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Association of Serum Uric Acid-to-Creatinine Ratio with Non-Alcoholic Fatty Liver Disease in the Population of Sargodha

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a growing global health concern, particularly in regions with high obesity rates. **Objectives:** To evaluate the serum uric acid to serum creatinine (sUA/sCr) ratio as a potential diagnostic biomarker for NAFLD in a Pakistani population. **Methods:** This cross-sectional study was conducted at the Department of Biochemistry, Niazi Medical and Dental College, Sargodha, from November 2023 to April 2024, with 246 participants presenting with signs and symptoms of NAFLD. Clinical and biochemical parameters, including BMI, waist circumference, blood pressure, fasting blood sugar, lipid profile, high-sensitivity C-reactive protein (hs-CRP), and liver enzymes, were assessed. Logistic regression was used to examine the relationships between these factors and NAFLD prevalence and severity. The serum uric acid/serum creatinine (sUA/sCr) ratio was evaluated as a potential biomarker for severe NAFLD. Data were analyzed using SPSS version 26.0 with ANOVA, chi-square tests, t-tests, and logistic regression.**Results:** NAFLD prevalence was 39%, with physical activity reducing the risk (OR: 0.65, p=0.015) and age, obesity, hypertension, high blood sugar, cholesterol, triglycerides, and hs-CRP identified as risk factors. Severe NAFLD was associated with increased waist circumference, hypertension, inflammation, and BMI. The sUA/sCr ratio demonstrated excellent predictive accuracy for severe NAFLD (AUC 0.90, sensitivity 85%, specificity 80%, p<0.001). **Conclusions:** It was concluded that sUA/sCr ratio was a promising non-invasive biomarker for diagnosing and assessing NAFLD severity in the population of Sargodha.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common hepatic metabolic disorder associated with obesity, insulin resistance, dyslipidemia and hypertension. The progression of nonalcoholic steatohepatitis carries the risk of cirrhosis and liver-related complications. NAFLD and other metabolic disorders have been connected to uric acid (UA), a byproduct of purine metabolism. Uric acid/creatinine (UA/Cr), as a predictor marker was used for both renal function and comprehensive metabolic deregulation and also could offer greater insight into disease profiling in early stages or risk stratification for NAFLD [1]. MetS stands for Metabolic Syndrome results in the occurrence of a series of diseases including diabetes, dyslipidemia, arteriosclerosis and other cardiovascular (CVD) or cerebrovascular diseases. The incidence of nonalcoholic liver disease has been increasing in the world and health issues due to higher all-inclusive medical costs, socio-economic burden and personal health-related complications [2]. The increasing prevalence of hyperuricemia and gout [which refers to a type of inflammatory arthritis triggered by crystallization due to accumulation of monosodium is becoming a significant issue for the general population. The rise can be explained by several factors such as the food mode, sedentary

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lifestyle and increasing numbers of aged people. Newer diets are often high in foods that contain purines, including large quantities of red and organ meats as well as certain types of fish and alcohol (especially beer) [3, 4]. When purines are metabolized by the body it produces uric acid as a waste product. High fructose diets (which are found in sugary beverages and processed foods) also lead to high uric acid levels. Compounded over the years, the increase in obesity, as well as a sedentary lifestyle, were only bringing higher rates of hyperuricemia. Over time hyperuricemia may induce insulin resistance, promoting oxidative stress and inflammation within different tissues i.e. muscle or liver. This reduces insulin sensitivity and contributes to the diminished functional mass of endocrine β-cells concerning impairs insulin signalling pathways [5, 6]. Dyslipidemia and NAFLD occur when lipid metabolism is disturbed in the host by persistently elevated uric acid. One possible mechanism where hyperuricemia leads to hepatic lipogenesis (liver fat production) while simultaneously inhibiting fatty acid oxidation is resulting in liver lipid accumulation [7, 8]. This model is based on the pathophysiological hypothesis that in NAFLD, insulin resistance drives de novo lipogenesis and inhibits beta-oxidation. The dysregulation of insulin signalling promotes hepatic glucose production and fat accumulation, thereby providing the pathogenic incentive needed for NAFLD to progress [9]. In the past few years, there have been several reports that suggest a significant and independent association between hyperuricemia with NAFLD, making increased uric acid levels one more marker for liver disease risk. This is more directly associated with an urge to monitor uric acid levels of NAFLD-susceptible individuals, especially those with metabolic syndrome [10]. This study aims to assess the sUA/sCr ratio as a diagnostic biomarker by evaluating the prevalence of moderate and severity of non-alcoholic fatty liver disease (NAFLD).

