DOI: 10.7860/JCDR/2025/78416.21030

Original Article

Biochemistry Section

Surrogate Markers of Insulin Resistance to Predict the Prognosis of COVID-19 Disease: A Retrospective Analysis

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) patients exhibit an extensive range of disease manifestations. Disturbances in metabolic and lipid profiles occur due to the release of cytokines. The lipid elements of the COVID-19 virus play a significant role in the fusion of the viral membrane to the host cell, in addition to replication. Although the COVID-19 scenario is multifaceted, high risks are observed in patients with co-morbidities such as Insulin Resistance (IR). Lipid ratios and the Triglyceride-Glucose index (TyG) could serve as simple biochemical markers of IR, thereby aiding in the assessment of prognosis in admitted COVID-19 patients, particularly those with comorbid conditions like IR.

Aim: To assess the severity of COVID-19 infection based on lipid ratios and the TyG index.

Materials and Methods: This retrospective study was conducted at Diamond Harbour Government Medical College and Hospital, 24 Parganas, West Bengal, India, data from 189 diagnosed COVID-19 patients, aged between 18 and 60 years in and around diamond harbour, were collected after obtaining the necessary ethical clearance. All the patients, including referred cases, were admitted to the COVID-19 ward of Diamond Harbour Government Medical College and Hospital. Data from biochemical tests, such as Fasting Blood Glucose (FBG), Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL) and C-Reactive Protein (CRP), which were analysed using an autoanalyser (Transasia XL 640), were recorded. The lipid ratios and TyG index were calculated. The optimal cut-off values for all the above indices were derived from the point with the maximum Youden index by plotting the Receiver Operating Curve (ROC). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Software version 20.

Results: The Fasting Blood Sugar (FBS), TG, TG/HDL, TC/HDL and TyG index levels were significantly higher in the severe COVID-19 patients ($p<0.05$). The optimal cut-off values calculated for the TyG index, TG/HDL and TC/HDL were 9.34, 3.55 and 3.83, respectively.

Conclusion: In COVID-19 patients, a TyG index and lipid ratios of TG/HDL and TC/HDL exceeding 9.34, 3.55 and 3.83, respectively, could serve as early indicators of COVID-19 severity, thus assisting in the assessment of prognosis.

Keywords: Blood sugar, Coronavirus disease-2019, Triglyceride-glucose index

INTRODUCTION

December 2019 marked the discovery of a rapidly spreading novel Coronavirus (2019-nCoV) in individuals with pneumonia in Wuhan, China [1]. This eventually led to the onset of the pandemic. COVID-19 disease ranges from mild to severe respiratory infection [2,3]. Data shows a bad prognosis and severe outcomes in people with co-morbidities [4,5], such as metabolic syndrome, increased blood pressure, Cardiovascular Disease (CVD) and Type 2 Diabetes Mellitus (T2DM) [5]. These co-morbidities are primarily associated with IR [5]. In older persons with obesity and diabetes, there is an impaired early antiviral interferon response [6], contributing to susceptibility to severe COVID-19 infection in these individuals. In addition, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection also exacerbates the existing chronic inflammatory state, resulting in severe disease [7].

Metabolic disruption, especially IR, is thought to be a possible risk factor for severity in COVID-19 [8-10]. Hyperinsulinaemia in patients with IR and diabetes can lead to increased SARS-CoV-2 viral load, as insulin enhances the membrane expression of Angiotensin-Converting Enzyme 2 (ACE2), which serves as a viral docking site for entry into cells [11]. Thus, early detection of IR plays a critical role in predicting the severity and management of the disease.

Routine assessments in COVID-19 patients have typically excluded IR [10]. A lack of awareness, time constraints and the increased cost of standard methods, such as the hyperinsulinaemic-euglycaemic clamp technique, may be contributing factors [12]. Additionally, the lack of standardisation and the availability of indirect estimations of IR, such as Homeostasis Model Assessment for IR (HOMA-IR), the Fasting Glucose to Insulin Ratio (FG-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI), pose difficulties in assessing IR [13]. Therefore, novel biochemical markers like the TG/HDL ratio [14], LDL/HDL ratio, TC/HDL ratio [15] and TyG index [16] seem to be simpler and more economical for the evaluation of IR in recent times [16]. A few other studies have also shown that lipid ratios and the TyG index may be better indicators of COVID-19 than the lipid profile at the time of diagnosis [17,18].

