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Original Article

Predictive Ability of Serum Uric Acid Levels in Assessing the Severity of Chronic Liver Disease

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Abstract

Background: Elevated serum uric acid levels are known to be associated with the progression of liver disease. However there is a paucity of literature in respect to its predictive value and its cut off scores in the current study setting. Hence the present study was conducted.

Objectives: The objectives of the study were as follows: (1) To assess the serum uric acid levels with the severity of chronic liver disease, (2) to determine the predictive ability of the serum uric acid levels in predicting the severity of chronic liver disease, and (3) to establish the cutoff uric acid levels to predict the severity of chronic liver disease in the present study setting.

Methods: This is a cross-sectional study conducted among 100 study subjects aged ≥18 years, with chronic liver disease (CLD) admitted under the Department of General Medicine, Kempegowda Institute of Medical Sciences, Bengaluru, for a period of 1 year. The data were collected, serum uric acid levels were determined, and the severity of CLD was assessed using Child-Turcotte-Pugh (CTP) scoring. Independent *t*-test and one-way ANOVA were used to find the difference in means. Receiver operating characteristic curve and Youden's index were used to assess the predictive ability of serum uric acid in detecting the severity of CLD. $P < 0.05$ was considered statistically significant.

Results: Majority, that is, 48.0% of the study subjects were in the age group of 41–60 years and 79.0% were male. About 57.0% had elevated uric acid levels. The uric acid levels were significantly higher among those with CTP Class C disease (8.74 ± 1.97 mg/dL) compared to Class A and B ($P < 0.05$). Serum uric acid levels showed very good accuracy in predicting severity of CLD (area under the ROC curve [AUC] = 0.86, $P < 0.001$). The cutoff of 7.75 mg/dL levels of uric acid showed highest specificity of 84.0% and a sensitivity of 74.0%.

Conclusion: Elevated serum uric acid levels were found in 57.0% of the study subjects and mean uric acid levels were higher among those with severe chronic liver disease. Serum uric acid levels were very good significant predictor of severity of chronic liver disease and can be used in the assessment of its severity with a specificity of 84%.

Key words: Chronic liver disease, Serum uric acid, Severe disease

INTRODUCTION

Chronic liver disease (CLD) is constituted by the continuous inflammation, destruction, and regeneration of liver parenchyma, leading to fibrosis and cirrhosis. It is associated with progressive deterioration of liver functions. The most common etiologies include alcoholic liver disease, NAFLD associated with metabolic syndrome, chronic viral hepatitis, genetic, autoimmune causes, and other miscellaneous causes.[1] In 2017, there has been an estimated 1.5 Billion cases of chronic liver disease worldwide which include 10.6 Million cases of decompensated cirrhosis.[2] It is one of the common causes of death, mainly in the developing world.[1] It alone contributed to 18.3% of the 2 million global liver disease-related deaths in 2015 and has been significant in India.[3] There are several markers that are used for assessing the severity of injury and uric acid being a product of purine metabolism, it is released following cellular deaths and deterioration of nuclear material, and in tissues, it stimulates inflammation and damages the tissues. Similarly, uric acid is released following cell injury in chronic liver disease, leading to cirrhosis.[4,5] The mechanisms for the inflammation in

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hyperuricemia include induction of endothelial dysfunction, insulin resistance, oxidative stress, and systemic inflammation.[6] There have been multiple scoring systems available for assessing liver function and the severity of liver injury, namely, Child-Turcotte-Pugh (CTP) score, the model for end-stage liver disease (MELD) score, and the MELD-sodium (MELD-Na) score, however, CTP scoring is commonly used to assess the severity of hepatic dysfunction in patients with cirrhosis.[7]

Literature reports significant elevation of serum uric acid level with the progression of disease and also has been suggested as an alternative marker to predict the severity of chronic liver disease and early detection of hyperuricemia could help in managing the development of liver tissue damage associated with inflammatory disorders.[4,8,9] Serum uric acid was also higher with higher CTP score which is considered an oxidative marker for liver damage.[10] Although there are many studies on this, there are no studies conducted in the present study setting, especially which suggests the cutoff scores to detect the severity. Hence, the present study was conducted to assess the serum uric acid levels with the severity of chronic liver disease, determine the predictive ability of the serum uric acid levels in predicting the severity of chronic liver disease, and also establish the cutoff uric acid levels to predict the severity of chronic liver disease in the present study setting.

