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Serum Uric Acid Level In Patients With Chronic Liver Disease And Its Association With Child-Pugh Score

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Abstract
Background: *Chronic liver disease (CLD) is a progressive liver disorder with a high risk of marked disability and early mortality. Recent evidence suggests that serum uric acid levels might be associated with the severity of CLD, offering a potential tool for prognosis, particularly in resource-limiting settings. The present study aimed to assess serum uric acid levels in patients with CLD and its association with Child-Pugh score, which is universally used to predict hepatic function and mortality in CLD patients.*
Methods: *This cross-sectional study was conducted on 80 purposively selected patients with confirmed diagnoses of CLD at Dhaka Medical College Hospital. Following informed written consent, all patients underwent face-to-face interviews, physical and clinical examination, and laboratory investigations including serum uric acid. Child-Pugh scores were calculated for each patient. Data were collected through a semi-structured questionnaire in separate case record form. Statistical analysis was conducted using SPSS V-23. The study was conducted in concordance with 'Declaration of Helsinki'.*
Results: *The mean age of the study patients was 44.71±5.52 (SD) years with a clear male preponderance (72.8% male). Viral hepatitis was the most common etiology (71.3%). Approximately 40% of patients had hyperuricemia, with a median serum uric acid level of 6.16 mg/dl. Hyperuricemia was significantly associated with more severe CLD (Child-Pugh class C). Median serum uric acid was significantly higher in patients of Child-Pugh class C than the patients of Child-Pugh class A and B. A positive linear correlation between serum uric acid levels and Child-Pugh scores was observed (rho .337, p<.05) indicating that Child-Pugh scores tend to increase with the increase of serum uric acid levels.*
Conclusion: *Serum uric acid levels significantly correlate with the severity of CLD as measured by the Child-Pugh score with a high frequency of hyperuricemia in CLD patients. Hence, further larger longitudinal studies are recommended.*
Keywords: *Chronic liver disease; CLD; Child-Pugh score; Serum uric acid; Hyperuricemia; Hepatic function; Liver cirrhosis*

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I. Introduction

Chronic liver disease (CLD) is a multifactorial and progressive condition characterized by destruction and regeneration of liver parenchyma which result in fibrosis and cirrhosis [1]. Due to poor prognostic nature and high burden of associated mortality and disability worldwide, CLD poses a significant threat to public health [2]. Intervention at an early phase of chronic liver disease might prevent the deterioration of the condition and improve the quality of life along with increase of life-expectancy. But to ensure the most effective intervention proper assessment of current hepatic function is crucial, but an overall assessment is challenging due to marked heterogenicity of CLD, complexity of liver function, influence of factors not included in hepatic system,

requirement of invasive procedures like liver biopsy, etc. So, for an easy and comprehensive assessment of hepatic function of CLD patients several measures have been invented and Child-Pugh score is one of the most practiced measures [3].

Child-Pugh score evaluates the hepatic function of CLD patients and predict the risk of mortality based on five clinical parameters- serum bilirubin level, serum albumin level, prothrombin time or international normalized ratio (INR), severity of ascites and grading of hepatic encephalopathy [4]. But for a resource limited developing country like Bangladesh, all these parameters cant be assessed readily in most healthcare facilities. Recently, several studies from different parts of the world pointed out a relation of serum level of uric acid with the severity and prognosis of chronic liver disease [5, 6].

Uric acid is the final oxidation product of purine metabolism which is mostly supposed to be excreted in urine.[7] An abnormally higher level of uric acid has been observed to be associated with hypertension, kidney disease, cardiovascular disease and metabolic syndrome [8]. Excessive serum uric induces endothelial dysfunction and oxidative stress along with insulin resistance and systemic inflammation [8]. It has been also observed that significant elevations in serum uric acid levels occur along with liver enzymes in conditions such as cirrhosis of the liver, amoebic liver abscess, and viral hepatitis [9]. So, hyperuricemia could potentially contribute to the inflammatory and necrotic processes within the liver, indicating a possible association between elevated uric acid levels and hepatic necro-inflammation and an independent relation between hyperuricemia and the severity of liver damage has been evident is different studies [10–12].