Consequently, there is a significant gap between the presence of dyslipidaemia and its relevance in assessing the severity of COVID-19. Due to the paucity of data, the aim of this study was to evaluate the possible association of lipid ratios and the TyG index as substitutes for estimating IR, in order to assess disease prognosis in hospitalised COVID-19 patients.

MATERIALS AND METHODS

The present was a retrospective analysis conducted at Diamond Harbour Government Medical College and Hospital, 24 Parganas, West Bengal, India using patient records from December 2020 to December 2021. The study was planned in October 2022 and executed in March 2023 after obtaining formal ethical clearance (IEC no. DHGMC/2023/412). After obtaining all the necessary official consents and ethical approvals from the Institutional Ethics Committee, the research was completed in accordance with ethical guidelines.

Inclusion and Exclusion criteria: Data were collected from the Diamond Harbour area, including referred cases of patients with

moderate (Group-1) and severe (Group-2) COVID-19 disease. Records of patients admitted to the COVID-19 ward (moderate to severe disease), aged between 18 and 60 years, irrespective of their gender, were taken into account. The selection of patients was based on the World Health Organisation (WHO) classification mentioned in [Table/Fig-1] [19]. Patients with critical disease, including those with Acute Respiratory Distress Syndrome (ARDS), shock, respiratory failure requiring mechanical ventilation, other organ failures requiring admission to the Intensive Care Unit (ICU) and pregnant women with COVID-19 were excluded from the study.

Disease severity		Description
Moderate disease	Pneumonia	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air. The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	Severe pneumonia	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea) plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% on room air. The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

[Table/Fig-1]: COVID-19 disease severity classification as per World Health Organisation (WHO) [19].
CT: Computed tomography; SpO_2: Oxygen saturation

Sample size: The study population consisted of 189 subjects, among whom 97 had moderate disease (54 males and 41 females), while 92 had severe disease (43 males and 51 females).

Study Procedure

Routine biochemical tests, such as FBG, TC, TG, LDL, HDL and CRP, were analysed using an autoanalyser (Transasia XL 640) by the endpoint method. The TG/HDL, TC/HDL and LDL/HDL ratios were calculated. The TyG index was calculated using the logarithm of {TG (mg/dL)×FBG (mg/dL)}/2 [20].

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS Statistics Software version 20.0. The differences between the two groups (moderate and severe) were assessed using student's t-test. The mean and Standard Deviation (SD) was calculated for continuous variables with a normal distribution. Cross-tabulation with the Chi-square test was applied to examine gender variation concerning the severity of the disease. Receiver Operating Characteristic (ROC) curve analysis was performed for lipid ratios and the TyG index and the best possible cut-off values for lipid ratios and the TyG index were derived from the point with the maximum Youden index.

RESULTS

The study population consisted of 189 subjects, among whom 97 had moderate disease (54 males and 41 females), while 92 had severe disease (43 males and 51 females). Cross-tabulation was performed to assess the association between sex and the severity of the disease. The Chi-square test, when applied, did not indicate any significant association (p=0.147) [Table/Fig-2]. The most common co-morbidities observed were diabetes mellitus, hyperlipidaemia and hypertension. The most prevalent symptoms were fever, fatigue, headache and dyspnoea, followed by chest pain, diarrhoea and sore throat. Smoking was also identified as a confounding factor [Table/Fig-3].

Gender* severity cross tabulation		Severity		Total n (%)
		Moderate n (%)	Severe n (%)	
Gender	Males	54 (55.7%)	43 (44.3%)	97 (100%)
	Females	41 (44.6%)	51 (55.4%)	92 (100%)
Total	Within both sexes	95 (50.3%)	94 (49.7%)	189 (100%)

[Table/Fig-2]: Association between gender and severity of disease (p=0.147).

