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CORRELATION OF HIGH-SENSITIVITY C-REACTIVE PROTEIN (hs-CRP) AND TRIGLYCERIDE-GLUCOSE (TYG) INDEX RELATED PARAMETERS WITH DISEASE SEVERITY IN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) PATIENTS

Roli Saxena[1], Nikhil Govil[2], Richa Goel[3], Himanshu Madaan[4], Meenakshi Puri[5*]

[1]Assistant Professor, Department of Biochemistry, Kalpana Chawla Government Medical College, Karnal.
[2]Associate Professor, Department of Medicine, Kalpana Chawla Government Medical College, Karnal.
[3]Assistant Professor, Department of Biochemistry, Kalpana Chawla Government Medical College, Karnal.
[4]Professor and Head, Department of Biochemistry, Kalpana Chawla Government Medical College, Karnal.
[5*]Associate Professor, Department of Biochemistry, Kalpana Chawla Government Medical College, Karnal.

***Corresponding Author:** Dr. Meenakshi Puri
*(MD Biochemistry), Email ID: research.biochem21@gmail.com, Mobile no: 9876828287

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD), a liver pandemic of the 21st century, impacts nearly 30% of the population worldwide. Since, chronic low-grade inflammation associated with the activation of innate immune system, plays an essential role in the pathogenesis of NAFLD, high sensitivity C-reactive protein (hs-CRP) levels, a known marker of chronic inflammation, can be of value for determining NAFLD severity. Also, since this sub-clinical inflammation has a causative role in generating insulin resistance, the prognostic value of triglyceride-glucose (TyG) index, an insulin resistance (IR) factor and its related indices: TyG combined with body mass index (TyG-BMI), waist circumference (TyG-WC) and TyG- waist circumference-to-height ratio (TyG–WHtR) were estimated Hence, in the present study, we aimed to elucidate the association of hs-CRP and TyG (its related parameters) with NAFLD severity. **Methods:** The study was conducted on 168 ultrasonographically confirmed NAFLD patients (Age group: 35-55 years) categorized into 2 groups: Group 1: Mild steatosis patients (n = 84) and Group 2: Moderate to Severe steatosis patients (n=84). Serum hs-CRP levels were estimated by immunoturbidimetric assay on fully automated analyzer. **Results:** The serum hs-CRP levels were found to be significantly raised ($p<0.05$) in group 2 patients w.r.t group 1 subjects. TyG-BMI and TyG- WC shared a potential significant association ($p<0.05$) with the disease occurrence and severity. **Conclusions**: Thus**,** these findings highlighted that hs-CRP, TyG related indices (TyG-BMI and TyG-WC) might act as potent non-invasive serum biomarkers in monitoring and predicting the severity of NAFLD, hence in the screening or risk assessment, early and targeted therapeutic management of such patients.

Keywords: NAFLD, steatosis, hs-CRP, Triglyceride-Glucose indices

INTRODUCTION

The American Association for the Study of Liver Diseases (AASLD) defines Non-alcoholic fatty liver disease as excessive hepatic fat accumulation with evidence of hepatic steatosis either on histology or radiological imaging; no significant alcohol consumption; lack of competing causes for hepatic steatosis and no concurrent causes of chronic liver disease.[1] NAFLD is a disorder, comprising a spectrum ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), consequently progressing to liver cirrhosis and cancer (HCC).[2] Considerable data has shown that an estimated 20%–25% of patients with NAFL progress to NASH, and up to 25% of patients with NASH progress to cirrhosis.[3] The diagnosis of NAFL requires the presence of >5% hepatic steatosis without evidence of hepatocellular injury, whilst NASH is defined by >5% steatosis with inflammation and hepatocellular injury. Several studies have linked it to obesity, hypertension and dyslipidemia, hence NAFLD is considered to be a hepatic manifestation of metabolic syndrome (MetS) i.e. Metabolic dysfunction associated fatty liver disease (MAFLD).

