Prognostic value of the TyG index for in-hospital mortality in nondiabetic COVID-19 patients with myocardial injury

Halil İbrahim Biter[1] , Muhsin Kalyoncuoğlu[1] , Aydın Rodi Tosu[1] , Sinem Çakal[1] , Ziya Apaydın[1] , Ayça Gümüşdağ[1] , Tufan Çınar[2]* , Ferhat Eyüpkoca[3] , Erdal Belen[1] , Mehmet Mustafa Can[1]

SUMMARY

OBJECTIVE: The purpose of this study was to explore the efficacy of the triglyceride glucose (TyG) index on in-hospital mortality in nondiabetic coronavirus disease 2019 (COVID-19) patients with myocardial injury.

METHODS: This was a retrospective study, which included 218 nondiabetic COVID-19 patients who had myocardial injury. The TyG index was derived using the following equation: log [serum triglycerides (mg/dL) ×fasting blood glucose (mg/dL)/2].

RESULTS: Overall, 49 (22.4%) patients died during hospitalization. Patients who did not survive had a higher TyG index than survivors. In multivariate Cox regression analysis, it was found that the TyG index was independently associated with in-hospital death. A TyG index cutoff value greater than 4.97 was predicted in-hospital death in nondiabetic COVID-19 patients with myocardial damage, with 82% sensitivity and 66% specificity. A pairwise evaluation of receiver operating characteristic (ROC) curves demonstrated that the TyG index (AUC: 0.786) had higher discriminatory performance than both triglyceride (AUC: 0.738) and fasting blood glucose (AUC: 0.660) in predicting in-hospital mortality among these patients.

CONCLUSIONS: The TyG index might be used to identify high-risk nondiabetic COVID-19 patients with myocardial damage.

KEYWORDS: Triglyceride. COVID-19. Myocardial. Damage.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a global pandemic since December 2019[1]. Although the lungs are its primary target, it can damage other organs and systems as well. Targeting the cardiovascular system is critical since the overall prognosis is poor, particularly in individuals with underlying cardiovascular disorders (CVD)[1]. Remarkably, severe COVID-19 individuals have higher risk of heart failure and thrombotic complications[1].

Insulin resistance (IR) is one of the most significant CVD risk factor[2]. In addition, IR is thought to be an independent risk factor for poor cardiovascular outcomes in diabetic individuals[3]. In addition, numerous cross-sectional and prospective studies have provided clinical evidence that IR is associated with elevated cardiovascular risk in nondiabetic individuals that is independent from other risk factors[4]. Although IR may be assessed directly using a hyperinsulinemic euglycemic glucose clamp or an insulin suppression test, these procedures are difficult, expensive, and complicated. The recently developed

triglyceride glucose (TyG) index, on the other hand, is an easily measurable indicator with good sensitivity and specificity in predicting the IR and its accompanying metabolic abnormalities. Recently, it has been proposed that the TyG index as a surrogate marker of IR is an independent risk predictor for adverse cardiovascular events in nondiabetic patients who are diagnosed with acute coronary syndrome undergoing percutaneous coronary intervention[5]. To the best of our knowledge, no data exist in the literature assessing the TyG index's prognostic value for in-hospital mortality in nondiabetic COVID-19 patients with myocardial damage. As a result, the focus of this research was to explore the prognostic accuracy of the TyG index for in-hospital mortality in nondiabetic COVID-19 subjects with myocardial injury.

METHODS

We evaluated the clinical notes of 350 consecutive individuals with a definite diagnosis of COVID-19 and myocardial damage in this retrospective, observational research. Patients who were

under the age of 18 (n=2), had diabetes (n=87), were pregnant (n=5), died at admission (n=7), were transported to another hospital (n=18), or had incomplete baseline data (n=13) were eliminated from the research.

The hospital electronic database was used to gather patients' baseline clinical and demographic properties such as body mass index (BMI), hypertension, diabetes mellitus (DM), current smoking status, coronary artery disease (CAD), chronic heart failure (CHF), chronic renal failure (CRF), cerebrovascular accident (CVA), cancer, and chronic obstructive pulmonary disease (COPD). A skilled team of physicians independently evaluated all data. Our study procedure followed the principles of the Helsinki Declaration, and it was approved by the Local Ethics Commission (decision number: 46-2022).

A positive SARS-CoV-2 laboratory report was interpreted as a positive finding on a real-time reverse-transcriptase polymerase chain reaction test of nasal or pharyngeal swab materials. According to the Fourth Universal Definition of Myocardial Infarction, myocardial damage was confirmed when the blood level of cardiac troponin surged over the 99th percentile upper reference threshold. The normal range of cardiac troponin in our institution was 0–14 pg/mL.