Co-morbidities	n (%)
Hyperlipidaemia	80 (42.32%)
Hypertension	59 (31.21%)
Diabetes mellitus	90 (47.6%)
COPD	11 (6%)
CKD	8 (4%)
CAD	0 (0%)
Previous history of myocardial infarction	0 (0%)
History of smoking	49 (25.92%)
Clinical feature	
Fever	105 (56%)
Headache	73 (38.6%)
Chest pain	45 (24%)
Dyspnoea	64 (34%)
Sore throat	31 (16.4%)
Fatigue	97 (51.26%)
Diarrhoea	32 (17%)

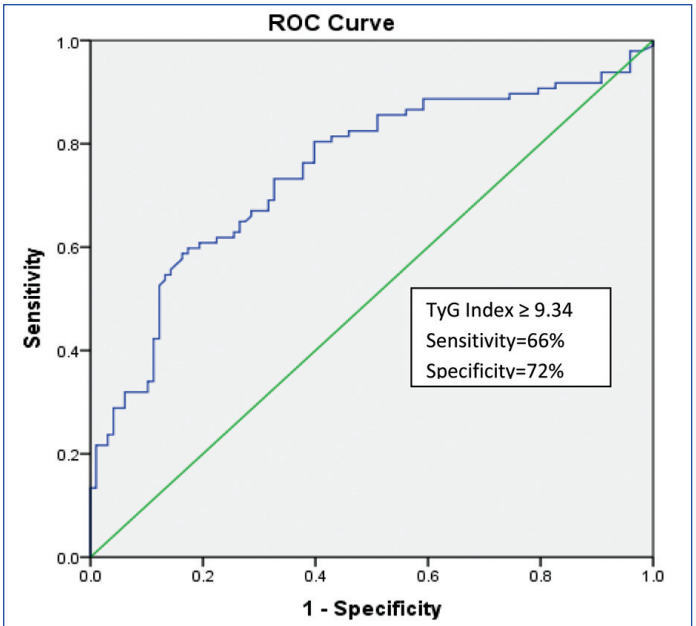
[Table/Fig-3]: Showing the percentage of co-morbidities in COVID-19 patients (N=189).
COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CAD: Coronary artery disease

The mean age of presentation was 53.48±12.63 years for moderate disease, while it was 51.14±15.51 years for severe disease, with ages ranging from 18 to 70 years. Furthermore, patients with severe disease exhibited statistically significantly higher values of FBS, TC, LDL, VLDL, TG, TG/HDL ratio, LDL/HDL ratio, CRP and TyG index (p<0.01) [Table/Fig-4].

Variables	Moderate (97)	Severe (92)	p-value
Age (y)	53.48±12.63	51.14±15.51	0.25
FBS (mg/dL)	173.72±8.61	291.11±23.16	<0.001*
TC (mg/dL	135.07±36.38	172.37±45.44	<0.001*
HDL (mg/dL)	39.51±9.9	40.19±8.33	0.45
LDL (mg/dL)	71.7±32.2	91.56±37.61	<0.001*
VLDL (mg/dL)	22.72±5.9	40.18±17.25	<0.001*
TG (mg/dL)	114.34±30.24	205.71±91.01	<0.001*
TG/HDL	3.07±1.17	5.43±3.05	<0.001*
TC/HDL	3.5±0.98	4.4±.1.47	0.65
LDL/HDL	1.88±0.93	2.35±1.13	0.002*
TyG index	9.07±0.54	9.7±0.81	<0.001*
CRP	34.36±57.73	14.48±22.84	0.002*

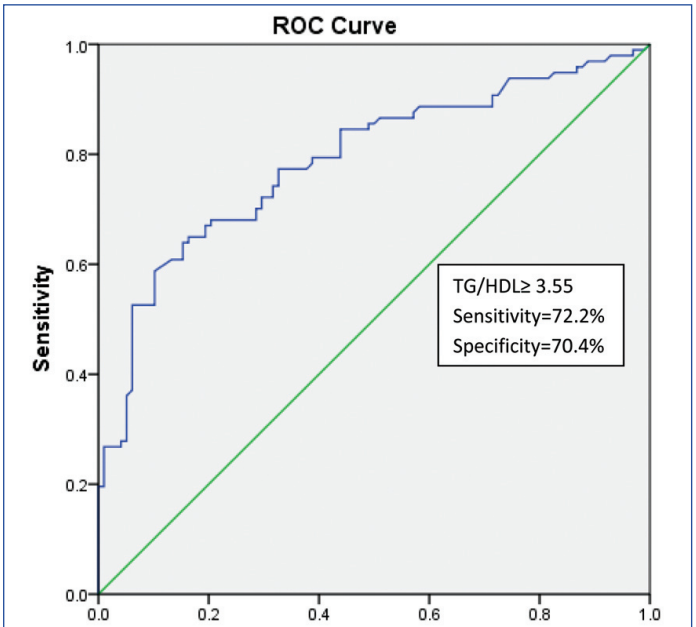
[Table/Fig-4]: Laboratory findings, lipid profile and lipid ratios of COVID-19 cases.
*p-value <0.05 was considered to be statistically significant

