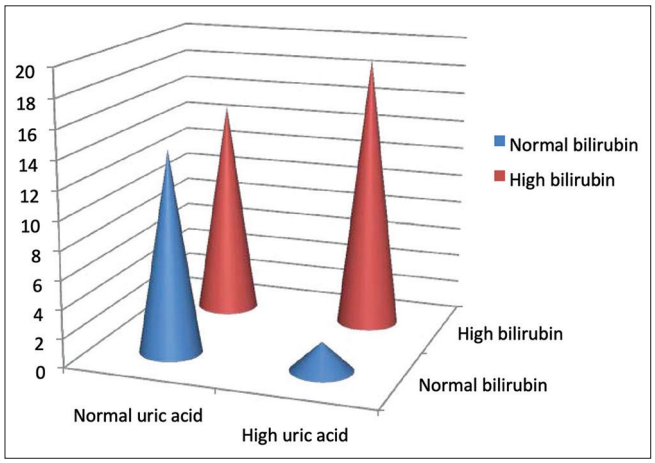

Figure 4: Association of serum total bilirubin and uric acid level

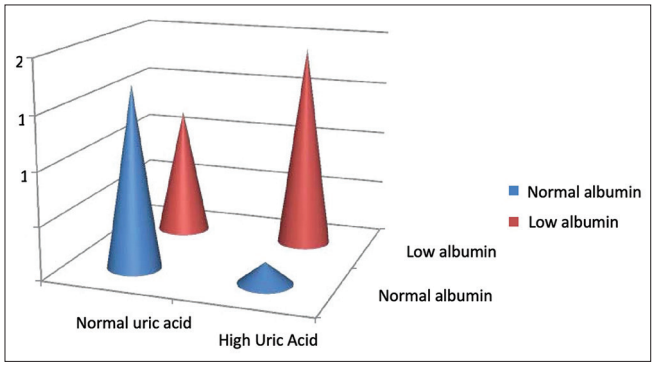

Figure 6: Association of serum albumin and uric acid level

Discussion

We found that most patients were male, 42 (84%), and only eight patients (16%) were female. In our study, most of the cases were