All fasting venous blood samples, including fasting blood glucose (FBG) and triglycerides, were obtained following admission. The TyG index was derived using the following equation: log [serum triglycerides (mg/dL) × FBG (mg/dL)/2]. The major goal of this study was to examine the COVID-19-related in-hospital mortality over the follow-up period. To acquire mortality data, the national death notification system and hospital records were analyzed.

Statistical analysis

Frequencies and percentages are used to represent categorical variables. The chi-square test was used to compare categorical data between groups. Continuous variables having a normal distribution were reported as mean (standard deviation [SD]), whereas those with a non-normal distribution were expressed as median (interquartile ranges [IQR]). The Kolmogorov-Smirnov test was used to determine the normality of variable distributions. The Student's t-test or Mann-Whitney U test was used to evaluate continuous variables between groups depending on distribution normality. Univariable and multivariable Cox regression analyses (enter technique) were used to determine the independent risk variables for in-hospital mortality. To identify the independent predictors of in-hospital death, parameters with a $p<0.05$ in univariable analysis were included in the multivariate Cox regression analysis. All findings provided as hazard ratio (HR) and 95% confidence interval (CI).

The TyG score and its variables (triglyceride and FBG) were not included in the same multivariable Cox regression analysis models to avoid model overfitting. Triglyceride and FBG levels were assessed using a different multivariate analytic model (model 1) that did not contain the TyG index. The receiver operating characteristics (ROC) curve analysis was performed to assess the sensitivity and specificity of the TyG index, as well as its cutoff value in predicting in-hospital mortality. The area under the curve (AUC) was calculated to assess the diagnostic accuracy and discriminatory capability of TyG, triglyceride, and FBG levels. Using Youden's index, the best cutoff value was derived from the point of maximum sensitivity and specificity. A pairwise evaluation of ROC curves was also conducted to examine the discriminatory performance of TyG, triglyceride, and FBG. The Kaplan-Meier and long-rank tests were used to evaluate survival for the low and high TyG groups. The statistical significance level was set at p=0.05. For all statistical analyses, the Statistical Package for the Social Sciences version 24.0 software program (IBM Corp., Armonk, NY, USA) was used. The models' ROC curves were compared using the MEDCALC program (Software bvba version 13, Ostend, Belgium).

RESULTS

This research consisted of 218 nondiabetic individuals with a median age of 62 (57–74) years who had COVID-19 and had experienced myocardial damage. During hospitalization, 22.4 % of the patients (n=49) died. The participants in the research were categorized into two groups: those who died (nonsurvivor group) and those who did not (survivor group). Patients who died were older and overweight and had a greater prevalence of CAD, CHF, CRF, COPD, and malignancies than those who lived. In regard to laboratory measurements, nonsurvivors had greater triglyceride, FBG, TyG index, uric acid, C-reactive protein (CRP), and D-dimer levels; but they had lower estimated glomerular filtration rate, albumin, and lymphocyte levels. In terms of admission cardiac troponin levels, there was no difference between the two groups. Table 1 shows the study cohort's detailed demographic, clinical, and laboratory data.

In multivariable models 1 and 2, age, CHF, malignancy, uric acid, and TyG index (HR: 3.704 (95%CI 1.997–6.869, p<0.001) were predictors of in-hospital death (Table 2). Remarkably, both triglyceride and FBG were not independently associated with in-hospital mortality. When the discriminating power of the triglyceride, FBG, and TyG indexes were compared, it was discovered that the TyG index outperformed both triglyceride and FBG (Figure 1). An ROC curve analysis revealed that a TyG index value greater than 4.92 was an independent predictor

Table 1. Demographic, clinical, in-hospital outcomes and laboratory parameters of the study cohort.