The ROC curve analysis was conducted to evaluate the ability of the TyG index, TC/HDL ratio and TG/HDL ratio to assess the severity of COVID-19. The AUC for the TyG index in predicting severe COVID-19 patients was 0.747 (95% CI 0.677–0.817), (p<0.001), as indicated in [Table/Fig-5]. The optimal cut-off value for the TyG index was 9.34, with a sensitivity of 66% and specificity of 72%. The AUC for the TG/HDL ratio in predicting severe COVID-19 patients was 0.788 (95% CI 0.724–0.853), (p=0.00), as specified in [Table/Fig-6]. The optimal cut-off value for the TG/HDL ratio was 3.55, with a sensitivity of 72.2% and specificity of 70.4%. The AUC for the TC/HDL ratio in predicting severe COVID-19 patients was 0.731 (95% CI 0.660-0.802), (p=0.00), as mentioned in [Table/Fig-7]. The optimal cut-off value for the TC/HDL ratio was 3.836, with a sensitivity of 62.9% and specificity of 70.4%.



AUC	Std. Error	p-value	CI (95%)
0.747	0.036	<0.001	0.677-0.817

[Table/Fig-5]: ROC curve of TyG index.



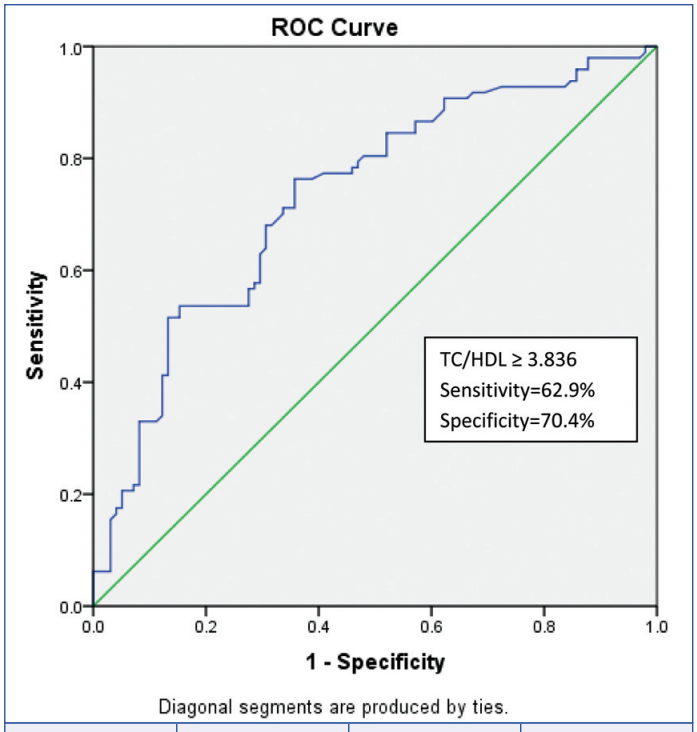
AUC	Std. Error	p-value	CI (95%)
0.788	0.033	<0.001	0.724-0.853

[Table/Fig-6]: ROC curve of TG/HDL index.

For the LDL/HDL ratio, although there was a significant difference between both groups, the values remained within normal limits. Therefore, the ROC curve was not plotted for the LDL/HDL ratio.

DISCUSSION

The present study data showed low HDL levels in both moderate and severe cases. Increased TG levels in severe cases during hospitalisation were also observed in this study. Thus, these factors can be considered high-risk markers. Furthermore, patients with a raised TyG index and TG/HDL ratio, with values above 9.34 and 3.55, respectively, should be regarded as early indicators of increasing severity. Including lipid profile alterations as prognostic criteria can aid the decision-making process, leading to earlier treatment intensification.



AUC	Std. Error	p-value	CI (95%)
0.731	0.036	<0.001	0.660-0.802

[Table/Fig-7]: ROC curve of TC/HDL index.

