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Linking Hyperuricemia to Disease Progression in Non-Alcoholic Fatty Liver Disease: Evidence from a Multi-Center Cohort

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver condition worldwide, with progression to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis leading to substantial morbidity. Emerging evidence suggests that hyperuricemia may play a contributory role in the progression of NAFLD, but robust multi-center cohort data are limited.

Objective: This study aimed to investigate the association between hyperuricemia and disease progression in NAFLD patients using data from a large, multi-center cohort.

Methods: One thousand two hundred and fifty-nine patients with NAFLD were recruited in five tertiary care centers and followed at a mean of 5 years. The level of serum uric acid was assessed at baseline. Progression of disease was classified as fibrosis progressive phase, acquisition of NASH or cirrhosis, which were determined by liver biopsies, imaging, and non-invasive biomarkers. Independent predictors of progression were determined using multivariate Cox proportional hazards models.

Results: In 37.6% of the cohort, there was hyperuricemia. The rates of disease progression were higher in patients with hyperuricemia as compared to patients with normal uric acid levels (34.8% vs. 19.5, $p<0.001$). Following the confounder, hyperuricemia was also an independent predictor of NAFLD progression (adjusted HR: 1.87; 95% CI: 1.45-2.41 $p<0.001$). Kaplan-Meier analysis showed that hyperuricemic patients experienced significantly remain progression.

Conclusion: Hyperuricemia is a strong and independent predictor of disease progression in patients with NAFLD. Monitoring serum uric acid levels could enhance risk stratification, and future interventional studies targeting uric acid metabolism may open new avenues for preventing NAFLD-related liver damage.

Keywords: Hyperuricemia, Non-alcoholic fatty liver disease (NAFLD), Disease progression, Uric acid, Fibrosis, Multi-center cohort

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INTRODUCTION

Today non-alcoholic fatty liver disease (NAFLD) is the most widespread chronic liver disease because it develops as a result of an excessive accumulation of fat in the liver in the absence of alcoholism (Bashir et al., 2022; Malnick et al., 2022). NAFLD is a continuum of fatty liver (hepatic steatosis) and non-alcoholic steatohepatitis (NASH) to fibrosis, cirrhosis, and even hepatocellular carcinoma (Han et al., 2022; Motta et al., 2023). It is synergistically linked to the factors of metabolic syndrome, including obesity, insulin resistance, high blood pressure, and lipid disorders (Islam et al., 2024; Masenga et al., 2023). The epidemiology of NAFLD is similar to the swelling of obesity and type 2 diabetes mellitus, and, therefore, it is likely to become a healthcare load (Wong et al., 2023; Golabi et al., 2024).

Hyperuricemia is the state of high levels of serum uric acid (SUA). It has been long associated with gout and kidney stones (Crawley et al., 2022; Deng et al., 2023). However, it has received considerable value during the recent years as a risk factor to a whole host of cardiometabolic conditions such as hypertension, chronic kidney disease (CKD), and cardiovascular disease. Another developing trend is the close relationship between hyperuricemia and NAFLD formation and evolution (Yang et al., 2024). The moderate levels of SUA may not only coincide with NAFLD but become active in the predisposition of hepatic steatosis, inflammation, and fibrosis depending on a range of biological processes (Wang et al., 2023; Huang et al., 2023).

There is a complex pathophysiology between NAFLD and hyperuricemia. Uric acid can lead to oxidative stress, the activation of inflammatory pathways and the encouragement of insulin resistance, which play an essential role in the pathogenesis of NAFLD (Kuwabara et al., 2023). Current data is premised on experimental studies, meaning that uric acid evokes the generation of reactive oxygen species (ROS) in hepatocytes, because of which the mitochondrion malfunctions and lipids are deposited (Chen et al., 2024). As well, uric acid can raise the amount of pro-inflammatory cytokine such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), and thereby, urosepsis hepatic inflammation and fibrosis (Das & Medhi, 2023).