Approximately, 25–29% of the general population have been afflicted with NAFLD globally and in Asia. Besides, a recent meta-analysis revealed the prevalence of NAFLD in 38.6% of adults and 35.4% of children.[4] Apart from afflicting the liver, NAFLD has recently been recognized as a multisystem disease, causing increased morbidity and mortality related to liver, cardiovascular system, chronic kidney disease, osteoporosis, and extrahepatic malignancy.[2] The prevalence of NAFLD in high-risk groups, like type 2 diabetes mellitus (T2DM) is even higher, being present in almost 70% of this group.[5] Other high-risk populations include those with hypertension, obesity, and dyslipidemia.[5] Thus, these reports suggested that NAFLD or MASLD to be closely related to the metabolic syndrome, with insulin resistance being a prominent feature of MetS. The chief clinical manifestations include chronic fatigue, mood alterations, obstructive sleep apnea, thyroid dysfunction, polycystic ovary syndrome and chronic pain syndrome.[6] Several reports have suggested that NAFLD and the associated disease states are associated with low-grade inflammation in liver. Out of the several inflammatory markers evaluated in NAFLD, hs-CRP is known to be associated with inflammation in the liver.[7] Apart from this, it is found to be elevated nonspecifically in bacterial infections, immuno-inflammatory diseases and malignant disorders.[8] Numerous prospective studies have shown that high hs-CRP levels predict the metabolic syndrome , type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD). In addition, hs-CRP was also a part of the scoring system in a Japanese study which predicts the disease progression in NAFLD.[9] However, studies on the role of hs-CRP as a potential marker of disease progression in NAFLD has been limited in India.

Further, NAFLD/MASLD is closely linked with metabolic syndrome and its associated components (hypertension, type 2 diabetes mellitus, dyslipidaemia and obesity) and insulin resistance is a key feature of Met S.[10] But, as measurement of circulating insulin is rarely being done in primary care, Triglyceride-Glucose index has emerged as an alternative IR evaluation method in recent times. Athough, some studies have linked this with new occurence of NAFLD and degree of hepatic steatosis, others have related this index with cardiovascular mortality in different populations. However, till date relatively fewer studies have determine the correlation between the TyG-related indices and disease severity in patients with NAFLD/MASLD.

With this background, this study was designed to determine and evaluate the role of non-invasive inflammatory marker hs-CRP and TyG (and its related parameters) in predicting NAFLD patients' disease severity.

AIMS AND OBJECTIVES:

1. To study the correlation between serum hs-CRP levels and NAFLD severity.
2. To correlate its levels with anthropometric parameters (Height, weight, body mass index, waist circumference) routine liver function tests (LFTs), fasting blood sugar (FBS), glycated

hemoglobin (HbA1C), coagulation profile and TyG and its related adiposity indices: TyG-BMI, TyG-WC, TyG-WHtR.

MATERIAL AND METHODS:

Study area: The present study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine, Kalpana Chawla Government Medical College, Karnal.

Study design: Observational study

Selection of patients: In this study, a 168 ultrasonographically confirmed NAFLD patients (Age group: 35-55 years), categorized into 2 groups (based on the severity of fatty liver) according to a standard criteria were included.[2]

Group 1: Mild steatosis patients (n = 84)

Group 2: Moderate to Severe steatosis patients (n = 84)

All the subjects were enrolled after taking their informed written consent.

INCLUSION CRITERIA:

The subjects with no history of alcohol consumption and showing evidence of hepatic steatosis by imaging were recruited in the study.[2]

EXCLUSION CRITERIA:

Following patients were excluded from the study: HIV +ve/ anti HCV +ve/ HBsAg +ve, alcoholics, history of autoimmune or any other chronic liver disease (cholestatic liver disorders, obstructive jaundice, hepatic malignancy), gastrointestinal bypass surgery and patient on drugs like statins, aspirin, which can alter the levels of these biomarkers.

Anthropometry:

Body mass index (BMI) was calculated by dividing the weight (in kg) by the squared height (in meters). Asia Pacific Criteria was used to define central obesity.[2]

For investigations:

Approximately 5ml of overnight fasting venous blood sample was drawn, from the antecubital vein under all aseptic conditions. Sample was processed within one hour of collection. After clotting, serum was extracted by centrifuging the sample at 3000rpm for 5 mins.