METHODOLOGY

This is a cross-sectional study conducted for a period of 1 year from July 2021 to June 2022 on patients diagnosed with chronic liver disease admitted and treated in the Department of General Medicine, Kempegowda Institute of Medical Sciences, Bengaluru.

Considering a prevalence of hyperuricemia (p) as 76.0% according to a previous study by Gupta *et al*.[11], q = 100-p, that is, 24.0%, and with an absolute precision of 10% (d), z value being 1.96 at 95% confidence interval, the total sample size was estimated to be 71 based on the formula, $n = z^2 (pq/d^2)$. Considering a non-response rate of 20.0% of 71, that is, 14.2, a total of 85 were rounded off to 100.

Using a purposive sampling, the study was conducted among the subjects who were aged 18 years and above and was diagnosed as having chronic liver disease were included and the subjects with known infections and patients with a history of recent surgery or trauma, patients having malignancy, pregnant and lactating women, moribund patients, and the subjects who were on allopurinol or thiazides or febuxostat or furosemide and on chemotherapy were excluded from the study.

Ethical clearance was obtained from the Institutional Ethics Committee. After obtaining a written informed consent, the data were collected using a semi-structured questionnaire consisting of different sections on sociodemographic profile, clinical history, and examination. Further, the patients were subjected for blood investigations, namely, liver function tests, and serum uric acid level was determined on the day of admission. The severity of chronic liver disease was assessed using Child-Turcotte-Pugh scoring as follows[4]:

Statistical Analysis

Data were tabulated into Microsoft Excel and statistical analysis was done using SPSS (version 20.0 for Windows; SPSS Inc., Armonk, NY: IBM Corp). The continuous parametric data were expressed in mean and standard deviation and continuous non-parametric data were expressed in median and range. The categorical variables were expressed in proportions. The mean values of serum uric acid levels were compared among the normal and abnormal liver functioning parameters using independent *t*-test. The mean values of serum uric acid levels were compared among the severity of Class A, B, and C of CTP scoring system using one-way ANOVA and Tukey's *post hoc* test. The Pearson correlation analysis was used for eliciting the relationship between quantitative variables such as serum uric acid and CTP scores. The association between categorical variables was assessed using Chi-square or Fisher's exact test. A receiver operating characteristic (ROC) curve was plotted to assess the predictive value of serum uric acid levels and was interpreted based on area under the curve. The sensitivity and specificity were assessed using Youden's index. $P < 0.05$ was considered statistically significant.

RESULTS

In the present study, out of 100 study subjects, majority, that is, 48 (48.0%) study subjects were in the age group of 41–60 years and the mean age was 49.9 ± 12.9 years. Most

Parameter	1 point	2 points	3 points
Total bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/L)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild or controlled by diuretics	Moderate to severe (or refractory to diuretics)
Hepatic encephalopathy	None	Grade 1–2	Grade 3–4

Class A=5–6, Class B=7–9, Class C=10–15

of them were male 79 (79.0%) and 50.0% of the study subjects belonged to CTP Class C classification, 27.0% had minimal hepatic encephalopathy, 34.0% had mild ascites, and 57.0% had elevated uric acid levels [Table 1].

The mean values of uric acid and serum albumin were 7.1 ± 2.7 mg/dL and 2.6 ± 0.6 mg/dL, respectively. The median values of serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), bilirubin, international normalized ratio (INR), and prothrombin time (PT) were 71 IU/L (10–2069), 38 IU/L (0.9–488), 3.3 mg/dL (0.2–31.4) 1.2 (0.9–12.8), and 17.7 in seconds (12.2–187), respectively [Table 2].