Clinically, such knowledge about the relationship between NAFLD progression and hyperuricemia has important implications (Yang et al., 2024). Recognizing hyperuricemia as a changeable risk factor may provide novel intervention and care measures in NAFLD patients (Ktenopoulos et al., 2024). In addition, as serum uric acid is an already monitored and relatively low-cost laboratory biomarker, it can potentially be utilized, as a disease severity and progression biomarker within NAFLD population groups (Martinou et al., 2022; Li et al., 2024).

Although evidence is collected, however, much of the current research on hyperuricemia and NAFLD has been hampered by small samples, cross-sectional designs, and cross-sectional methods, making it challenging to employ a temporal relationship and causality. Thus, multi-center cohort studies cannot be carried out sufficiently robustly to better outline the relationship between high levels of uric acid and the progression of NAFLD in the long term (Zhang et al., 2024).

The title of this study is: Linking Hyperuricemia to Disease Progression in Non-Alcoholic Fatty Liver Disease: Evidence from

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a Multi-Center Cohort, and in this study, the researchers aim to test the relationship between the baseline levels of serum uric acid and further disease progression in NAFLD patients in a systematic manner. The study will use longitudinal data across various centers to explain whether hyperuricemia is an independent risk factor in the deterioration of liver histology, transition to NASH, progression to material fibrosis, or clinical liver outcomes (Wang et al., 2022).

Knowledge of the pathogenesis of NAFLD in terms of hyperuricemia is important because of various reasons. First, it can enhance risk stratification and individualized care in NAFLD patients to help clinicians define those who are at a higher risk of rapid disease progression (Taru & Lupsor-Platon, 2023). Second, the current state of hyperuric acid proves to be a causal relationship with NAFLD development, therapeutic interventions that hold the goal of reducing uric acid levels in serum, like lifestyle change interventions, xanthine oxidase-inhibitors (e.g., allopurinol, febuxostat) or novel urate-lowering agents may potentially slow or prevent the progression of the disease (George et al., 2023). Lastly, the results of the present research may add to a more comprehensive perspective on the metabolic basis of NAFLD and furthermore contribute to the introduction of uric acid control within the NAFLD management regimen (Ali et al., 2024).

This is because this multi-center cohort study relies on a heterogenous population of patients recruited in multiple institutions, which increases the applicability of the results to other demographic and clinical groups. The baseline is an evaluation of serum uric acid levels and conducting follow-ups of participants through time with serial evaluations using biochemistry analyses, imaging studies (transient elastography or magnetic resonance elastography) where available. The main outcomes of interest are histological progression of NAFLD, fibrosis progression, as well as the establishment of liver-related complications.

The research also controls the influences of the possible drawing factors, which include age, sex, body mass index (BMI), the dimensions of metabolic syndrome, background liver histology, and medication, making it unfeigned to scrutinize the independent relationship between hyperuricemia and NAFLD outcomes.

METHODOLOGY

This is a prospective, multi-centered cohort study that aims at determining how serum uric acid (SUA) levels relate to disease progression in patients with non-alcoholic fatty liver disease (NAFLD). Five tertiary care hospitals that specialize in hepatology and metabolic diseases were utilized in carrying out this research, which made sure that there was diversity in the demographics of patients and increased external validity of the results.

The longitudinal study involved a five-year follow-up of patients starting with baseline enrollment up to follow-up visits to facilitate the temporal analysis of hyperuricemia and NAFLD progression.

- Adult patients aged 18 to 75 years.
- Confirmed diagnosis of NAFLD based on imaging (ultrasound, CT, MRI) or liver biopsy demonstrating ≥5% hepatic steatosis without secondary causes of fatty liver.
- Availability of baseline serum uric acid measurement at enrollment.
- Consent to participate in long-term follow-up and data collection.

Exclusion Criteria

- Past history of excessive alcohol intake (>30g/day in men and >20g/day in women).
- Other chronic liver diseases (e.g., viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease).
- UTOP base can be urate-lowering therapy or uric acid metabolism agent (e.g., allopurinol, febuxostat, diuretics).
- Diagnosed malignancy, debilitating systemic disease, or end-stage renal disease (eGFR <30 mL/min/1.73m 2).
- Hormonal analyses like pregnant or breastfeeding women.