METHODS

A cross-sectional study was conducted at the Department of Biochemistry, Niazi Medical and Dental College, Sargodha, from November 2023 to April 2024. The study population includes Sargodha region where the patients were studied. The study employed a stratified random sampling technique to ensure that the sample was representative of the target population. Approved by Niazi Medical and Dental College Sargodha Hospital Institutional Review Board on (IRB Number: IRB/NM&DC/57). The total number of participants was n=246 and divided into three groups Non-NAFLD (n=150), mild-NAFLD (n=60) and moderate-to-severe NAFLD (n=36). Adults aged >18 years with symptoms of non-alcoholic fatty liver disease (NAFLD), including abdominal discomfort, fatigue, or elevated liver enzymes, were included. Participants also needed to be willing to provide informed consent and undergo a liver biopsy. Participants with a history of alcohol intake >20g/day for men or >10g/day for women, chronic liver infections, viral hepatitis, autoimmune liver disease, advanced kidney dysfunction (eGFR <30 mL/min/1.73 m^2), or those taking medications affecting uric acid levels (e.g., diuretics, allopurinol), were excluded. Patients experiencing acute illness or infection were also excluded. Alcohol intake was quantified by self-reported daily consumption (in grams). The study ensured that no participant exceeded 20 grams of alcohol intake on any given day. Physical activity was classified into two groups using the Kuwait Physical Activity Questionnaire (K-GPAQ): low (<600 METs/week) and active (>600 METs/week). METs (Metabolic Equivalent of Task) measure the intensity of physical activity. BMI was calculated based on weight (kg) divided by height (m^2), and categorized as normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). Blood pressure was categorized as normal (<120/80 mmHg), elevated (120-129/<80 mmHg), and hypertension (≥130/80 mmHg), as per the American College of Cardiology guidelines. NAFLD diagnosis was based on ultrasound findings, categorizing participants into three groups: (1) No NAFLD (normal liver), (2) Mild non-cirrhotic fatty liver, and (3) Moderate-to-severe hepatic steatosis (with or without cirrhosis). The ultrasound was used to assess liver echo patterns in comparison to the right kidney. After a 12-hour fast, participants had blood drawn to measure liver enzymes (Alanine aminotransferase [ALT], Aspartate aminotransferase [AST], Gamma-glutamyl transferase [γ-GT]), serum creatinine, serum uric acid (UA), high-sensitivity C-reactive protein (hs-CRP), and lipid profile (Total Cholesterol [TC], Triglycerides [TG], High-density Lipoprotein [HDL], and Low-density Lipoprotein [LDL]). Data were analyzed using IBM SPSS Statistics (version 26.0). Continuous variables were compared using Student's t-test or ANOVA, and categorical variables were compared using Pearson's χ^2 test. A multi-logistic regression model was used to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the serum uric acid/creatinine (sUA/sCr) ratio, adjusted for potential confounders. A receiver operating characteristic (ROC) curve was plotted to assess the diagnostic capacity of the sUA/sCr ratio for NAFLD. The optimal cut-off value to separate positive from negative cases was selected based on maximizing sensitivity and specificity. Statistical significance was set at $p<0.05$.

RESULTS

The analysis reveals that moderate-to-severe NAFLD is significantly associated with older age (mean 50.0 years vs. 46.0 and 44.0 years for mild NAFLD and non-NAFLD,

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respectively; p=0.020) and (increased from 70.0 g/week in mild NAFLD to 90.0 g/week in moderate-to-severe NAFLD; p<0.001). Moderate-to-severe NAFLD participants also showed higher waist measurement (97.2% vs. 58.3% and 53.3% obesity rates; p<0.001) and BMI (30.0 kg/m^2 vs. 27.5 kg/m^2 and 24.8 kg/m^2; p<0.001). Hypertension prevalence increased (55.6% in moderate-to-severe vs. 33.3% in mild and 20.0% in non-NAFLD; p=0.005), alongside worse metabolic markers, such as fasting blood sugar (102.0 mg/dL) and total cholesterol (210.0 mg/dL; p=0.002 and p=0.004). Liver dysfunction markers and systemic inflammation (hs-CRP 4.5 mg/L; p<0.001) were significantly higher in moderate-to-severe cases. These findings indicate advanced metabolic dysfunction and liver impairment in more severe NAFLD cases, necessitating aggressive intervention strategies (Table 1).