Mean uric acid levels were 4.03 ± 2.14 mg/dL, 5.17 ± 2.24 mg/dL, and 8.74 ± 1.97 mg/dL among the subjects having CTP Class A, B, and C, respectively. Based on the severity of chronic liver disease, on applying Tukey's *post hoc* test, it was observed that the uric acid levels were significantly higher in the CTP Class C disease (8.74 ± 1.97 mg/dL) compared to Class A (4.62 ± 2.14 mg/dL) and B (5.91 ± 2.25 mg/dL) (F [2, 97] = 33.08, $P < 0.001$) [Graph 1].

The mean values of uric acid levels were compared among the study subjects with normal and abnormal liver function tests. It was found that mean uric acid levels were significantly ($P < 0.05$) higher among those with abnormal values of SGOT (7.5 ± 2.7), SGPT (7.7 ± 2.7), bilirubin (7.7 ± 2.5), serum albumin (7.3 ± 2.6), and INR (8.0 ± 2.3) compared to those having normal values of SGOT (5.6 ± 2.1), SGPT (6.4 ± 2.5), bilirubin (4.5 ± 1.6), serum albumin (5.4 ± 2.8), and INR (4.9 ± 2.3), respectively. Mean uric acid levels were significantly ($P<0.05$) higher in those with hepatic encephalopathy (8.4 ± 2.1) and ascites (8.1 ± 2.3) compared to those without hepatic encephalopathy (5.2 ± 2.3) and ascites (4.7 ± 1.9), respectively [Table 3].

With increase in uric acid levels, bilirubin, SGOT, and SGPT levels increased and serum albumin decreased but correlation between uric acid and SGOT and SGPT lacked the statistical significance ($P > 0.05$) [Table 4 and Graph 2a-d].

On plotting ROC curve for serum uric acid levels in predicting severity of CLD, area under the curve (AUC) was found to be significant with very good accuracy (AUC = 0.86, $P < 0.001$). The cutoff of 7.75 mg/dL levels of uric acid showed highest specificity of 84.0% and 74.0% sensitivity [Graph 3].

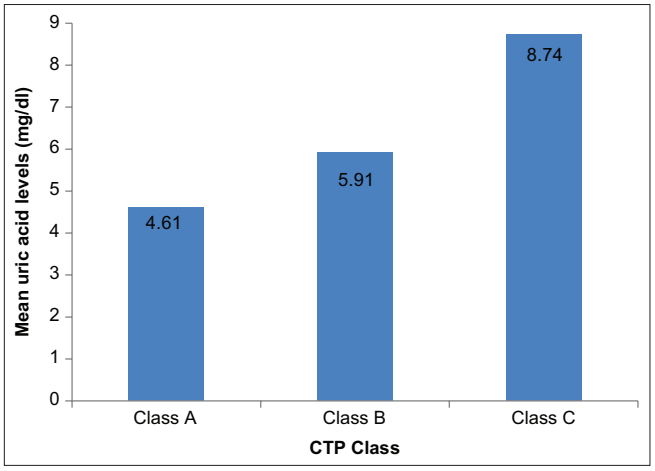
Association of uric acid with sociodemographic and clinical variables was studied. Higher proportion of the study subjects with abnormal uric acid levels were in the age

Table 1: Characteristics of the study population (*n*=100)

