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CORRELATION OF SERUM URIC ACID CONCENTRATIONS AND THE CHILD-TURCOTTE-PUGH (CTP) SCORE IN PATIENTS WITH CHRONIC LIVER DISEASE

Badam Manoj Kumar [1], G Reddi Prasad [2]

1. **Assistant Professor, Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar, Telangana State.**
2. **Assistant Professor, Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar, Telangana State.**

Corresponding Author: Dr. G Reddi Prasad

Abstract

Background: Chronic liver disease involves the progressive destruction of liver tissue, leading to fibrosis and eventually cirrhosis. Elevated serum uric acid levels may contribute to insulin resistance, metabolic syndrome, and oxidative stress, all of which are risk factors for the progression of liver disease. This study aimed to measure uric acid levels and assess their relationship with the severity of liver disease.
Methods: A total of 50 patients diagnosed with chronic liver disease, aged 20 to 65 years and of either gender, were included in the study. Based on the Child-Pugh score, patients were classified as A, B, and C. Serum uric acid levels were measured and compared across these three groups.
Results: There's a trend of increasing mean uric acid levels with higher CTP scores (severity). Class A (least severe) has the lowest mean uric acid level (4.39 ± 1.09 mg/dL). Class B has a moderately higher mean uric acid level (5.48 ± 1.55 mg/dL). Class C (most severe) has the highest mean uric acid level (8.19 ± 2.24mg/dL). The P-value (0.012*) indicates a statistically significant difference in uric acid levels between the groups. Patients with higher uric acid levels (>7.2 mg/dL) generally have worse liver function compared to those with lower uric acid levels (< 7.2 mg/dL).
Conclusion: The current study suggests a link between increasing serum uric acid levels and worsening chronic liver disease (CLD) severity. Higher uric acid levels, often observed alongside elevated liver enzymes, maybe a potential risk factor for CLD progression.

Keywords: Hyperuricemia, Child-Pugh Score, Cirrhosis, Inflammation, Liver Disease.

Introduction

Liver disease is a global health concern, affecting millions of people worldwide. [1] Cirrhosis, a condition marked by scarring and nodule formation in the liver, is a major consequence of chronic liver damage. Common causes include heavy alcohol consumption, viral hepatitis, Non-Alcoholic Fatty Liver Disease (NASH), and autoimmune diseases. Alcohol is a major culprit, responsible for over half of all cases, while viral infections account for 30-70% [2]. Recent analysis suggests a link between uric acid levels and liver damage. In humans and some primates, uric acid is the end product of purine metabolism and gets eliminated through urine [3]. The enzyme xanthine oxidase (XO) plays a key role in its production by converting hypoxanthine to xanthine and then to uric acid [4]. Traditionally, uric acid was seen as a simple byproduct of cellular breakdown, particularly during nuclear material degradation. However, recent research suggests a more complex role for uric acid. It appears to act as a mediator of inflammation and tissue damage [5]. Within tissues, uric acid might activate inflammasomes, contributing to further tissue injury [6]. This has led to increased recognition of hyperuricemia as a marker of inflammation and cardiovascular risk. While the significance of uric acid in CLD is not fully understood, its potential role as an inflammatory mediator and cardiovascular risk factor warrants further investigation.

Liver fibrosis and cirrhosis, characterized by excessive scarring, have a main culprit: activated hepatic stellate cells. These cells, also known as Ito cells or perisinusoidal cells, reside near the liver's blood vessels. Various factors can trigger their activation, including Inflammatory molecules like tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), and interleukin-17 (IL-17) Changes in the surrounding matrix that supports cells, Toxins, Reactive oxygen species (ROS), unstable molecules that damage cells [7]. Once activated, these stellate cells overproduce components of the extracellular matrix, the scaffold that holds cells together. This overproduction includes collagen, a protein that forms scar tissue. This excessive collagen buildup stiffens the liver and disrupts its normal function, leading to fibrosis and potentially cirrhosis. The availability of liver transplants has highlighted the need for accurate methods to predict patient outcomes and guide timely referrals [8]. The Child-Turcotte-Pugh (CTP) score, despite its ease of use, is a widely used but limited tool for assessing prognosis in patients with alcoholic cirrhosis [9]. The Model for End-Stage Liver Disease (MELD) score was developed to assess prognosis in patients undergoing a procedure called Transjugular Intrahepatic Portosystemic Shunt (TIPS). It uses blood levels of creatinine, bilirubin, and prothrombin time (PT/INR) for calculation. The United Kingdom Model for End-Stage Liver Disease (UKELD) serves a similar purpose in the UK healthcare system. The present study was planned to study the association of uric acid with CP scores in patients with CLD.