	Survivors (n=169)	Non-survivors (n=49)	p-value
Male gender, n (%)	110 (65.1)	32 (65.3)	0.978
Age, year	60 [51-73]	71 [61-82]	<0.001
BMI, kg/m²	25.9±2.6	27.1±2.9	0.005
Risk factors, n (%)			
CAD	31 (18.3)	19 (38.8)	0.003
CHF	20 (11.8)	14 (28.6)	0.004
Hypertension	66 (39.1)	23 (46.9)	0.323
CRF	28 (16.6)	15 (30.6)	0.030
Current smoking	49 (29)	14 (28.6)	0.954
COPD	31 (18.3)	17 (34.7)	0.015
Cancer	15 (8.9)	10 (20.4)	0.026
CVA	10 (5.9)	3 (6.1)	0.957
ACEI/ARB use history	49 (29)	14 (28.6)	0.954
In-hospital outcomes			
Needing ICU, n (%)	16 (9.5)	25 (51)	<0.001
Invasive mechanical ventilation, n (%)	6 (3.6)	21 (42.9)	<0.001
ARDS, n (%)	15(8.9)	18 (36.7)	<0.001
MOF, n (%)	3 (1.8)	7 (14.3)	<0.001
Acute kidney injury, n (%)	4 (2.4)	6 (12.2)	0.004
Fatal ventricular arrhythmia	1 (0.6)	5 (10.2)	<0.001
High grade AV block	2 (1.2)	0 (0)	0.444
Hospitalization period, days	7 [5-13]	13 [9-16]	<0.001
Laboratory findings			
Blood glucose, mg/dL	118 [93.5-153]	151 [107.5-223]	<0.001
Triglyceride, mg/dL	144 [103-200]	216 [165-344]	<0.001
TyG	4.86 [4.66-5.10]	5.25 [5.0-5.52]	<0.001
Uric acid, mg/dL	5.6±2.3	7.2±3.2	<0.001
eGFR, mL/min/1.73m²	82 [63-100]	69 [42-83]	0.014
WBC, 10^3/uL	7.8 [5.1-10.1]	9.2 [6.5-13.5]	<0.001
Neutrophil, 10^3/uL	5.9 [3.6-8.2]	7.3 [5.2-12.4]	<0.001
Lymphocyte, 10^3/uL	1.0 [0.7-1.3]	0.7 [0.5-1.0]	<0.001
Hemoglobin, g/L	12.3±2.1	11.7±2.6	0.085
Platelet, 10^3/uL	211 [159-281]	219 [171-333]	0.537
D-Dimer, μg FEU/mL	0.7 [0.3-1.5]	1.5 [0.8-2.4]	<0.001
Ferritin, ng/mL	414 [158-757]	429 [138-1009]	0.364
CRP, mg/L	74 [32-155]	138 [64-243]	<0.001
Albumin, g/L	33.6±5.2	30.4±4.7	<0.001
Hs-Troponin I, pg/mL	45.8 [28 -91]	46.4 [24-118]	0.329

Continuous variables are presented as median (interquartile range) or mean (SD), Nominal variables presented as frequency (%). BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; CRF: chronic heart failure; COPD: chronic obstructive lung disease; CVA: cerebrovascular accident; ACEI/ARB: angiotensinogen converting enzyme/angiotensinogen receptor blockers; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; MOF: multi organ failure; AV: atrioventricular; TyG: triglyceride glucose; eGFR: estimated glomerular filtration; WBC: white blood cell; CRP: C-reactive protein.

of in-hospital death with 89% specificity and 56% sensitivity in nondiabetic COVID-19 patients with myocardial damage. According to the Kaplan-Meier curves, individuals with a TyG index had a considerably increased risk of in-hospital death.

DISCUSSION

The following are the main results of this study:

1. In hospitalized nondiabetic COVID-19 patients with myocardial injury, the TyG index was independently related with in-hospital mortality;
2. TyG index was a better predictor than both triglyceride and FBG; and
3. Patients with TyG index greater than 4.92 were at high risk for in-hospital mortality in nondiabetic COVID-19 patients having myocardial injury.

The most common clinical manifestation of COVID-19 infection is lung involvement, although it can also cause cardiac complications, leading to poor prognosis[6]. Several recent investigations have found that the presence of CVD, in particular, is a risk factor in the progression of COVID-19 disease[1]. The presence of CHF was linked to in-hospital mortality in the current research. Although CAD was not determined to be a predictor, it was more prevalent in nonsurvivors. In keeping with earlier findings, nonsurvivors had higher rates of CRF, COPD, and cancer than survivors[7]. As a result, people with comorbidities such as CVD are not only more likely to become infected, but they are also more likely to develop more severe and fatal infections.

One of the primary causes of mortality from COVID-19 is myocardial damage[8]. According to several retrospective investigations, the incidence of cardiac myocyte damage in COVID-19 individuals ranges between 5 and 28%[9]. Cardiac troponin

levels are strong indicators of worse outcomes in COVID-19 patients, in which may have a predictive role in optimizing risk categorization in such individuals[10,11]. Furthermore, elevated blood glucose levels upon admission and throughout hospitalization are linked to severe COVID-19 infection[12]. Although the cause of altered glucose and lipid metabolism in COVID-19 patients is unknown, the possible cause of high blood glucose during SARS-CoV-2 infection is connected to new-onset IR instead of insulin insufficiency. Further, it has been shown that IR may persist even after the virus has been eradicated[13].