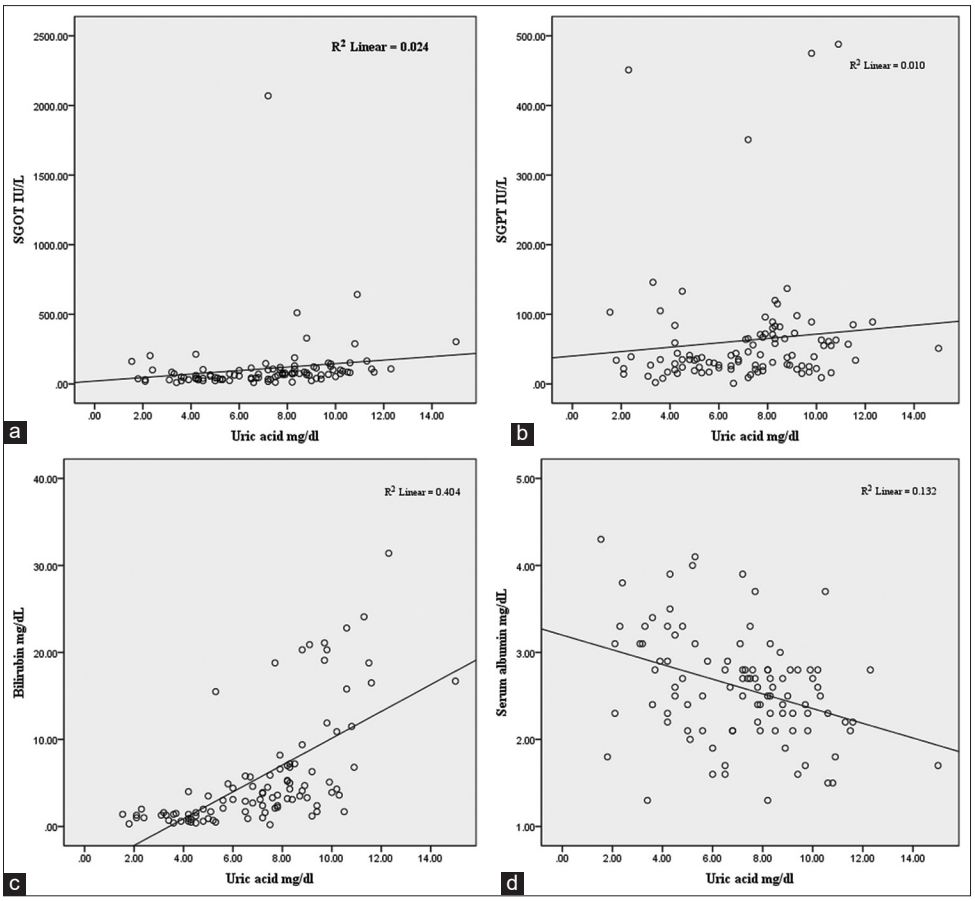
Characteristics of the study participants	
Age in years (mean±SD)	49.9±12.9
21–40	29 (29.0)
41–60	48 (48.0)
61–80	23 (23.0)
Gender (%)	
Males	79 (79.0)
Females	21 (21.0)
CTP Class	
A	18 (18.0)
B	32 (32.0)
C	50 (50.0)
Hepatic encephalopathy	
No	40 (40.0)
Minimal	27 (27.0)
Grade 1	13 (13.0)
Grade 2	15 (15.0)
Grade 3	05 (05.0)
Ascites	
No ascites	29 (29.0)
Mild	34 (34.0)
Moderate	19 (19.0)
Severe	10 (10.0)
Gross	08 (08.0)
Uric acid mg/dL	
<3.1	06 (06.0)
3.1–7	37 (37.0)
>7	57 (57.0)

Table 2: Average values of liver function test parameters

Parameters	Average values
Uric acid mg/dL (mean±SD)	7.1±2.7
SGOT IU/L (median [range])	71 (10–2069)
SGPT IU/L (median [range])	38 (0.9–488)
Bilirubin mg/dL (median [range])	3.3 (0.2–31.4)
Serum albumin mg/dL (mean±SD)	2.6±0.6
INR (median [range])	1.2 (0.9–12.8)
Prothrombin time in seconds (median [range])	17.7 (12.2–187)