Table 1: Characteristics of the Participants (n=246)

Characteristics	Total (n=246)	(n=150)	Mild NAFLD (n=60)	Moderate-to-Severe NAFLD (n=36)	p-value
Age (years)	45.5 ± 10.0	44.0 ± 9.5	46.0 ± 10.0	50.0 ± 9.5	0.020
Gender (n, %)					
Male	150 (61.0%)	90 (60.0%)	40 (66.7%)	20 (55.6%)	0.470
Female	96 (39.0%)	60 (40.0%)	20 (33.3%)	16 (44.4%)	
Alcohol Intake (g/Week)	50.5 ± 30.5	30.0 ± 20.0	70.0 ± 25.0	90.0 ± 30.0	0.009
Physical Activity (METs/Week)					
Low Physical Activity	100 (40.7%)	60 (40.0%)	25 (41.7%)	15 (41.7%)	0.960
Activity	146 (59.3%)	90 (60.0%)	35 (58.3%)	21 (58.3%)	
BMI (kg/m^2)	26.5 ± 4.2	24.8 ± 3.9	27.5 ± 4.0	30.0 ± 4.5	<0.001
Blood Pressure (mmHg)					
Hypertension (≥140/90)	70 (28.5%)	30 (20.0%)	20 (33.3%)	20 (55.6%)	0.005
Waist Circumference (cm)					
Obese (men ≥90, women ≥5)	150 (61.0%)	80 (53.3%)	35 (58.3%)	35 (97.2%)	<0.001
Fasting Blood Sugar (mg/dL)	95.0 ± 15.0	90.0 ± 12.0	95.0 ± 14.0	102.0 ± 16.0	0.002
Total Cholesterol (mg/dL)	190.5 ± 30.0	180.0 ± 25.0	190.0 ± 28.0	210.0 ± 32.0	0.004
LDL Cholesterol (mg/dL)	110.5 ± 25.0	100.0 ± 20.0	110.0 ± 22.0	130.0 ± 28.0	0.001
HDL Cholesterol (mg/dL)	50.0 ± 15.0	55.0 ± 10.0	48.0 ± 12.0	42.0 ± 14.0	0.015
Triglycerides (mg/dL)	150.0 ± 40.0	130.0 ± 30.0	150.0 ± 35.0	180.0 ± 50.0	0.005
Liver Enzymes (AST, ALT, γ-GT)					
AST (U/L)	30.5 ± 10.0	25.0 ± 8.0	30.0 ± 9.0	40.0 ± 12.0	<0.001
ALT (U/L)	28.0 ± 9.0	22.0 ± 6.0	30.0 ± 8.0	38.0 ± 10.0	<0.001
γ-GT (U/L)	40.0 ± 15.0	30.0 ± 10.0	40.0 ± 15.0	55.0 ± 20.0	<0.001
Serum Creatinine (mg/dL)	0.9 ± 0.2	0.85 ± 0.15	0.90 ± 0.20	1.00 ± 0.25	0.020
Serum Uric Acid (mg/dL)	5.5 ± 1.0	5.0 ± 0.8	5.5 ± 0.9	6.5 ± 1.2	<0.001
hs-CRP (mg/L)	3.0 ± 1.5	2.0 ± 1.0	3.5 ± 1.5	4.5 ± 1.8	<0.001
Ultrasound Findings					
Fatty Liver Diagnosis (n, %)	96 (39.0%)	150 (100%)	60 (100%)	36 (100%)	<0.001

Important NAFLD predictors are found via the logistic regression analysis. The risk is increased by older age (OR: 1.05, p=0.003) and higher alcohol intake (OR: 1.02, p=0.005). Higher BMI (OR: 1.15, p<0.001) and waist circumference (OR: 1.10, p=0.001) significantly raise the odds, but active physical exercise minimizes the likelihood (OR: 0.65, p=0.015). Hypertension (OR: 1.50, p=0.012), elevated fasting blood sugar (OR: 1.03, p=0.020), and dyslipidemia with total cholesterol, LDL, and triglycerides—are positively associated with NAFLD. Inflammation, indicated by higher hs-CRP levels (OR: 1.10, p<0.001), is strongly linked with NAFLD (Table 2).