ROUTINE INVESTIGATIONS: All the routine biochemical parameters were estimated on the same day on the fully automated analyzer (Cobas 501, Roche Diagnostics). LFT [bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-Glutamyltransferase (GGT), total protein, albumin, globulin (calculated)], Lipid profile [total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL) (calculated)] and fasting blood glucose (FBG). Lipid profile cut-off values were based on criteria laid down by the National Cholesterol Education Programme (NCEP)/Adult Treatment Panel (ATP) III guidelines.[2]

Indices: TyG Index, modified TyG-related parameters were calculated using the formula[11]:

TyG index = ln [fasting serum TG (mg/dL) × fasting plasma glucose (mg/dL)/2]

TyG- Body Mass Index = [TyG index × BMI]

TyG-Waist circumference = [TyG × WC]

TyG-WHtR = [TyG× WC/height]

B. SPECIAL INVESTIGATIONS: For the batch analysis of hs-CRP, samples were stored at -20℃ (≤1 month). hsCRP estimation was carried out by immunoturbidimetric assay on fully automated analyzer.[12,13] HbA_1C estimation was done the same day by turbidimetric inhibition immunoassay.[9] Total leukocyte count (TLC), Platelet count and Hb were determined by flow-cytometry and

electrical impedance based fully automated analyzer while Prothrombin time (PT) was estimated by fully automated coagulation analyzer.

STATISTICAL ANALYSIS

The Normality of quantitative data was checked by measures of Kolmogorov-Smirnov tests of Normality. Skewed data was presented as Median and interquartile range, whereas normally distributed data was given as mean and standard deviation. For normally distributed data, t-test was applied for statistical analysis of 2 groups. Group comparisons of values of skewed data was carried out by Mann-Whitney test for 2 groups**.** Spearman correlation coefficient (ρ) was calculated to see the relationship between different variables. Receiver Operating Characteristic (ROC) curve was calculated to find maximal cut-off value of hsCRP (mg/L). The ROC curve is a plot of sensitivity versus 1-specificity for maximal cut-off values. All the statistical tests were two-sided and were performed at a significance level of α=0.05. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

RESULTS

A total of 168 NAFLD patients were enrolled in this study. The general characteristics of the patients recruited have been mentioned below (**Table1**). The median age of group 2 patients (46 years) was slightly higher in comparison to group 1 (44 years) patients, recruited in the present study. The variables like weight (kg), BMI (kg/m^2) and waist circumference (inch) were found to be significantly greater ($p<0.05$) in group 2 patients w.r.t group 1 patients. There was no significant difference in diastolic/systolic blood pressure (DBP/SBP) values in the two groups.

Table 1: General characteristics of study subjects

Parameters	Group 1 (Mild steatosis) (n=84)	Group 2 (Moderate to Severe steatosis) (n=84)	P value
Age (yrs)	44(37-57)	46(39-55.75)	0.25
Height (cm)	157.48(152.4-167.23)	160.02(153.98-167.0)	0.33
Weight (kg)	70(61.25-79.75)	75 (65-90)	**0.02***
BMI (kg/m^2)	27.34(24.23-31.15)	28.3 (25.2-33.12)	**0.04***
Waist cir (inch)	38.25(35-41)	40(36.25-43)	**0.04***
DBP (mmHg)	80.92±12.32	83.58±12.35	0.16
SBP (mmHg)	125.5(114-137.5)	129(118-147)	0.13

Data represented as mean ± SD or median and interquartile ranges, as appropriate. *$p<0.05$ w.r.t Group 1