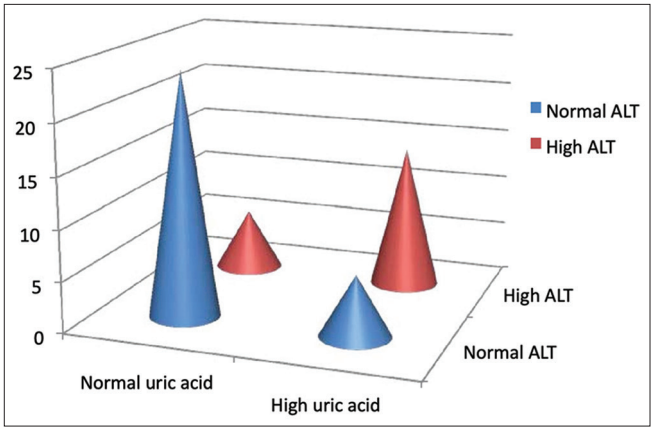

Figure 3: Association of serum ALT level and uric acid level

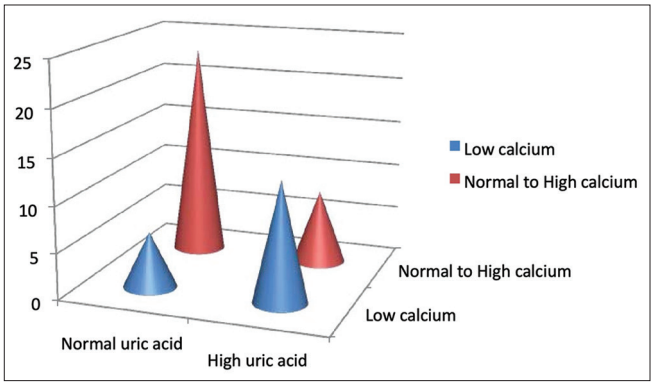

Figure 5: Association of serum calcium and uric acid level

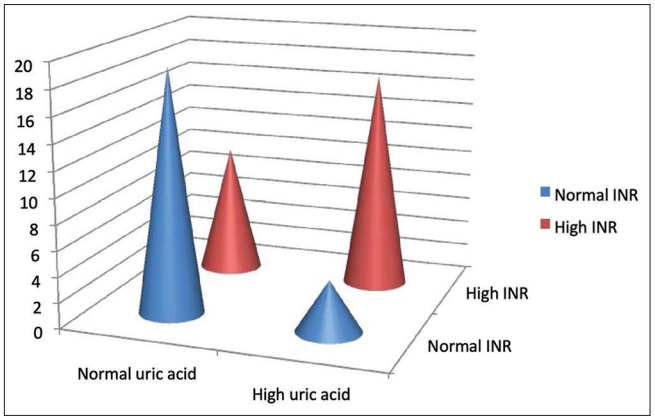

Figure 7: Association of INR value and uric acid level

in the 41–50 yrs of age group and the minimum cases were in the 24–30 yrs of age group. In our study, most of the patients were having alcoholic liver disease (ALD) (80%) followed by Hep B (12%), Hep C (6%), and autoimmune hepatitis (2%). The majority of European studies showed ALD followed by viral hepatitis as a major cause of CLD.

Ray *et al.*[11] found the highest incidence of cryptogenic cirrhosis followed by Hep B and Hep C with a gradually increasing trend of ALD. In another study from India, Dhiman and Duseja[12] found a higher prevalence of ALD. Jain *et al.*[13] found an increased incidence of cryptogenic cirrhosis followed by ALD.

In our study, ALD patients had higher serum UA levels (mean 6.52 mg/dl) as compared to Hep B (mean 6.34 mg/dl) and Hep C (mean 6.16 mg/dl), which was the same as demonstrated by Raut Sayali *et al.*[14] that there is a significant ($P < 0.0001$) increase in serum UA with the increasing quantity of alcohol.

In our study, maximum UA levels were present in CTP class C patients. In CTP class C, the serum UA level mean value was 8.295 mg/dl. Both of these conditions are associated with the progression of CLD. As the CTP class increases, the serum UA level increases. Paul *et al.*[15] demonstrated that serum UA levels increased with high CTP class in CLD patients.

In our study, serum AST level (mean 61.39 mg/dl, P value < 0.05) and serum ALT level (mean 48.92 mg/dl, P value < 0.05) were higher in patients with high serum UA levels as compared to patients with normal serum UA levels. Afzali *et al.*[16] demonstrated that high serum UA levels were associated with the development of cirrhosis and the presence of elevated serum liver enzymes.

In our study, serum total bilirubin (mean 4.56 mg/dl, P value < 0.05) was higher in patients with high serum UA levels as compared to patients with normal serum UA levels. A previous study conducted by B. C. Prakash and Sanjana K. Rai demonstrated that serum UA showed a statistically significant positive correlation with total bilirubin, serum creatinine, and prothrombin time/INR with a P value of 0.003, <0.001, and 0.030, respectively, and negative correlation with serum albumin with a P value of <0.001.[17]

In our study, INR values (mean 1.513, P value < 0.05) were higher in patients with high serum UA levels as compared to patients with normal serum UA levels. A previous study by Siddiqui *et al.*[18] demonstrated that coagulation abnormalities were profound in CLD patients.

In our study, serum calcium levels were low (mean calcium level 8.77 mg/dl, P value < 0.05), in patients with high serum UA levels as compared to patients with normal serum UA levels, but in a previous study by Miroliaee *et al.*[19] in Saudi Arabia, there was no significant difference between serum calcium and UA levels.

In our study, serum albumin levels (mean 2.8 mg/dl, P value < 0.05) were low in patients with high serum UA levels as compared to patients with normal serum UA levels. A previous study by Ernst Hasch *et al.*[20] demonstrated low serum albumin levels in CLD patients.

However, a study conducted by Wei *et al.*[21] in patients with idiopathic membranous nephropathy suggests that elevated serum albumin is independently and positively associated with an increased risk of hyperuricemia in people, especially in participants with BMI ≥25 kg/m^2.

Strength and Limitation

The strength of this study is that it has shown a direct correlation with all the liver parameters and severity of disease, and this is a cheap and easily available test and can be used for the prognostication of patients. This UA can serve as a marker for severity in CLD patients. The limitation of the study was a small sample size, restricted to one state of India, and all etiologies were not considered.

Conclusion

In conclusion, our study demonstrates that serum UA levels are significantly associated with the severity of CLD. The highest levels of UA were found in patients with ALD and those classified as CTP class C. Moreover, various liver function parameters were also found to be associated with UA levels. As UA has been shown to be a mediator of inflammation and tissue damage, our findings suggest that serum UA may serve as a valuable marker of the severity of CLD. Furthermore, understanding the role of UA in the pathogenesis of liver disease may provide new insights into potential therapeutic targets for this complex and challenging condition.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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