Child-Pugh score is considered as a standardized and globally accepted tool for assessing the severity of liver disease and predicting prognosis in CLD patients. This scoring system involves five clinical parameters- ascites, encephalopathy, serum bilirubin, serum albumin, and prothrombin time or INR (international normalized ratio). From the final scores, patients are categorized into three categories: class A, class B, or class C where a higher Child-Pugh score indicates a more severe liver disease and poorer prognosis. This scoring system helps clinicians make treatment decisions and determine the appropriate level of care for patients with chronic liver disease.

The present study aimed to understand the association between uric acid level and the Child-Pugh score in patients with diagnosed CLD. The findings might provide a valuable insight into the underlying pathophysiology and potential prognostic marker for disease progression, especially for resource limited settings.

II. Methods

Study design and setting

This study was a cross-sectional study conducted at the Department of Medicine and Hepatology, Dhaka Medical Hospital over a period of 1 year.

Study participants

Patients admitted in studied hospital with a confirmed diagnosis of CLD aged ≥ 30 years were approached for inclusion in this study population. CLD was confirmed by attending consultant physician considering the combination of clinical features, radiological findings, and biochemical reports. A total of 80 patients were selected purposively according to selection criteria. Patients with a history of taking drugs that cause alterations in uric acid levels (allopurinol, febuxostat, thiazides, frusemide, etc.), history of recent surgery, trauma, chronic kidney disease, hypothyroidism, hepatorenal syndrome, lymphoproliferative disease, myeloproliferative disease, polycythemia vera, Paget disease, sarcoidosis, psoriasis, diagnosis of any malignancy, pregnancy and present history of lactating were excluded.

Data collection

Data collection involved a semi-structured questionnaire, including both demographic (age, gender) and necessary clinical information (etiology of CLD, severity of CLD, laboratory findings, etc). Before data collection informed written consent was obtained from each patient. All patients underwent a face-to-face interview, physical and clinical examination, and laboratory investigations. Blood samples were collected from each patient to evaluate serum uric acid levels and liver function tests.

Child-Pugh score and class: Five clinical measures of liver disease are needed to obtain Child-Pugh score ─ total bilirubin, serum albumin, prothrombin time, severity of ascites, and grading of encephalopathy. Laboratory assessments were conducted to determine the level of total bilirubin, serum albumin, and prothrombin time. Serum bilirubin and serum albumin level were evaluated by uricase method and bromocresol green dye binding method using dry chemistry on VITROS 5600 analyzer. Prothrombin time was estimated using the Nephromatic method. The severity of ascites[13] and grading of encephalopathy[14] were assessed through clinical and radiological examination (ultrasonography). Based on the points assigned according to the severity of each parameter[15, 16] total Child-Pugh score was calculated. Bilirubin levels <2 mg/dL scores 1 point, levels 2–3 mg/dL scores 2 points,

and levels 3 mg/dL scores 3 points. For serum albumin, a level above 3.5 g/dL scores 1 point, levels between 2.8–3.5 g/dL scores 2 points, and levels below 2.8 g/dL scores 3 points. Prothrombin time less than 4 seconds above control scores 1 point, a prolongation of 4.0–6.0 seconds scores 2 points, and a prolongation of more than 6 seconds scores 3 points. Ascites is graded as none for 1 point, mild or medically controlled for 2 points, and moderate to severe or refractory for 3 points. Hepatic encephalopathy is also scored based on its severity, with no encephalopathy scoring 1 point, Grade I-II encephalopathy scoring 2 points, and Grade III-IV scoring 3 points. The total Child-Pugh score ranges from 5-15 which has been categorized into three classes: Class A (total score 5-6), Class B (total score 7-9) and Class C (total score 10 or above). Class A is considered to have good hepatic function with 10% predicted mortality, class B is considered to have moderately impaired hepatic function with 30% predicted mortality and class C is considered to have advanced hepatic dysfunction with 70-80% predicted mortality [17].

Serum uric acid level: Serum Uric acid was evaluated by uricase method using dry chemistry on VITROS 5600 analyzer. Male patients with serum uric acid >7mg/dl and female patients with >6mg/dl for female was considered as cases with hyperuricemia [18].