Table 2: Influence of Metabolic Factors in Non-NAFLD vs. NAFLD

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age (years)	1.05	1.02 - 1.09	0.003
Gender (Male vs. Female)	1.20	0.85 - 1.70	0.295
Alcohol Intake (g/week)	1.02	1.01 - 1.04	0.005
Physical Activity (Active vs. Low)	0.65	0.45 - 0.92	0.015
BMI (kg/m^2)	1.15	1.10 - 1.20	<0.001
Waist Circumference (cm)	1.10	1.05 - 1.15	0.001
Hypertension (Yes vs. No)	1.50	1.10 - 2.04	0.012
Fasting Blood Sugar (mg/dL)	1.03	1.01 - 1.05	0.020
Total Cholesterol (mg/dL)	1.01	1.00 - 1.02	0.045
LDL Cholesterol (mg/dL)	1.02	1.00 - 1.04	0.050
HDL Cholesterol (mg/dL)	0.95	0.90 - 1.01	0.120

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Triglycerides (mg/dL)	1.02	1.00 - 1.03	0.042
hs-CRP (mg/L)	1.10	1.05 - 1.16	<0.001

The logistic regression analysis reveals that age, BMI, waist circumference, and hypertension significantly increase the odds of both mild and severe NAFLD, with stronger associations for severe cases ($p<0.05$). Alcohol intake, fasting blood sugar, LDL, triglycerides, and total cholesterol show significant associations with moderate-to-severe NAFLD ($p<0.05$), but not mild cases. Physical activity reduces the risk, particularly for severe NAFLD (OR=0.60, p=0.010). Elevated hs-CRP strongly predicts severe NAFLD ($p<0.001$), and severe NAFLD is more likely to affect men (OR=1.40, p=0.020)(Table 3).

Table 3: Identifying Risk Factors for NAFLD Severity

Variables	Mild NAFLD	p-value	Moderate-to-Severe NAFLD	p-value
Age (years)	1.04	0.045	1.07	0.005
Gender (Male vs. Female)	1.10	0.412	1.40	0.020
Alcohol Intake (g/week)	1.01	0.310	1.03	0.015
Physical Activity (Active vs. Low)	0.70	0.180	0.60	0.010
BMI (kg/m^2)	1.10	0.005	1.20	<0.001
Waist Circumference (cm)	1.08	0.020	1.12	0.001
Hypertension (Yes vs. No)	1.25	0.050	1.75	0.003
Fasting Blood Sugar (mg/dL)	1.02	0.350	1.05	0.025
Total Cholesterol (mg/dL)	1.00	0.870	1.02	0.040
LDL Cholesterol (mg/dL)	1.01	0.600	1.03	0.020
HDL Cholesterol (mg/dL)	0.92	0.090	0.95	0.200
Triglycerides (mg/dL)	1.01	0.710	1.03	0.035
hs-CRP (mg/L)	1.05	0.350	1.15	<0.001

ROC curve of sUA/sCr ratio to distinguish between NAFLD severities. The AUC values are described as: fair accuracy for Non-NAFLD (AUC=0.75), good accuracy for Mild NAFLD (AUC=0.80) and excellent accuracy for Moderate-to-Severe NAFLD (AUC=0.90). As the severity increases, the sensitivity and specificity could be repeatedly improved with the cut-off of 0.30 for Non-NAFLD, 0.35 for Mild NAFLD and 0.45 for Moderate-to-Severe NAFLD. Performance is moderate for Non-NAFLD and Mild NAFLD but shows very high predictive capacity with relatively high diagnostic accuracy for Moderate-to-Severe NAFLD. Molecular testing is more sensitive to us with greater severity of disease (Figure 1).