Table 2: Biochemical parameters of study participants

Parameters	Group 1 (Mild steatosis) (n=84)	Group 2 (Moderate to Severe steatosis) (n=84)	P value
Total Cholesterol (mg/dL)	182.21±37.88	196.31±44.04	**0.03***
Triglycerides (mg/dL)	144(102.57-213.07)	153.15(120.47-207.3)	0.48
HDL(mg/dL)	41.8(33.85-49.5)	43(35.62-50.07)	0.37
LDL(mg/dL)	107.60±33.18	116.27±36.39	0.11
VLDL (mg/dL)	28.5(20.25-41.75)	31(25-41)	0.31
AST(IU/L)	27.65(21.7-43.45)	32.35(23.42-45.9)	0.09
ALT(IU/L)	30.05(20.67-47.75)	32.7(24.85-60.32)	0.12
ALP (IU/L)	116.9(92.82-132.67)	118.5 (93.2-143.75)	0.58
T.Bil (mg/dL)	0.48(0.34-0.74)	0.46(0.33-0.66)	0.72
Total Protein (g/dL)	8.05(7.7-8.4)	7.9(7.5-8.2)	0.08
Albumin (g/dL)	4.8(4.6-5.0)	4.7(4.4-4.9)*	**0.03***
Globulin (g/dL)	3.1(2.8-3.6)	3.1(2.72-3.5)	0.85

GGT(IU/L)	24.5(15.25-42.75)	36.5(18.25-56.5)	**0.04***
hsCRP(mg/L)	2.69(1.09-6.62)	3.76(2.21-8.8)	**0.03***
FBS (mgdL)	93.5(86.12-117.7)	96.45(89.27-105.5)	0.47
HbA1C (%)	5.9(5.62-6.77)	6.15(5.7-6.87)	0.38

Data represented as mean ± SD or median and interquartile ranges, as appropriate. *p<0.05 w.r.t Group 1

As shown in **Table 2**; biochemical parameters viz. Total cholesterol, GGT and hs-CRP were markedly more (p<0.05) in group 2 as compared to group 1. However, albumin parameter was significantly raised (p=0.03) in group 1 in comparison to group 2 subjects.

Table 3: TyG index and its related parameters in NAFLD patients

Parameters	Group 1 (Mild steatosis) (n=84)	Group 2 (Moderate to Severe steatosis) (n=84)	P value
TyG	8.98±0.68	9.04±0.66	0.52
TyG-BMI	247.6±50.2	264.9±50.3	**0.03***
TyG-WC	872.01±137.1	917.47±131.84	**0.03***
TyG-WHtR	5.45±0.90	5.71±0.91	0.15

Data represented as mean ± SD or median and interquartile ranges, as appropriate. *p<0.05 w.r.t Group 1

As shown in **Table 3**, Tyr-BMI and Tyr-WHtR indices were observed to be significantly associated (p<0.05) with NAFLD pathophysiology.

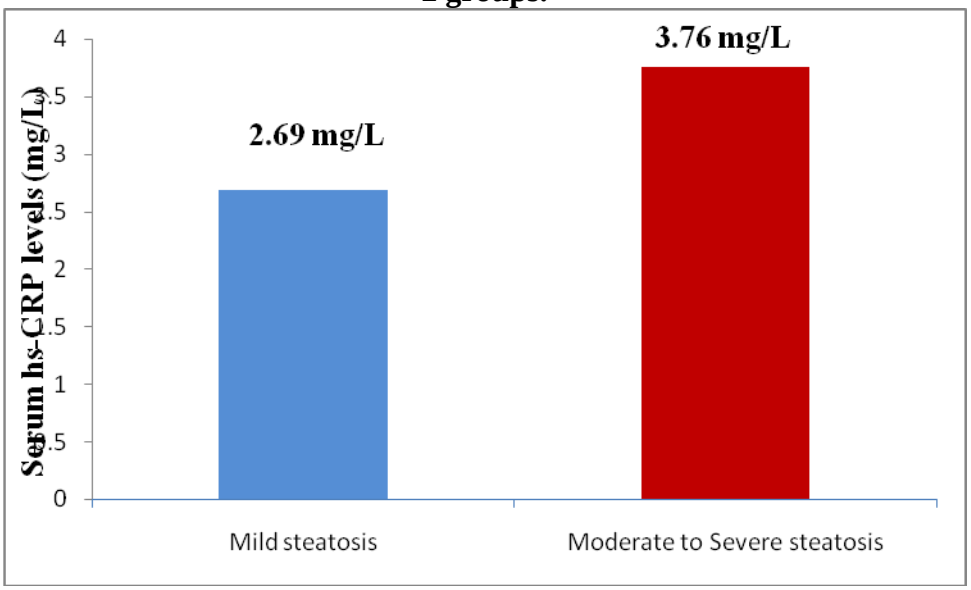
Table 4: Coagulation profile of study subjects