Statistical analysis

The statistical analysis was conducted using SPSS 23.0. The data were explored for normality using the Shapiro-Wilk test. The association between hyperuricemia and the Child-Pugh class was assessed using the chi-square test. The statistical difference in serum uric acid levels among patients in Child-Pugh classes A, B, and C was assessed using non parametric test (Kruskal-Wallis test). To investigate the linear relationship, the Spearman rank test was used, and a p value of less than .05 was considered as statistically significant. The results were visually presented through a scatter plot diagram.

Ethical issue

Prior initiation of the study, ethical clearance was obtained from Ethical Review Committee of Dhaka Medical College (ERC-DMC/ECC/2020/368). Ethical considerations were maintained with highest priority in this study according to the 'Declaration of Helsinki',

III. Result

In the study, the mean age of patients with CLD was 44.71±5.52 (SD) years where more than one-third were in the age group 41-50 years. Male preponderance was observed with a percentage of 73.8%. Viral hepatitis was the most common etiology with a percentage of 71.3%. Other etiologies were non-alcoholic fatty liver disease (NAFLD), unknown, alcohol and autoimmune hepatitis.

Regarding the severity of chronic liver disease (CLD), nearly half of the patients were classified as Child-Pugh class C (48.8%), indicating a severe stage of liver disease. **(Table 1)**

Table 1: Baseline characteristics of the study patients with CLD (n=80)

Variables	n (%)
Age groups (years)	
31-40	12 (15)
41-50	30 (37.5)
51-60	21 (26.3)
61-70	12 (15)
71-80	5 (6.3)
Mean±SD	44.71±5.52
Gender	
Male	59 (73.8)
Female	21 (26.3)
Etiology	
Chronic viral hepatitis	57 (71.3)
NAFLD	9 (11.3)
Unknown	8 (10)
Alcohol	3 (3.8)
Autoimmune hepatitis	3 (3.8)
Child-Pugh class	
Class A	11 (13.8)
Class B	30 (37.5)
Class C	39 (48.8)

Median serum uric acid among study patients was 6.16 mg/dl with a range of 10.92. **(Figure 1a)** Median serum uric acid was significantly higher in CLD patients of Child-Pugh class C than that of class B and class A (p<.001). **(Figure 1b)**

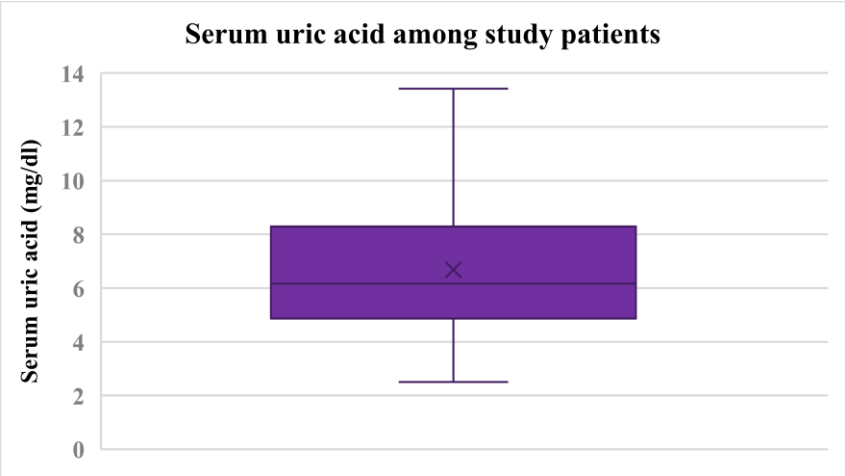

Figure 1a: Distribution of serum uric acid levels in CLD patients (n=80)