Graph 1: Mean uric acid according to CTP class



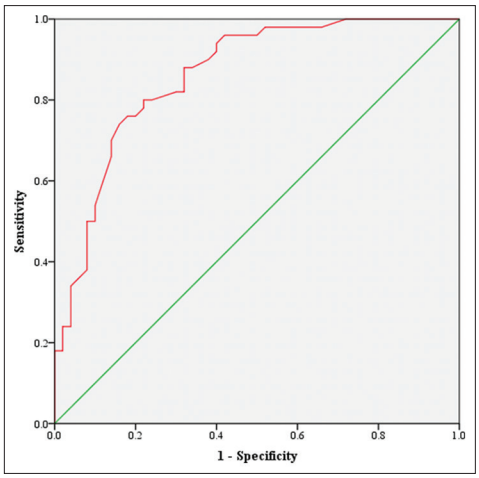
Graph 2: (a-d) Correlation of uric acid with 4A serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase, bilirubin, and serum albumin

Table 3: Comparison of mean uric acid levels with parameters of liver function

Liver function tests	Mean uric acid levels	t-value (95% CI)	*P*-value
SGOT IU/L			
Normal	5.6±2.1	−3.2 (−3.2 to−0.7)	0.002*
Abnormal	7.5±2.7		
SGPT IU/L			
Normal	6.4±2.5	−2.6 (−2.4 to−0.3)	0.01*
Abnormal	7.7±2.7		
Bilirubin mg/dL			
Normal	4.5±1.6	−5.1 (−4.5 to−1.9)	<0.001*
Abnormal	7.7±2.5		
Serum albumin mg/dL			
Normal	5.4±2.8	−2.0 (−3.7 to−0.04)	0.04*
Abnormal	7.3±2.6		
INR			
Normal	4.9±2.3	−6.3 (−4.1 to−2.1)	<0.001*
Abnormal	8.0±2.3		
Hepatic encephalopathy			
Absent	5.2±2.3	−7.3 (−4.1 to−2.4)	<0.001*
Present	8.4±2.1		
Ascites			
Absent	4.7±1.9	−6.9 (−4.4 to−2.4)	<0.001*
Present	8.1±2.3		

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate pyruvate transaminase, INR: International normalized ratio

group of 21–40 years (69.0%), were female (71.4%) but there was no statistically significant association ($P > 0.05$). Whereas significantly higher proportions of the study subjects with abnormal uric acid levels (100.0%) had



Graph 3: Receiver operating characteristic curve for serum uric acid levels in severity of chronic liver disease (area under the ROC curve = 0.86, *P* < 0.001)

Grade 2, Grade 3 hepatic encephalopathy and severe, gross ascites ($P < 0.05$) [Table 5].

DISCUSSION

Uric acid levels are found to be high in chronic liver diseases of different etiologies, and the levels have been found to correlate directly with the level of tissue damage.[5] We, therefore, undertook this study to determine the uric acid levels in patients of chronic liver disease and also to assess the predictive ability of the serum uric acid levels in predicting severity of chronic liver disease and also establish the cutoff levels.

In the present study, majority, that is, 48 (48.0%) study subjects were in the age group of 41–60 years with a male preponderance of 79 (79.0 %) similar to the study findings of Gupta *et al.*[1] About 50.0% of the study subjects belonged to CTP Class C classification whereas according to Gupta *et al.*[11] and Paul *et al.*,[12] majority of their study subjects belonged to CTP Class B classification.

About 57.0% had elevated uric acid levels and the mean values of uric acid were 7.1 ± 2.7 mg/dL in our study whereas according to Gupta *et al.*, mean uric acid (mg/dL) among the study subjects was 6.69 ± 2.92 and 76% of the subjects reported higher uric acid levels.[11]

This study reported increased uric acid levels with rise in severity of disease with mean uric acid being significantly higher in CTP Class C (8.74 ± 1.97) compared to Class A and B similar to the findings of Gupta *et al.* who also noted that mean uric acid levels were higher in CTP Class C (8.94) compared to Class A (4.03) and Class B (5.17).[11] Prakash *et al.* also noted a significant, positive correlation between uric acid level and CTP score and the finding was in line with Manomenane *et al.*[4]

Table 4: Correlation of uric acid with various parameters

Variables	*r* value	*P* value
SGOT IU/L	0.155	0.124
SGPT IU/L	0.100	0.321
Bilirubin mg/dL	0.635	<0.001*
Serum albumin mg/dL	−0.363	<0.001*