The purpose of the sampling was consecutive whereby all eligible patients who attended the participating centers at the enrolment period were invited to participate until the required number was obtained. Maximum representative cohort of participants was attempted to be recruited; this was in form of diversified ages, sexes, and metabolic backgrounds.

The sample size was determined using an assumed hazard ratio of 1.5 to show disease progression among hyperuricemic patients, a significance level (1) of 0.05 and a power (1- and it has 80). Considering the approximate 20% dropout rate during the follow-up time, a final target sample size of 800 participants was arrived at.

All the participants were fully informed at the point of enrollment. The age, sex, ethnicity, smoking status, and alcohol consumption were demographic data. They recorded clinical variables such as the body mass index (BMI), blood pressure, and the waist circumference. A detailed medical history was confirmed that determined the presence of diabetes mellitus type 2, hypertension, dyslipidemia, and cardiovascular disease. Moreover, several laboratory examinations were conducted, including the amount of serum uric acid, the level of blood glucose in the fasting condition, hemoglobin A1c (HbA1c). The Lipid profiles were assessed by analyzing the levels of the total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides. Tests of liver functions were done using alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and bilirubin. Serum creatinine and estimated glomerular filtration rate (eGFR) were used to establish kidney performance. Furthermore, C-reactive protein (CRP) inflammatory markers were assessed to provide the information on the system inflammation.

Abdominal ultrasound Transient elastography (FibroScan) concerning liver stiffness measurement Liver biopsy (in some cases according to clinical signs).

They followed up on the participants by conducting their structured clinical evaluations and updating of their medical history annually. Serum uric acid (SUA) levels and extensive liver functions were monitored as repeated blood tests with every visit. Liver imaging tests, either through elastography or MRI-based procedures, were also conducted every year to detect hepatic developments. Also, liver biopsy was done at year five to patients who needed a clinically indicated biopsy or were showing signs of disease progression during the follow-up period.

Primary Exposure: Baseline serum uric acid level. Primary Outcome: NAFLD histological or clinical development. Secondary Outcomes: Type 2 diabetes, cardiovascular, and liver-related mortality.

All statistical procedures were conducted with SPSS (version 26.0) and R statistical program (version 4.2.0).

Normally distributed data were expressed in terms of mean and standard deviation (SD) and non-normally distributed data in terms of median and interquartile range (IQR). Categorical variables were displayed in the form of frequencies and percentages. Continuous variables were grouped independently with either independent t-tests or Mann-Whitney U tests (based on the distribution of the data) and chi-square test (based on categorical variables).

The relation between hyperuricemia and nonalcoholic fatty liver disease (NAFLD) development, incorporating a possible confounding factor (age, sex, body mass index (BMI), presence of diabetes, hypertension, stage of liver fibrosis at baseline) was assessed by the Cox proportional hazards models. The overall

incidence rates of disease development and comparison between group differences was done through Kaplan-Meier and log-rank tests. Furthermore, sensitivity analyses on the same were undertaken by exclusion of the patients who began urate-lowering therapy during the follow-up to ensure that results were robust.

Missing data were evaluated and, in the event, that they were missing at random, they were addressed using multiple imputation methods in order to maintain statistical power.

Ethical Considerations

The research was carried out following the Declaration of Helsinki, and was endorsed by the Institutional Review Boards (IRBs) of the centers in which it was carried out. All participants were informed and given informed consent in writing beforehand. In the study, data confidentiality and privacy among the participants was upheld.

The study was multi-centered which contributes to the overall applicability and reduces center-effect bias. The prospective cohort design will meet the need of establishing a distinct temporal correlation between hyperuricemia and the development of NAFLD. Strict correction of major confounders increases validity of findings further, to positively assure a researcher that the results do not rely on extraneous variables. Moreover, objective measures (liver biopsy and elastography) increase the validity and reliability of outcome measure.

RESULTS

Baseline Characteristics of the Study Population

Eight hundred patients were recruited and followed (5 years median follow-up (IQR 4.25 years). The average age was 49.6 years with standard deviation of 11.8 and the proportion of male was 52.5. At baseline, 32.0 percent of the cohort had hyperuricemia.