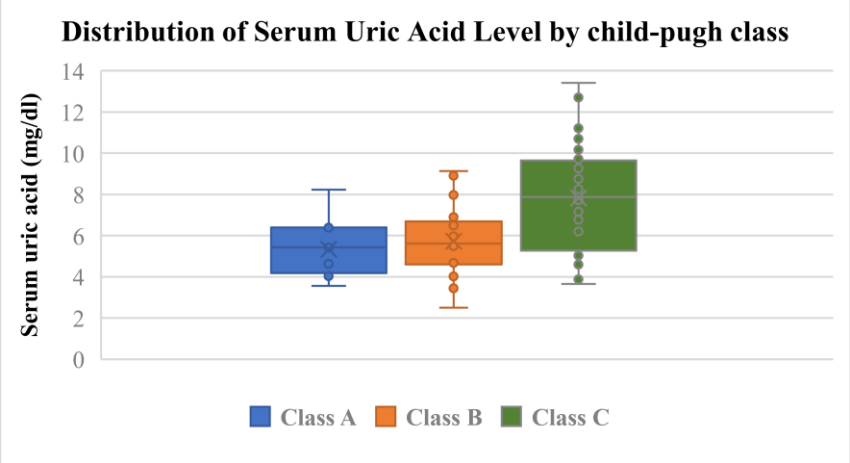

Figure 1b: Distribution of serum uric acid levels in CLD patients by Child-Pugh classification (n=80)

About 40% of the study patients had hyperuricemia. **(Figure 2)** A significant association between higher Child-Pugh classes and elevated serum uric acid levels was observed **(Table 2).**

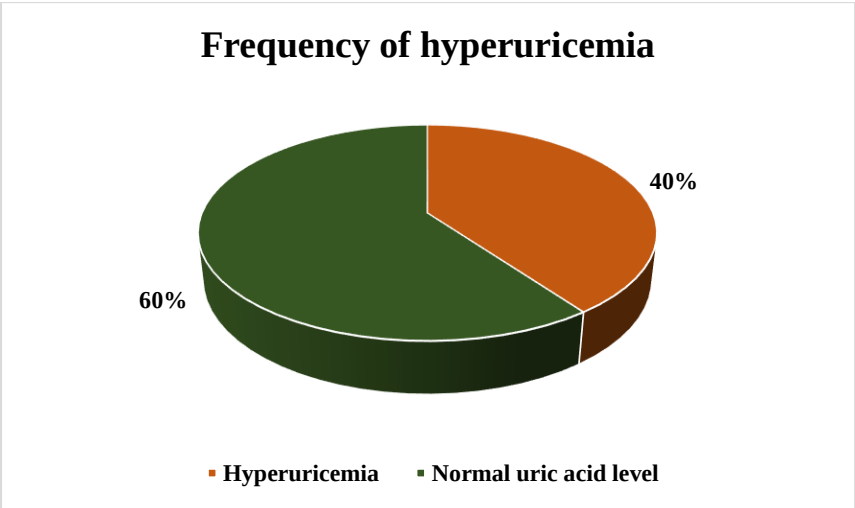

Figure 2: Frequency of hyperuricemia among study patients with CLD (n=80)

Table 2: Association between Child-Pugh score classification and hyperuricemia among the study patients (n=80)

Child-Pugh class	Hyperuricemia n=32	Normal level of uric acid n=48	p value
Class A	2 (6.2)	9 (18.8)	**<.001**
Class B	5 (15.6)	25 (52.1)	
Class C	25 (78.1)	14 (29.2)	

p value was determined by chi-square test

A scatter plot demonstrated a clear positive correlation between serum uric acid levels and Child-Pugh scores with statistical significance (rho .337, p .002). **(Figure 3)**

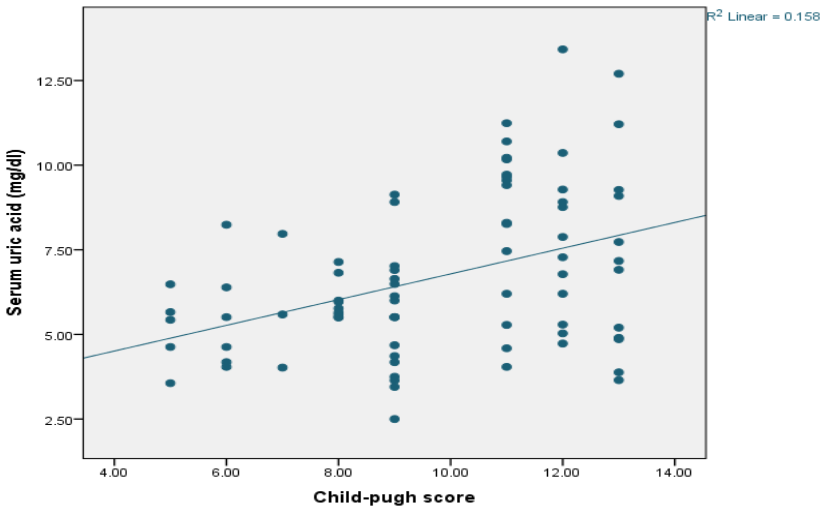

Figure 3: Scatter plot showing a correlation between serum uric acid and Child-Pugh score among study patients with CLD (n=80)