Parameters	Group 1 (Mild steatosis) (n=84)	Group 2 (Moderate to Severe steatosis) (n=84)	P value
Hb (g%)	12.7(11.42-14.45)	12.8(11.65-14.32)	0.97
TLC*10^3 (/uL)	7.6(6.5-8.8)	7.23(5.98-8.51)	0.36
Platelet count*10^3 (/uL)	262.5(199.75-331.5)	227(164.75-303)	**0.04***
PT (sec)	11(10.6-11.67)	11.15(10.5-12.1)	0.56

Data represented as median and interquartile ranges. *p<0.05 w.r.t Group 1

The coagulation profile assessed in this study **(Table 4),** indicated that the platelet count was significantly elevated (p<0.05) in group 1 patients w.r.t group2.

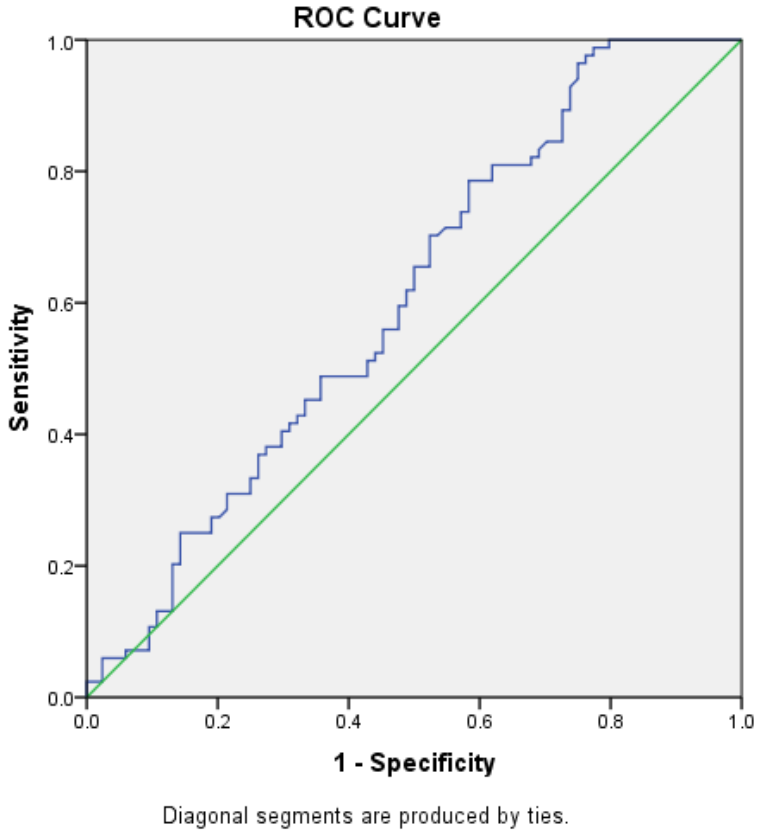
Figure 1: The serum levels (median values) of high-sensitivity C-reactive protein (hs-CRP) in 2 groups.



As evident from the **Fig. 1**, the median values of serum hs-CRP was found to be significantly higher ($p<0.05$) in group 1 (mild steatosis) patients (2.69mg/L) in comparison to the group 2 (moderate to severe steatosis) (3.76mg/L) NAFLD subjects.

Table 4: Area under receiver operating characteristic curve (AUROC) and odd's ratio (OR) analysis of serum hs-CRP levels: Analysis done between group 1 and group 2 revealed that the area under the curve was 0.61, cut off value was 2.75mg/L, sensitivity = 62%, specificity = 52%, OR(95%CI)= 1.7(0.92-3.15); p=0.02. This has indicated that serum hs-CRP levels' measurement might have a moderate diagnostic ability in assessing the severity of NAFLD. However, this diagnostic ability can be enhanced by combining hs-CRP with other inflammatory markers and this needs to be explored further.