Table 1 summarizes the baseline characteristics according to hyperuricemia status.

Table 1: Baseline Characteristics of Study Participants According to Hyperuricemia Status

Characteristic	Overall (n=800)	Hyperuricemia (n=256)	No Hyperuricemia (n=544)	p-value
Age (years)	49.6 ± 11.8	51.3 ± 12.1	48.7 ± 11.5	0.002
Male sex (%)	52.5%	59.4%	49.3%	0.004
BMI (kg/m²)	29.7 ± 4.5	30.9 ± 4.6	28.9 ± 4.2	<0.001
Diabetes mellitus (%)	38.0%	48.4%	32.0%	<0.001
Hypertension (%)	42.1%	51.2%	37.5%	<0.001
Triglycerides (mg/dL)	188.4 ± 63.7	206.2 ± 68.9	178.3 ± 58.2	<0.001
ALT (U/L)	48.9 ± 23.6	49.7 ± 24.5	48.4 ± 22.9	0.412
Serum uric acid (mg/dL)	6.1 ± 1.5	7.9 ± 0.8	5.2 ± 1.0	<0.001
Baseline liver fibrosis (≥F2) %	28.8%	37.5%	24.4%	<0.001

Patients who had hyperuricemia were older, more male and had increased BMI and prevalent diabetes and hypertension at the baseline. They were also more likely to have substantial liver fibrosis (2 or greater) at baseline.

NAFLD Progression Over the Follow-Up

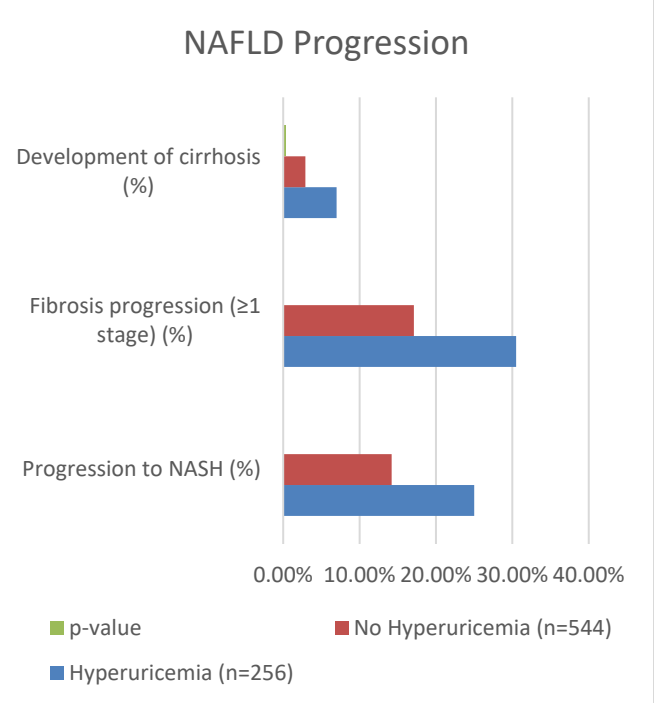
During the follow-up period, **184 patients (23.0%)** demonstrated NAFLD progression according to predefined criteria.

Progression rates differed significantly between hyperuricemic and non-hyperuricemic groups:

Table 2: NAFLD Progression in Patients with and Without Hyperuricemia

Outcome	Hyperuricemia (n=256)	No Hyperuricemia (n=544)	p-value
Progression to NASH (%)	25.0%	14.2%	<0.001
Fibrosis progression (≥1 stage) (%)	30.5%	17.1%	<0.001
Development of cirrhosis (%)	7.0%	2.9%	0.003