IV. Discussion

This cross-sectional observation assessed the level of serum uric acid among CLD patients and observed that hyperuricemia was present in 40% of the study patients. A significant association of hyperuricemia was observed with more sever class of CLD according to Child-Pugh score. Several previous studies also have reported an increased frequency of hyperuricemia among patients with Chronic Liver Disease (CLD) [6, 19]. In a prior study carried out in Bangladesh focusing on patients with liver cirrhosis, a high prevalence of hyperuricemia was similarly reported [20]. The median value of serum uric acid was notably higher in patients of Child-Pugh class C than class B and A. Additionally, significantly positive linear correlation was also observed between serum uric acid and Child-Pugh score in the study patients.

The present study findings indicate a trend where more severe hepatic impairment corresponds with elevated levels of serum uric acid with statistical significance which further suggest a potential utility of serum uric acid as a prognostic marker for liver disease severity. As an end product of purine metabolism, uric acid is derived from both endogenous and exogenous sources and metabolized by muscles, intestines, and liver. Approximately two-thirds of uric acid is excreted in the urine, and the remaining one-third is excreted in feces. In case of individuals with compromised hepatic function, uric acid level in blood might tend to increase primarily due to the impaired metabolism in liver. And liver usually facilitates the excretion of uric acid into the bile, which is then eliminated through fecal excretion and during chronic liver disease due to any cause, this excretory pathway may become compromised. As a consequence, the level of uric acid in the bloodstream tends to increase with the worsening of chronic liver disease [21–23]**.** These findings are supported by several previous studies [10, 24, 25].

In this study the average age of the CLD patients was 44 years while maximum of them were in 4th and 5th decades of their life. A clear male predominance was observed with almost three-fourth male patients. Similar age and gender pattern were reported in several previous studies [10, 26–28]. The most common etiology of CLD in study patients was viral hepatitis which is not corroborated the studies conducted in other countries [29]. But prior studies conducted in Bangladesh reported viral hepatitis as prime etiology of CLD [30–32].

The observed hyperuricemia in CLD patients could be multifactorial and the exact mechanism is yet to reveal. However, as liver function deteriorates, the serum uric acid level increases. This interrelationship

emphasizes the importance of monitoring serum uric acid levels as part of the comprehensive management of CLD patients. Furthermore, the high prevalence of viral hepatitis for regions like Bangladesh, where hepatitis B and C are significant public health concerns indicate the necessity of targeted interventions such as vaccination and screening, to manage and prevent the progression of CLD in these populations. The present findings also suggest that serum uric acid levels may serve as an accessible biomarker for monitoring disease progression in resource-limited settings where the full spectrum of liver function tests may not be available.

The study was not beyond limitations and the one among them was its cross-sectional design. Further longitudinal studies involving multiple centers would be required to determine the change of serum uric acid through the disease courses. Additionally, the sample size was relatively small and conducted at a single center, which may limit the generalizability of the findings.

V. Conclusion:

A significant association between serum uric acid level and the severity of chronic liver disease (CLD) was demonstrated in this study where two-fifth of the study patients had hyperuricemia. So, serum uric acid might have potential to assess the disease progression for or severity. Further longitudinal studies involving multiple centers are recommended to better understand the role of serum uric acid in the progression of CLD.

Declarations

Ethics approval: The study protocol was reviewed and approved by the Ethical Review Committee of Dhaka Medical College. Ethical issues were maintained in accordance with the Helsinki Declaration.

Consent for publication: none

Availability of data and materials: The data and other necessary details are available and can be found upon reasonable request to the corresponding authors.

Conflict of interest: None

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Formal analysis: SKN, MAR, SB
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Supervision: SKN, MAH, MSJS, MMR
Writing – original draft: SKN, MSJS, MMR, MAY
Writing – review & editing: SKN, SB

Use of ChatGPT: ChatGPT 3.5 was used for language editing and to improve clarity of the manuscript.

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