Material and Methods

This prospective study was conducted in the Department of General Medicine, Prathima Institute of Medical Sciences, Nagunur, Karimnagar. Institutional ethical approval was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the vernacular language. Successive patients diagnosed with chronic liver disease were included in the study.

Inclusion criteria

1. Patients diagnosed with liver disease
2. Cirrhosis of liver
3. Aged 20 years and above
4. Males and females

Exclusion criteria

1. Patients on drugs such as allopurinol, Thiazide, Furosemide and Febuxostat
2. Patients with co-existing chronic kidney disease
3. Hypothyroidism, Diabetes mellitus, Hepatorenal syndrome
4. Patients on chemotherapy

Blood tests were performed on all participants to measure several important markers of liver function. These markers included:

- Uric acid: This test measures the level of uric acid in the blood, a waste product the body excretes.
- Bilirubin: This test measures the level of bilirubin in the blood, a yellow pigment produced during the breakdown of red blood cells. High levels of bilirubin can indicate liver problems.
- Albumin: This test measures the level of albumin, a protein made by the liver. Low levels of albumin can also indicate liver problems.
- The tests were done using a dry chemistry method on a VITROS 5600 chemistry analyzer. Additionally, a separate test measured prothrombin time, which is a clotting factor produced by the liver. The Child-Pugh (CP) Score was calculated based on table 1 given below

Table 1: The CP score was calculated based on the chart below:

Factor	*1 point*	*2 points*	*3 points*
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	3.0-3.5	<3.0
Prothrombin time (Seconds Prolonged INR)	<1.7	1.7-2.3	>2.3
Ascites	None	Slight	Moderate
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4

CP Class A: 5-6 points; Class B: 7-9 points; Class C: 10-15 points

The study participants were stratified into three groups (A, B, and C) for analysis. Serum uric acid levels were compared between groups using one-way analysis of variance (ANOVA) with SPSS software to assess for statistically significant differences. Spearman's rank correlation coefficient was additionally employed to evaluate the potential association between elevated serum uric acid and Child-Pugh (CP) scores.

Results

This study included 50 cases of chronic liver disease. The majority of them (60%) were in the age group of 41 – 50 years. The mean age of the population was 45.25 ± 5.5 years. Males were 40(80%) and females were 10(20%) of cases. The male-to-female ratio was 4:1.