The number of cases in the present study was limited to 189, as lipid profiling was not a frequently requested test compared to other parameters. Studies by Masana L et al., and Kumari A et al., also suggested similar findings [21,22]. Although HDL levels were low in both moderate and severe cases in the present study, these findings were not statistically significant. Masana L et al., found that reduced HDL levels combined with elevated TG levels are significant high-risk markers for hospitalised COVID-19 cases [21]. In addition to the above findings, the current study demonstrated a significant rise in FBS, VLDL, TG/HDL ratio, LDL/HDL ratio and TyG index in severe cases. Similar findings were also evident in a meta-analysis consisting of 19 studies, which supported the role of lipid profiling in assessing the severity and prognosis of COVID-19 disease [23].

There was no gender bias regarding the severity of the disease in the current study. Total cholesterol levels were significantly higher in severely affected patients compared to those with moderate disease. This contrasts with the studies by Tsegay YG et al., and Rohani-Rasaf M et al., [24,25], which showed a decline in serum TC, HDL and LDL in the severe group when compared with the mild and moderate groups.

Patients with COVID-19 exhibit a wide array of manifestations, ranging from milder symptoms and good prognosis to severe fatal respiratory infections [3,4]. Although IR plays an important role in these lipid abnormalities, the pathophysiology of these modifications is more complex. Several theories about the mechanisms show the connection between lipids and COVID-19. Scientific literature also emphasises the complexities of lipid pathways in the presence of inflammation or infections [26]. A key enzyme involved in these alterations is Lipoprotein Lipase (LPL). It has been recognised that many cytokines, as well as inflammatory markers, are released at different phases of infection. LPL and its regulatory proteins interact with these molecules. LPL is also inhibited by bacterial products and modified lipoproteins [27]. When LPL action is hindered, the conversion of TG-rich lipoproteins to LDL is reduced, leading to increased TG levels and low HDL levels. Other causes of low HDL levels include reduced Cholesteryl Ester Transfer Protein (CETP) function, insufficient Apo-A1 synthesis and rapid HDL clearance [27].

It is a well-established fact that IR and its associated diseases, such as metabolic syndrome, CVD and T2DM, are linked with poor outcomes in COVID-19 patients [28-30]. In agreement with earlier research [30,31], the current study also demonstrated the presence of co-morbidities, such as T2DM, chronic kidney disease, hyperlipidaemia, hypertension and Coronary Artery Disease (CAD) in moderate and severe COVID-19 cases.

It is already known that direct and indirect methods for evaluating IR are technically challenging, lengthy and costly [18,32]. Recently, some researchers have suggested that lipid ratios could serve as important substitutes for evaluating IR, in contrast to the widely used test panels, due to their analytical and economic advantages [32-34]. The present study results revealed that an increase in the TG/HDL ratio and TyG index was positively associated with disease severity. This aligns with the findings of Rohani-Rasaf M et al., who also exhibited similar results among Iranian patients diagnosed with COVID-19 [25]. Thus, the present study established increased TG/HDL, LDL/HDL and TyG indices as reliable surrogate markers of IR, with a definite link to COVID-19 severity.

It has also been acknowledged that elevated insulin levels due to IR promote SARS-CoV-2 viremia through membrane upregulation of ACE2 in pneumocytes, which is involved in SARS-CoV-2 cell infection [14]. Increased insulin levels raise inflammatory markers, impair fibrinolysis and amplify the risk of coagulation and thrombosis [35].

Consequently, it is recommended that the evaluation of the TyG index and lipid ratios be considered as biochemical markers for estimating IR with predictive efficacy in the routine clinical evaluation of COVID-19 patients. This approach will also aid therapeutic interventions and improve COVID-19 outcomes.

Limitation(s)

The paucity of data regarding previous lipid profiles before diagnosis in COVID-19 cases, along with a small sample size due to incomplete lipid profile data in some patients, are the main limitations of this study. Therefore, a larger study with a bigger population size and if possible, multi-centric studies may help establish more definitive conclusions.

CONCLUSION(S)

Lipid ratios, along with the TyG index, may be used as tools to evaluate the progression of the disease, thereby assisting in appropriate treatment and its outcomes. The optimal cut-off values for the TyG index, TG/HDL ratio and TC/HDL ratio were 9.34, 3.55 and 3.836, respectively. These measures may be employed to detect IR in COVID-19 patients and facilitate therapeutic management.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 04, 2025
- Manual Googling: May 01, 2025
- iThenticate Software: May 03, 2025 (12%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 01, 2025**
Date of Peer Review: **Feb 22, 2025**
Date of Acceptance: **May 05, 2025**
Date of Publishing: **Jun 01, 2025**