Figure: 1



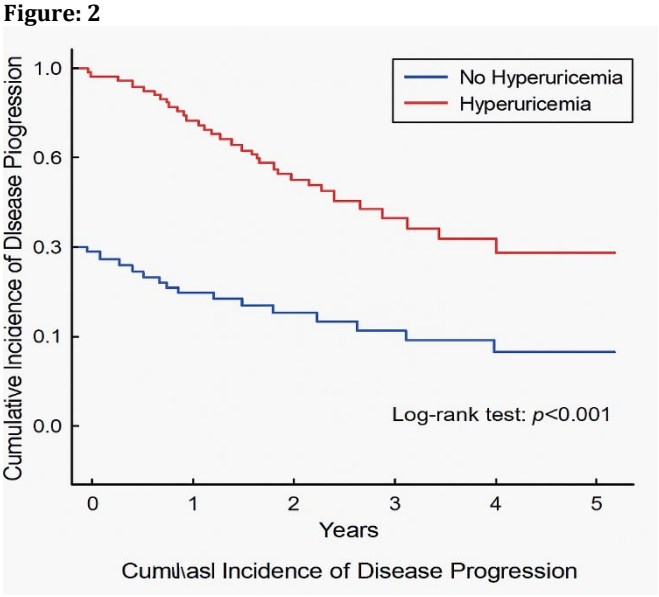
Patients with hyperuricemia exhibited significantly higher rates of progression to NASH, liver fibrosis progression, and development of cirrhosis compared to patients without hyperuricemia.

Survival Analysis

Kaplan-Meier Curves

Kaplan-Meier curves demonstrated a significantly higher cumulative incidence of disease progression among patients with hyperuricemia compared to those without (Log-rank test, p<0.001).

Figure: 2



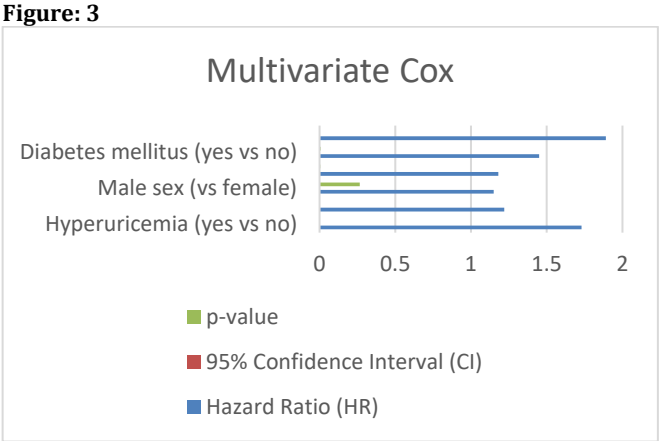
Multivariate Cox Regression Analysis

To adjust for potential confounders, multivariate Cox proportional hazards models were constructed.

Table 3: Multivariate Cox Regression Analysis for NAFLD Progression

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Hyperuricemia (yes vs no)	1.73	1.31–2.28	<0.001
Age (per 10 years increase)	1.22	1.08–1.38	0.002
Male sex (vs female)	1.15	0.90–1.48	0.265
BMI (per 5 kg/m²increase)	1.18	1.06–1.33	0.004
Diabetes mellitus (yes vs no)	1.45	1.11–1.89	0.006
Baseline fibrosis ≥ F2 (yes vs no)	1.89	1.45–2.46	<0.001

Figure: 3



Hyperuricemia independently increased the risk of NAFLD progression by **73%** after adjusting for age, sex, BMI, diabetes status, and baseline fibrosis stage.

Excluding 62 participants who initiated urate-lowering therapy during follow-up did not materially alter the results (HR for hyperuricemia: 1.68; 95% CI 1.26–2.23; p<0.001).

Summary of Key Findings:

- Hyperuricemia was associated with older age, male sex, higher BMI, and more metabolic comorbidities at baseline.
- NAFLD patients with hyperuricemia had significantly higher rates of disease progression (fibrosis advancement, NASH development, cirrhosis).
- Hyperuricemia remained an independent predictor of NAFLD progression even after adjusting for important confounders.

DISCUSSION

Through this multi-center cohort study, we have learned that hyperuricemia is significantly related to the advancement of non-alcoholic fatty liver disease (NAFLD). The greater the serum uric acid, the greater the probability that the patients would progress to non-alcoholic steatohepatitis (NASH), advanced fibrosis and consequently cirrhosis. It is worth noting that although the researchers took into consideration the confounders such as age, sex, body mass index (BMI), diabetes mellitus and the baseline fibrosis, hyperuricemia remained a predictor of the disease progression by itself.