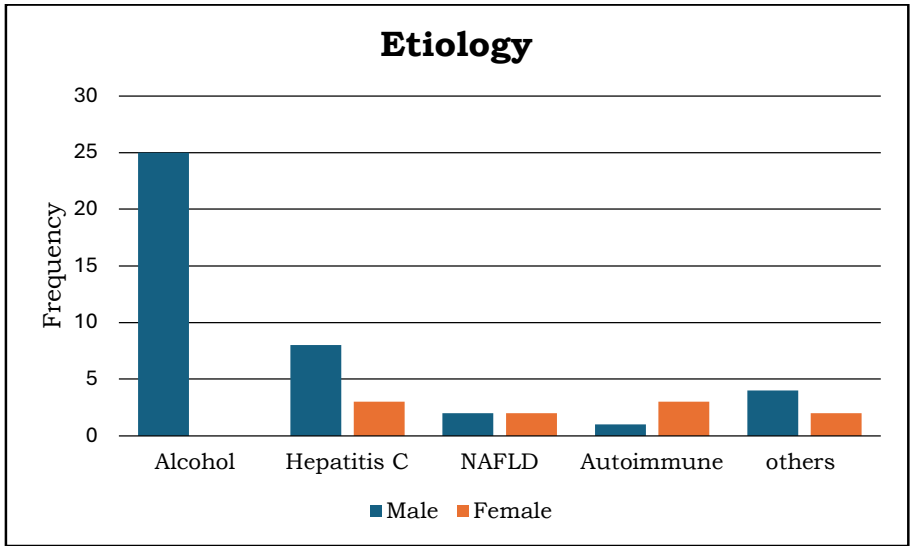

Figure 1: showing the etiological factors responsible for chronic liver disease in cases of the study

Figure 1 shows the etiology of chronic liver diseases in cases of the study. *Alcohol:* The most common cause of CLD is alcohol, affecting 25 males (50% of male patients) and no females. *Hepatitis C:* The second most prevalent cause is Hepatitis C, with 8 male patients (16% of males) and 3 female patients (33.33% of females). *NAFLD:* NAFLD is relatively evenly distributed across genders, affecting 2 males and 2 females. *Autoimmune Hepatitis:* This appears to be more common in females, with 1 male patient and 3 female patients (100% of female cases). The category "Others" includes a combined total of 4 males and 2 females. This data suggests that alcohol consumption is a major risk factor for CLD, particularly in males. Hepatitis C is also a significant cause, affecting both genders but with a higher proportion of males. NAFLD seems to be less gender-specific. Autoimmune Hepatitis appears to be more prevalent in females in this study population.

Table 2: Comparison of mean Baseline Biochemical Parameters Among Patients Based on Uric Acid Levels

Parameter	*Serum uric acid level < 7.2 mg/dl*	*Serum uric acid level > 7.2 mg/dl*	*P value*
Bilirubin (mg/dl)	2.13 ± 1.08	4.97 ± 2.12	0.001
AST (U/L)	45.67 ± 19.67	60.27 ± 29.14	0.012
ALT (U/L)	50.33 ± 27.64	85.91 ± 38.32	0.019
ALP (IU/L)	119.52 ± 35.46	151.27 ± 42.97	0.022
Albumin (g/dl)	3.67 ± 0.43	2.41 ± 0.48	0.001
INR	1.21 ± 0.11	1.57 ± 0.20	0.014

A critical analysis of Table 2 shows that patients with higher uric acid levels (> 7.2 mg/dL) generally have worse liver function compared to those with lower uric acid levels (< 7.2 mg/dL). This is reflected in all the parameters measured: Bilirubin, AST, ALT, and ALP levels are all significantly higher (p-value < 0.05) in the high uric acid group. Albumin levels are significantly lower (p-value < 0.05) in the high uric acid group, indicating poorer protein synthesis by the liver. INR is also significantly higher (p-value < 0.05) in the high uric acid group, suggesting potential abnormalities in blood clotting.

Table 3: Mean uric acid levels CP class among the 50 cases of chronic liver disease

CP class	CP Score	Frequency	Minimum	Maximum	Mean uric acid	P value
A	5 – 6	10	3.32	6.15	4.39 ± 1.09	0.012*
B	7 – 9	19	5.15	7.88	5.48 ± 1.55	
C	10 – 15	21	7.56	11.25	8.19 ± 2.24	

Table 3 shows the CP scores and mean uric acid levels in the cases of the study. Critical analysis of the table shows that there's a trend of increasing mean uric acid levels with higher CP scores (severity). Class A (least severe) has the lowest mean uric acid level (4.39 ± 1.09 mg/dL). Class B has a moderately higher mean uric acid level (5.48 ± 1.55 mg/dL). Class C (most severe) has the highest mean uric acid level (8.19 ± 2.24 mg/dL). The P-value (0.012*) indicates a statistically significant difference in uric acid levels between the groups. This data suggests a potential association between the severity of chronic liver disease and uric acid levels. Patients with more severe liver dysfunction (higher CTP score) tend to have higher uric acid levels. Uric acid might be a marker of disease severity in CLD.