	AUC	Cut-Off value	Sensitivity (%)	Specificity (%)	OR	95% CI	P value
hs-CRP(mg/L)	0.61	2.75mg/L	62	52	1.7	0.92-3.15	**0.02***



Spearman's rho (ρ) correlation analysis:
This was done to assess the relationship between hs-CRP and various clinical parameters studied. hs-CRP was found to be positively correlated with prothrombin time (Spearman's rho correlation ρ coefficient = 0.168, p =0.03) when the 2 groups were combined and also individually in group 1 patients (**ρ** = 0.291, p =0.007). In group 2, a significant positive correlation with TLC (**ρ** = 0.229, p =0.036) was evident.

DISCUSSION

NAFLD, a global public health concern, is considered to be an important etiology for the development of chronic liver disease worldwide.[7] Owing to its associations to obesity,

hypertension, dyslipidemia, and insulin resistance, NAFLD is traditionally considered a hepatic component of MetS.[14] Recently, studies have reported that NAFLD is an independent risk factor of numerous diseases, including diabetes, cardiovascular disease, hypertension, kidney disease and colon cancer.[15]

Inflammation is critical in the early phase of non-alcoholic fatty liver disease and plays a crucial role in driving the initiation and progression of liver damage. A series of pro-inflammatory proteins and cytokines including IL-6, IL-1B, TNF-α have been implicated in hepatic inflammation, signifying their usefulness as noninvasive soluble biomarkers for NAFLD/NASH diagnosis and prognosis. Numerous studies have directly associated this with different inflammatory cytokines. hs-CRP is one of the important acute phase proteins, widely implicated as a disease marker in many chronic, non-communicable diseases, such as cardiovascular and dysmetabolic diseases in recent times. In addition to this, unlike most of the inflammatory markers, hs-CRP is considered to be a relatively low cost inflammatory biomarker, having a prognostic role in predicting hepatic damage progression in NAFLD.[14] However, this association has not being studied much in Asian Indians, till date. In this regard, the present study was designed to analyse association of hs-CRP levels with the NAFLD progression/severity in north India.

hs-CRP, is synthesized by hepatocytes and its production is regulated by proinflammatory cytokines like IL-1β, IL-6.[9] It has been observed that rapid and marked increase in hs-CRP levels occurs during inflammation, infection, trauma and tissue necrosis. Many studies have been conducted on the association of hsCRP with the severity of inflammation in liver disease, such as chronic hepatitis C. Further, hsCRP was found to have a diagnostic role in diagnosing HCC in patients with HBV related liver cirrhosis.[16] Apart from this, numerous studies have also revealed hs-CRP's association with atherosclerosis, type 2 diabetes, carotid intimal medial thickness, and metabolic syndrome.[13]

Our research findings have also shown markedly elevated ($p<0.05$) hs-CRP levels in moderate to severe steatosis NAFLD patients in comparison to mild steatosis patient group. In line with this, some studies have revealed a significant correlation of hsCRP levels with liver histology in NAFLD patients, suggesting that NAFLD may be associated with sub-clinical inflammation in the liver.[11] Besides, in a Japanese study, serum hsCRP was proposed as part of a scoring system to predict disease progression in NAFLD.[9] Similarly, a study conducted by Tannaz et al., showed association of hs-CRP with any degree of histologically diagnosed liver damage and a reasonable specificity for predicting biopsy-proven steatosis and fibrosis in obese individuals.[14] Further, a study conducted by Zhu et al., highlighted a potential association of elevated serum hsCRP levels with increased risk of MAFLD among Chinese obese patients.[17] In addition to this, elevated hs-CRP levels were also found to increase the risk of heart failure hospitalization in MAFLD patients.[18] Moreover, in the present study hs-CRP was found to be a significant risk factor ($p<0.05$) for NAFLD development/severity with an acceptable sensitivity (62%) and specificity (52%) towards liver steatosis, reflecting moderate diagnostic performance in predicting disease severity. This was consistent with the findings of a study conducted by Tannaz et al.[14]Thus, this association may be attributed to inflammatory process, dyslipidemia, excess weight, and/or elevated liver enzymes.