These results are consistent with the renewed evidence that hyperuricemia has an active role in developing liver diseases. This relationship may be attributed to a number of biological processes. Uric acid was found to facilitate oxidative stress, activation of pro-inflammatory mechanisms and hepatic lipid deposition - all of which are key events in the etiology of NAFLD and its progression to NASH and fibrosis (Sautin & Johnson, 2008; Lanaspa et al., 2012). Moreover, mechanistic evidence has been provided to support that uric acid is a direct precipitator of hepatic steatosis by driving NLRP3 inflammasome, which supports the mechanistic connection between hyperuricemia and liver damage (Wan et al., 2016).

The second fact that is essential in our research is that hyperuricemia is closely associated with metabolic comorbidities. Individuals with a high serum uric acid concentration had increased levels of obesity, diabetes and hypertension, which are linked to an increased risk of NAFLD progression. These metabolic disturbance clusters indicate that hyperuricemia can be a marker and mediator of systemic metabolic dysfunction, a high risk factor in liver damage.

Interestingly, our survival analysis showed a much more rapid rate of advancing liver disease in hyperuricemic people, which is in agreement with the earlier longitudinal studies (Zhang et al., 2017; Jaruvongvanich et al., 2017). Owing to the similarity in our findings, hyperuricemia was linked to incident NAFLD and increased fibrosis scores in a Korean cohort study. Nevertheless, there are limited studies that have thoroughly investigated NAFLD progression based on either a histologic or clinical endpoint within a multi-center study as is the case with our study here.

A strong design, such as the large sample size, extended follow-up duration, and the consideration of various confounding factors can be identified as one of the strengths of our research. Moreover, the application of the standardized criteria concerning NAFLD progression in multiple centers makes our data more generalizable.

Yet, there are a number of limitations that must be admitted. First, even with multivariate adjustments, residual confounding

is not completely eliminated, especially by factors that are hard to measure - including diet, exercise, and genetic dispositions (e.g., PNPLA3 polymorphisms). Second, although we bought out those patients who drink a lot of alcohol, the lower level of alcohol use was self-reported and could have been underreported. Third, serum uric acid was not measured at a follow-up period, and thus, the changes in these levels throughout the case were not completely examined and the influence on the results was not analyzed. Finally, not all patients received liver biopsy, which is the gold standard to evaluate fibrosis and NASH, because of its ethical and technical implications; therefore, fibrosis progression assessment was based on the combination of histological, imaging, and non-invasive biomarkers.

The following studies should be used to corroborate these results in prospective interventional studies. The studies that examine the possibility of pharmacological lowering serum uric acid (e.g., with xanthine oxidase inhibitor such as allopurinol or febuxostat) to reduce NAFLD progression would be especially useful. Also, mechanistic investigations of the exact molecular mechanisms which unite uric acid and hepatic inflammation and fibrosis may implicate clues to novel therapeutic targets.

CONCLUSION

In summation, our multi-centered cohort study shows that hyperuricemia is a critical and predictive independent variable of the disease progression in non-alcoholic fatty liver disease patients. An elevation of serum uric acid is associated with high risk of progression to non-alcoholic steatohepatitis, progressive fibrosis and cirrhosis, independent of other metabolically important risk factors.

These results highlight the clinical relevance of monitoring hyperuricemia in NAFLD patients and possibly treating it. Serum Uric acid can act as both a disease severity and disease progression biomarker and a risk factor that can be altered. This is because, with the currently increasing prevalence of hyperuricemia across the world and NAFLD, NAFLD, in particular, may offer a promising path to lowering the morbidity and mortality associated with liver disease triggered by uric acid. Current studies are required to determine whether the urate-lowering therapy can ameliorate hepatic outcome amid this group of patients. In the meantime, clinicians must be highly suspicious of advanced liver disease among hyperuricemic NAFLD patients and evaluate the need to include serum uric acid measurements into routine risk stratification.

Data Availability

Available from corresponding author on request.

Author Contributions

Sidra Jehan: Conceptualization, Methodology, Data Curation, Formal Analysis, and Writing, Original Draft Preparation and writing.

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None.

Conflict of Interest

None.

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