Discussion

Clinicians widely use the Child-Pugh (CP) score to gauge the progression of chronic liver disease (CLD). This score incorporates five key variables: hepatic encephalopathy, ascites (fluid accumulation in the abdomen), serum bilirubin levels, albumin levels, and INR (a measure of blood clotting). Based on these variables, the CP score categorizes disease severity into classes A (mildest), B (moderate), and C (most severe). This study observed a correlation between increasing uric acid levels and worsening CLD severity, as measured by the CP score. Similar findings were reported by Paul et al. [10] in their study suggested uric acid as a potential marker for CLD severity with levels tending to be higher in patients with higher CP grades. This implies that uric acid might serve as a surrogate marker to assess CLD prognosis. To understand uric acid's role, it's important to remember that it's the final product of purine metabolism, originating from both the body's processes (endogenous) and dietary sources (exogenous) [11]. The body breaks down uric acid primarily in muscles, intestines, and the liver, with an enzyme called xanthine oxidase (XO) playing a crucial role in this process. The majority (around two-thirds) of uric acid is eliminated through urine, with the remaining third excreted in feces [12]. Serum uric acid is widely recognized for its role in the onset of gout. However, it also contributes to the development of chronic nephropathy and arthritis. Elevated uric acid levels are linked with cardio-metabolic diseases, including cardiovascular diseases and various conditions associated with metabolic

syndrome [13]. In populations with high uric acid levels, there is a notable prevalence of metabolic syndrome components such as hypertension, hyperinsulinemia, hypertriglyceridemia, and diabetes. [14, 15] Borghi C et al. [16] noted that serum uric acid levels are compelling and may be useful in determining whether hyperuricemia acts as a cause or simply a marker, with higher uric acid levels correlating with more advanced CP grades. Patients with CP Class C exhibit higher uric acid levels than those in Class B and Class A. [17] Elevated uric acid levels indicate oxidative stress in tissues and also serve as markers of metabolic syndrome. These conditions are linked with liver damage and the severity of CLD. [17] Liver injury is characterized by elevated levels of oxidative markers in the blood, indicating oxidative stress. Uric acid levels have been shown to increase with rising CP grades. In studies, hyperuricemia has been associated with endothelial dysfunction due to reduced bioavailability of endothelial nitric oxide in rats [17]. Additionally, high uric acid levels cause oxidative changes in adipocytes and inflammation, a key process in the development of metabolic syndrome in obese mice [18]. Benerji GV et al. [19] found significant increases in serum uric acid levels in conditions such as cirrhosis of the liver, amoebic liver abscess, and viral hepatitis. Therefore, elevated serum uric acid levels, along with traditional liver enzymes, could pose a risk factor for the occurrence of CLD. Afzali A et al. [17] also reported similar results Lombardi R et al. [20] identified that serum uric acid contributes to pathogenic mechanisms, particularly oxidative stress and insulin resistance, among other metabolic abnormalities where obesity and type 2 diabetes mellitus are most significant. Serum uric acid has been recognized as a potential indicator of liver damage and hepatic steatosis, playing a significant role in complications related to non-alcoholic fatty liver disease (NAFLD). Bansal A et al. [21] in a similar study noted that an increased concentration of serum uric acid is a risk factor in NAFLD. Pasalic D et al. [22] discovered a strong link between uric acid levels and the onset of inflammatory diseases. Early detection of hyperuricemia could therefore be crucial in predicting inflammation and aiding in the management of liver tissue damage linked to inflammatory conditions.

Conclusion

The current study suggests a link between increasing serum uric acid levels and worsening chronic liver disease (CLD) severity. Higher uric acid levels, often observed alongside elevated liver enzymes, maybe a potential risk factor for CLD progression. This association is further supported by the finding that uric acid levels correlate with higher Child-Pugh (CP) scores, a measure of CLD severity. Uric acid's potential as a surrogate marker for CLD prognosis across various causes, including alcoholism, hepatitis, NAFLD, autoimmune disorders, and drug-induced liver injury, warrants further investigation.

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