Our study showed significantly raised ($p<0.05$) platelet count in group2 patients in comparison to group 1. Also, spearman's correlation analysis indicated a significant positive correlation of hs-CRP with TLC ($\rho = 0.229$, $p =0.036$) in moderate to severe steatosis patients. This was consistent with a study conducted in urban south Indians.[13] An elevated leukocyte count has also been reported to be a predictor of cardiovascular mortality independent of traditional cardiovascular risk factors In addition to this, some studies have also reported an elevated leukocyte count in subjects with type 2 diabetes, prediabetes and the metabolic syndrome. Also, both leukocyte count and hsCRP were shown to be significantly correlated with insulin resistance among Asian Indians. Thus it is

speculated that the proposed mechanism connecting increased leukocyte count and hsCRP with NAFLD could be insulin resistance, oxidative stress and chronic low-grade inflammation.[13]
Besides, hs-CRP was also found to be positively correlated with prothrombin time ($\rho = 0.168$, $p = 0.03$) when the 2 groups were combined and also individually in group 1 patients ($\rho = 0.291$, $p = 0.007$). The possible explanation for this is that as NAFLD is found to be independently associated with endothelial vascular dysfunction and atherosclerosis, both related to a chronic proinflammatory state, this could lead to a prothrombotic state caused by derangements in several components or mechanisms involved in the hemostatic process, including endothelial and platelet dysfunction, alterations in the coagulation cascade, decreased fibrinolytic activity, or a combination.[19,20]
Although, hs-CRP is a readily-available and low cost non-invasive biomarker, but due to complex pathogenesis of NAFLD, better characterization of the different pathways involved is required. This would aid in developing new non-invasive markers of NASH and fibrosis, which can simultaneously take into account the numerous implicated factors in the pathogenesis of NAFLD.
We also evaluated the triglyceride-glucose (TyG) index, considered to be associated with new-onset NAFLD and the degree of hepatic steatosis but found no significant association between the two. On the contrary, Wang et al. showed a positive correlation between the TyG index and NAFLD risk in Japanese non-obese population.[11] In addition to this, a study conducted by Zhao et al., indicated TyG index to be positively correlated with risk of coronary heart disease and coronary atherosclerosis severity among NAFLD patients.[18] However, TyG related parameters (TyG-BMI, TyG-WC indices TyG-WHtR) were also calculated in the present study and a significant association ($p<0.05$) was found between the TyG indices TyG-BMI and TyG-WC and the participants with NAFLD. This was in line with the study done by Chen at al., where analysis showed that TyG-BMI and TyG-WC indices were more suitable for predicting mortality in patients without advanced fibrosis in comparison to single TyG index.[10] A positive correlation between the TyG index and TyG-BMI with the risk of NAFLD was also found in non-obese individuals in China. Wang et al. Since TyG related parameters are early indicators of insulin resistance, associated with endothelial dysfunction, oxidative stress and inflammatory response of the systemic metabolism, these indices might highlight the participants' pro-inflammatory condition and indicate their vulnerability to disease progression and severity.[10] Also, this diversified approach may improve the accuracy of NAFLD predictions by considering various metabolic factors, thereby demonstrating greater strength than the TyG index itself.

However, till date, few studies have evaluated the correlation between the TyG-related indices and disease risk/severity in patients with NAFLD. Moreover, based on the current findings, there is a dire need of exploring new insights into the NAFLD pathophysiology/severity which will aid in elucidating a potential combination of validated predictive non-invasive biomarkers, accurately assessing disease prognosis and therapeutic response.

CONCLUSION:

Thus, the findings of the present study indicate that hs-CRP might act as a potential serum non-invasive biomarker in the assessment of NAFLD disease severity. Hence, timely monitoring of hs-CRP levels should be closely followed for potential NAFLD development and its associated co-morbidities. Also, TyG index and its related parameters play a crucial role in predicting the pathogenesis of liver steatosis. However, there is a need for large scale population based studies for further validating these preliminary results.

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Conflict of interest – No competing financial interests exist.

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