ABSTRACT

BACKGROUND
Elevated serum uric acid (UA) level strongly reflects and may even cause oxidative stress, metabolic syndrome and insulin resistance which are risk factors for progression of liver disease. Hepatic injury is associated with distortion of the metabolic function. Hepatic disease/Cirrhosis of liver can be evaluated by biochemical analysis of serum tests, includes levels of serum alanine and aspartate amino transferases, alkaline phosphatase, and also by uric acid estimation. In chronic liver disease, high serum uric acid is associated with more severe disease. However, there are limited numbers of studies showing the association of uric acid with different parameters of liver dysfunction.

METHODS
In this study a total of 66 patients of known chronic liver disease of different causes were included. All patients were above 18 years of age. Patients with factors that influence the serum uric acid level were excluded. A thorough history was obtained, and physical examination was done. Various laboratory data including serum uric acid level and liver function test were measured. Using different parameters, Child Turcotte Pugh (CTP) score was calculated for each patient. Using suitable statistical method, data was analysed for any association between serum uric acid level and different causes of chronic liver disease and disease severity using Child Turcotte Pugh (CTP) grading.

RESULTS
In our study, out of 66 patients suffering from chronic liver disease, 48 (72.7%) were male. Alcohol was the most common cause (69.7%) of CLD followed by chronic hepatitis C (15.2%). A higher serum uric acid level was observed among patients with non-alcoholic fatty liver disease (NAFLD) (7.04±1.61) and patients with CTP class C (8.26±1.75).

CONCLUSIONS
From our study, we can conclude that uric acid is higher in patients with NAFLD as hyperuricemia is associated with many risk factors for NAFLD such as obesity, insulin resistance and metabolic syndrome. Serum uric acid is also higher with higher CTP score which is an oxidative marker for liver damage.

KEYWORDS
Uric Acid, Oxidative Stress, Metabolic Syndrome, Insulin Resistance, Chronic Liver Disease (CLD), Child- Turcotte-Pugh (CTP), NAFLD

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which hyperuricemia could actually cause them. It has been shown that hyperuricemia can induce endothelial dysfunction, insulin resistance, oxidative stress, and systemic inflammation.\textsuperscript{4,5} Oxidative stress, insulin resistance and systemic inflammation are now known to be important risk factors for the development or progression of various chronic liver diseases. These conditions are considered central in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).\textsuperscript{6} In addition, they contribute to the progression of hepatitis C virus and alcoholic liver diseases.\textsuperscript{7} High Uric Acid levels are found in NAFLD and alcoholic liver disease as an independent aetiology and secondary to alcohol metabolism respectively. In different biological studies, serum UA has been found to correlate directly with the level of tissue injury.\textsuperscript{8} On this background, this study is done to measure the serum UA level and to correlate with the disease severity and etiology, if any among patients of chronic liver disease.

This study was undertaken to measure the serum uric acid level in patients of chronic liver disease and to correlate with Child-Turcotte-Pugh (CTP) grading.

**METHODS**

This study is a hospital based observational, cross sectional on time study. A total of 66 patients of known Chronic Liver Disease (CLD) of any aetiology who were either admitted in the medicine ward or attending OPD of medicine of our hospital Jawaharlal Nehru Institute of Medical Sciences (JNIMS) Imphal, Manipur from January 2019 to June 2019 were included in this study. Patients with known history of Hyperuricemia, Gout, and malignancy, currently alcoholic or on chemotherapy, Allopurinol, febuxostat, Thiazide, frusemide which may cause altered Uric acid (UA) level were not included in this study. A thorough history including pattern of alcohol intake was taken from the patient and their relatives and a thorough clinical physical examination with special attention to abdomen and nervous system was done. Blood sample were sent for all patients for Liver function test including bilirubin, enzymes, protein, albumin, prothrombin time (PT). Uric acid (UA) was measured for each patient using Uricase end point method. Radiological imaging with ultrasonography (USG) of abdomen was done to know the degree of ascites. Child Turcotte Pugh score was calculated using various parameters (Bilirubin, Albumin, Prothrombin time, Degree of Hepatic encephalopathy and amount of Ascites) and patients were grouped into 3 CTP Classes of A, B, C. Statistical analysis was done using SPSS software and results were expressed as mean with standard deviation.

**Inclusion Criteria**

Patients of chronic liver disease both male and female, above 18 years of age.

**Exclusion Criteria**

Patients with known history of Hyperuricemia, Gout, and malignancy and who are currently alcoholic or on chemotherapy or drugs like Allopurinol, Febuxostat, Thiazide, and Frusenide which may cause altered serum Uric acid (UA) level are not included in this study.