*Statistically significant

Table 5: Association of uric acid levels with various factors

Variables	Uric acid		χ^2–value (*P*-value)
	Normal (*n*=37)	Abnormal (*n*=63)	
Age group in years			
21–40	09 (31.0)	20 (69.0)	0.94 (0.63)
41–60	20 (41.7)	28 (58.3)	
61–80	08 (34.8)	15 (65.2)	
Gender			
Males	31 (39.2)	48 (60.8)	0.81 (0.37)
Females	06 (28.6)	15 (71.4)	
Hepatic encephalopathy¥			
Minimal, Grade 1	12 (30.0)	28 (70.0)	(0.005)*
Grade 2, Grade 3	00 (0.0)	20 (100.0)	
Ascites¥			
Mild, moderate	17 (32.1)	36 (67.9)	(0.004)*
Severe, gross	00 (0.0)	18 (100.0)	

¥ Fisher's exact test

Hepatic encephalopathy and ascites are the components of CTP score along with serum bilirubin, albumin, and INR which are used to assess the severity of chronic liver disease.[4] In this study, it was observed that the mean uric acid levels were significantly ($P < 0.05$) higher in those with hepatic encephalopathy (8.4 ± 2.1 mg/dL) and ascites (8.1 ± 2.3 mg/dL) compared to those without the manifestation and all the study subjects with abnormal uric acid levels (100.0%) had Grade 2, Grade 3 hepatic encephalopathy and severe, gross ascites and this association was statistically significant ($P < 0.05$) indicating higher mean serum uric acid among those with severe disease manifestation. Furthermore, the mean uric acid levels were significantly ($P < 0.05$) higher among those with abnormal values of SGOT (7.5 ± 2.7), SGPT (7.7 ± 2.7), bilirubin (7.7 ± 2.5), serum albumin (7.3 ± 2.6), and INR (8.0 ± 2.3) compared to those having normal values. This is in line with the observations of Gupta *et al.* who concluded that with the increase in uric acid level, that is, 3.1–5, 5–7, and >7 mg/dL, respectively, total bilirubin (mean values: 2.43, 2.86, and 5.21, respectively), SGOT (mean: 52.68, 59.87, and 118.41), and SGPT (mean values: 54.39, 59.96, and 119.81) also increased significantly ($P < 0.05$).[11] Afzali *et al.*

noted that a higher serum uric acid level was associated with a greater probability of elevated serum liver enzymes which are associated with the development of cirrhosis[13] similar to the present study but for the significance in terms of correlation between uric acid levels and SGOT and SGPT. Prakash *et al*., also in his study, observed a significant, positive correlation between uric acid level with total bilirubin and negative correlation with serum albumin similar to the present study findings.[4] Gupta *et al*. in his study noted a significant positive correlation between uric acid and total bilirubin, SGOT, and SGPT.[11] The difference in the findings may be due to the difference in the disease presentation and disease severities among the study subjects in different study settings.

ROC curve for serum uric acid levels showed a good accuracy (AUC = 0.86) in predicting severity of CLD and the cutoff of 7.75 mg/dL levels of uric acid showed highest specificity of 84.0% and a sensitivity of 74.0%. According to Zheng *et al*., the prevalence of fatty liver increased progressively with serum uric acid levels and the AUC for detecting mild fatty liver based on SUA was 0.70 and the AUC for detecting moderate and severe fatty liver based on SUA was 0.78.[14] Wei *et al*., in their study, have found serum uric acid to be correlated positively with NAFLD, and elevated SUA level to be an independent predictor for the incidence of NAFLD and the cutoff levels were found to be ≥288.5 μmol/L, that is, 4.85 mg/dL, that showed a sensitivity of 75.5% and specificity of 46.5% with area under the curve 0.637. The difference in the findings might be due to the fact that it was to predict the incidence of NAFLD in their study and it was to predict the severity of chronic liver disease in ours; hence, the cutoff value is higher in our study.[15] Hejazi *et al*. reported a strong correlation between the uric acid and the development of inflammatory disease, hence, early detection of hyperuricemia can serve as a predictor of inflammation.[9] Singh *et al*. also have concluded serum uric acid levels as an oxidative marker for liver damage.[10] There are not many studies eliciting the cutoff scores to predict the severity of chronic liver disease.