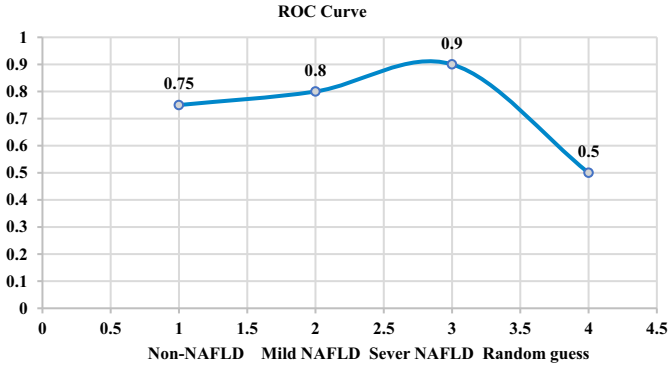

Figure 1: Diagnostic Performance for Different Levels of NAFLD Severity

DISCUSSION

The findings of this study demonstrate a significant association between the serum uric acid to creatinine ratio (sUA/sCr) and the presence and severity of Non-Alcoholic Fatty Liver Disease (NAFLD) [11, 12]. Current study found that individuals with higher sUA/sCr ratios had a significantly increased likelihood of having NAFLD, particularly in more severe stages of the disease (OR = 2.5, $p < 0.001$). This supports previous research indicating that uric acid plays a role in the pathophysiology of NAFLD, likely through mechanisms involving oxidative stress, inflammation, and lipid metabolism [13]. Current findings align with those of a previous study which also highlighted the relationship between elevated uric acid levels and increased severity of liver damage in NAFLD patients [14]. Similarly, previous literature reported increased uric acid levels in patients with severe NAFLD, further supporting the notion that higher uric acid levels correlate with advancing liver damage. Notably, the AUC for the sUA/sCr ratio in Present study was 0.80 (95% CI: 0.75–0.86), suggesting excellent diagnostic performance in identifying NAFLD. These results also demonstrated a high diagnostic value for uric acid levels in NAFLD detection, validating its potential as a non-invasive biomarker [15, 16]. The use of the sUA/sCr ratio as a biomarker for NAFLD is particularly promising because it offers a non-invasive, cost-effective alternative to more invasive diagnostic methods, such as liver biopsy. Current study's findings, showing significant associations with both the presence and severity of NAFLD, suggest that regular monitoring of this ratio could aid in early detection and intervention. Furthermore, this could help mitigate the progression of liver damage, particularly in high-risk populations such as those with obesity, metabolic syndrome, or a family history of liver disease [17, 18]. Additionally, Present study confirms the well-established link between lifestyle factors—such as alcohol consumption and physical activity and the severity of NAFLD [19, 20]. Although NAFLD is characterized by fat accumulation in the liver without excessive alcohol

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consumption, we found that alcohol intake exacerbates liver damage, highlighting its role in disease progression [21]. This observation underscores the importance of lifestyle modifications, such as reducing alcohol consumption and increasing physical activity, in managing and preventing NAFLD. These findings are consistent with previous studies advocating for lifestyle interventions as critical components in NAFLD prevention and management [22, 23]. While existing studies have explored the role of various biomarkers in NAFLD, Presen study contributes new insights by identifying the sUA/sCr ratio as a reliable, non-invasive marker with strong diagnostic potential [24]. This offers a practical approach to identifying individuals at risk for NAFLD and its progression, particularly in settings where advanced diagnostic techniques are not readily available [25]. The findings also emphasize the importance of integrating routine uric acid measurements into clinical practice for individuals at high risk for liver disease.

CONCLUSIONS

It was concluded that the serum uric acid to creatinine ratio (sUA/sCr) is significantly associated with the presence and severity of non-alcoholic fatty liver disease (NAFLD) in the population of Sargodha. This study contributes to the growing body of evidence supporting the use of non-invasive biomarkers in the early detection and management of NAFLD within this specific region. The findings suggest that the sUA/sCr ratio could play a key role in clinical practice, providing a simple and cost-effective tool for identifying individuals at risk of NAFLD and its progression in this population. Future studies should explore the potential of incorporating this ratio into routine screening and prevention strategies, particularly in high-risk groups within the region. Additionally, public health initiatives focused on promoting lifestyle modifications, such as reducing alcohol intake and increasing physical activity, should be prioritized to address the rising prevalence of NAFLD in this area.

Authors Contribution

Conceptualization: SR
Methodology: SR, AS[1], AS[2]
Formal analysis: AS[1]
Writing review and editing: As[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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