**RESULTS**

In this study a total of 66 patients with known Chronic liver disease of different aetiology were studied. Out of 66 patients, 48 (72.7%) were male and 18 (27.3%) were female. Among all causes, alcohol was the most common cause of CLD (46 cases; 69.7%) out of which 39(84.8%) were male and 7(15.2%) were female. Second most common cause was HCV (10 cases, 15.2%). We had 8 cases of NAFLD out of which 7(87.5%) cases were female compared with only 1(12.5%) male. Auto immune hepatitis (AIH) was the least common type of CLD with only 2 cases (3%) both being female. Table 2 shows that mean serum uric acid was higher among NAFLD patients (6.42±1.95) compared with Alcohol (5.59±2.25), HCV (5.51±1.44) and AIH (4.75±0.59). As shown in table 3, we had 30 patients in CTP class B which is followed by 20 patients in CTP class C and 16 patients in class A. The mean serum uric acid level was higher among patients with CTP class C (8.26±1.75) than class A and B.

**DISCUSSION**

Mean serum uric acid values of adult men and premenopausal women are 6.8 mg/dl and 6 mg/dl respectively. After menopause values for women increases to approximate those of men. Elevated uric acid level reflects oxidative stress in tissue and is also a marker of metabolic syndrome. Both these conditions are associated with progression of CLD.\textsuperscript{9} A study from United States found that patients with high serum uric acid level had higher risk of cirrhosis associated hospitalization or death.\textsuperscript{9} In our study a high serum uric acid level was seen among certain group of patients. We found in our study a high uric acid in Non-alcoholic fatty liver disease (NAFLD) patients (7.04±1.61). A study from China reported that among 8925 employees of a chemical company, the serum UA level was associated with ultrasonographic NAFLD after adjustment of 10 anthropometric and metabolic potential confounder.\textsuperscript{10}
(although insulin resistance was not estimated). Another study from Italy also showed that 60 patients with ultrasonographic NAFLD had higher serum uric acid level than 60 historical controls without NAFLD. These studies suggest that hyperuricemia is associated with NAFLD; this would be expected because hyperuricemia is associated with many risk factors for NAFLD such as obesity, insulin resistance and metabolic syndrome. Our study did not find high uric acid level in Chronic hepatitis C unlike other study. This may be because of the fact that in our study majority of patient (8 out of 10) was under treatment with DAA. In our study we also found a higher uric acid level with higher Child Turcotte Pugh (CTP) grading. Thus, serum Uric acid was higher in patients with CTP class C than class B and class A. Uric acid is also considered as an oxidative marker of tissue damage and thus liver damages. Two different studies from India also found higher UA among patients with higher Child Turcotte Pugh (CTP) grade. These studies show that with increasing severity of Chronic liver disease (CLD) is associated with higher Uric Acid. A Korean study also found a significant relation of UA with liver histology grade. Although our study is limited by being a small size study sample and being cross-sectional one-time study still this study shows an association between serum Uric acid level and different parameters of chronic liver disease. Studies regarding uric acid level in Chronic liver disease are still rare. Majority of the studies had been done among NAFLD patients where there is associated higher uric acid level. It has been proposed recently that hyperuricemia rather than being simply a marker might contribute to the cause of insulin resistance, oxidative stress, systemic inflammation and metabolic syndrome. Because these conditions can cause NAFLD, promotes its progression to steatohepatitis or even promotes the progression to steatohepatitis or even promote the progression of viral and alcoholic hepatitis, they represent the mechanism by which hyperuricemia can directly cause cirrhosis. Hyperuricemia can induce endothelial dysfunction and reduced bioavailability of endothelial nitric oxide in rats. Furthermore hyperuricemia induces inflammatory and oxidative changes in adipocytes and this process is crucial in causing metabolic syndrome in obese mice. Liver injury is characterized by high blood level of oxidative marker. Uric Acid may be considered as a marker of oxidative stress. The level is found to correlate with higher CTP grade.

CONCLUSIONS
Elevated serum UA level might be a risk factor for the incidence of chronic liver disease. However, a crucial question raised by our finding is whether hyperuricemia directly causes hepatic necroinflammation and cirrhosis or whether it is just a marker for an adverse metabolic profile that leads to NAFLD/NASH or promotes progression of viral or alcoholic hepatitis. Observational studies such as ours cannot definitely distinguish between these two possibilities, but it is tempting and potentially useful to speculate whether hyperuricemia is a cause or a marker. Future studies should investigate whether this association is causal or has clinical utility in the prediction of the presence or incidence of liver disease. Nonetheless, even hyperuricemia proves in the future to be only marker for the presence of hepatic necroinflammation or the development of cirrhosis and not a cause, it is likely to be a useful marker. It may thus act as a surrogate marker for assessing the prognosis of CLD. However, further larger prospective case control studies are needed to show the relationship between serum uric acid and severity of chronic liver disease. If this is confirmed, uric acid can be used as a marker of severity of CLD and can be used in the assessment of prognosis of CLD.

REFERENCES