Since it is a cross-sectional study, serum uric acid was measured only once, further studies with larger sample size and follow-up of patients are required to generalize the study findings.

CONCLUSION

Elevated serum uric acid levels were found in 57.0% of the study subjects. Mean uric acid levels were significantly higher with severe manifestation of the disease, that is, CTP Class C disease, abnormal SGOT, SGPT, bilirubin, serum albumin, INR, and presence of Grade 2 and 3 hepatic encephalopathy and severe, gross ascites. Serum uric acid had a very good accuracy in determining the severity of the disease; hence, uric acid can be used as a marker of severity of chronic liver disease with a specificity of 84.0% and a sensitivity of 74.0%.

REFERENCES

1. Sharma A, Nagalli S. Chronic liver disease. In: StatPearls. Treasure Island: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554597 [Last accessed on 2022 Jul 04].
2. Vento S, Cainelli F. Chronic liver diseases must be reduced worldwide: It is time to act. Lancet Global Health 2022;10:e471-2.
3. Mondal D, Das K, Chowdhury A. Epidemiology of liver diseases in India. Clin Liver Dis (Hoboken) 2022;19:114-7.
4. Prakash BC, Rai SK. Study of serum uric acid in liver cirrhosis and its correlation with child turcotte pugh, MELD and UKELD score. Int J Res Med Sci 2020;8:1-5.
5. Manomenane M, Viswanathan KN, Badrinath AK, Karthik J, Mohan R. Study of serum uric acid level in chronic liver disease and its correlation with child-turcotte-pugh score and platelet indices. J Med Sci Clin Res 2022;10:93-8.
6. Hasan R, Roy PK, Khan MM, Ahmed F, Alam MR, Gain G. Relation of serum uric acid concentrations with etiology and severity in patients with cirrhosis of liver. Banglad Med J 2021;50:46-51.
7. Shafiq S, Khan MN, Majumder B, Alam MS, Islam MS, Sultana T. Correlation of albumin-bilirubin (ALBI) score with child-turcotte-pugh (CTP) score in the evaluation of liver cirrhosis. Am J Lab Med 2019;4:60-4.
8. Choudhary J, Fiza B, Sinha M. Serum uric acid level and its association with child pugh score in chronic liver disease. Int J Med Res Prof 2019;5:13-5.
9. Hejazi AA, Tabash AM, Afana WM, Mustafa AM. Inflammatory biomarkers status and liver enzyme among hyperuricemia patients in Gaza strips. Arch Clin Case Stud 2019;1:1-4.
10. Singh MB, Singh KA, Singh MR. Study of serum uric acid levels among patients of chronic liver disease. J Evid Based Med Healthc 2019;6:2629-32.
11. Gupta PK, Agarwal H, Singhal S, Manocha K. Study of association between serum uric acid levels and chronic liver disease. Eur J Mol Clin Med 2021;8:1169-73.
12. Paul R, Chakravarti HN, Mandal SK, Chatterjee S, Choudhury PS. Study of serum uric acid in chronic liver disease and its relation with other parameters. Int Res J Pharm 2013;4:162-5.
13. Afzali A, Weiss NS, Boyko EJ, Ioannou GN. Association between serum uric acid level and chronic liver disease in the United States. Hepatology 2010;52:578-89.
14. Zheng X, Gong L, Luo R, Chen H, Peng B, Ren W, *et al*. Serum uric acid and non-alcoholic fatty liver disease in non-obesity Chinese adults. Lipids Health Dis 2017;16:202.
15. Wei F, Li J, Chen C, Zhang K, Cao L, Wang X, *et al*. Higher serum uric acid level predicts non-alcoholic fatty liver disease: A 4-year prospective cohort study. Front Endocrinol (Lausanne) 2020;11:179.

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