Hyperinsulinemia may contribute to greater SARS-CoV-2 viremia in individuals with IR and diabetes because insulin enhances membrane transcription of angiotensin-converting enzyme 2 (ACE 2) in
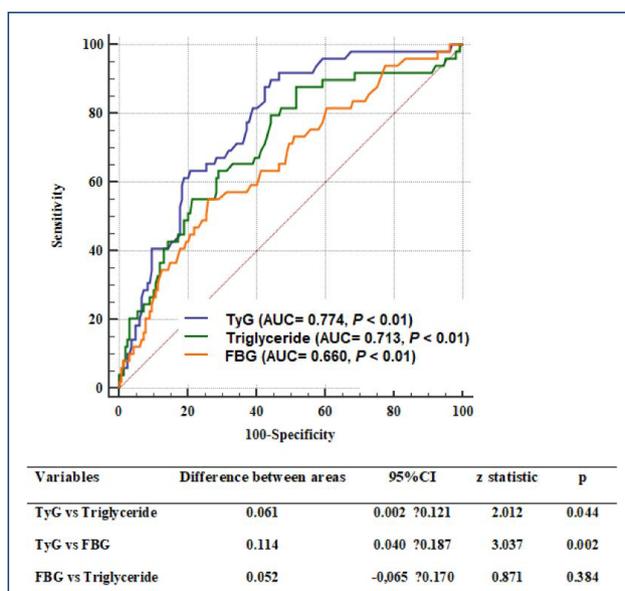

Variables	Difference between areas	95%CI	z statistic	p
TyG vs Triglyceride	0.061	0.002 ?0.121	2.012	0.044
TyG vs FBG	0.114	0.040 ?0.187	3.037	0.002
FBG vs Triglyceride	0.052	-0.065 ?0.170	0.871	0.384

Figure 1. Diagnostic accuracy and discriminatory performance of triglyceride glucose, triglyceride, and blood glucose for detecting the in-hospital mortality using area under curve values.

Table 2. Independent risk factors that were found to be independently associated with in-hospital mortality according to univariate and multivariate models[*].

	Univariate HR (95%CI)	p-value	Multivariate-1 HR (95%CI)	p-value	Multivariate-2 HR (95%CI)	p-value
Age	1.042 (1.017-1.067)	0.001	1.032 (1.006-1.058)	0.016	1.030 (1.005-1.055)	0.017
CAD	1.952 (1.088-3.502)	0.025	1.157 (0.594-2.253)	0.669	1.146 (0.541-2.023)	0.894
CHF	3.890 (2.029-7.461)	<0.001	2.216 (1.002-4.902)	0.049	2.274 (1.041-5.056)	0.039
Cancer	2.269 (1.126-4.570)	0.022	2.295 (1.048-5.022)	0.038	2.407 (1.146-5.056)	0.020
Uric acid	1.177 (1.076-1.288)	<0.001	1.139 (1.031-1.259)	0.011	1.130 (1.025-1.246)	0.014
Glucose	1.004 (1.002-1.007)	0.001	1.003 (1.000-1.006)	0.058	-	-
TG	1.001 (1.000-1.003)	0.008	1.001 (1.000-1.003)	0.054	-	-
TyG	3.711 (2.174-6.336)	<0.001	-	-	3.704 (1.997-6.869)	<0.001

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method.
HR: hazard ratio; CI: confidence interval; CAD: coronary artery disease; CHF: congestive heart failure; TG: triglyceride; TyG: triglyceride glucose.

the pneumocyte, which acts as a SARS receptor. Hyperinsulinemia and hyperglycemia can promote clotting, hence raising inflammation and the risk of thrombosis. Hyperinsulinemia raises plasminogen activator type 1 levels, which promotes thrombosis by blocking fibrinolysis, whereas hyperglycemia raises blood coagulation and the generation of pro-inflammatory cytokines, such as TNF-alpha and IL-6[14]. The mentioned factors may help explain the link between IR and unfavorable cardiovascular events in COVID-19 disease.

Even though IR may be determined directly using a hyperinsulinemic euglycemic glucose clamp or an insulin suppression test, these procedures are complex and costly in medical practice. Given the difficulties of directly assessing insulin action and the lack of a standardized insulin test, the TyG index may be related to CVD as a proxy of IR. The TyG index has been connected to CVD risk factors such as hypertension and metabolic syndrome. Some studies found that the TyG index was correlated to CVD in high-risk individuals, such as those with DM or CRF[15,16]. An elevated TyG index was also demonstrated to be a valuable alternative instrument for evaluating cardiovascular risk in nondiabetic individuals at the preclinical condition[17]. While some researchers have examined the relationships between the TyG index, IR, and CVD in the non-COVID-19 population. To the best of our knowledge, this is the first study to focus at the TyG index's prognostic value in nondiabetic COVID-19 patients with myocardial damage. The likely explanation behind the TyG index relation with worse cardiovascular outcome in COVID-19 has not yet been explained; however, we believe the following hypotheses may be relevant. First, the TyG index can indicate IR, which has been linked to endothelial dysfunction, oxidative stress, and inflammatory reaction. Second, the TyG index is related to IR, which can generate an instability in glucose metabolism, resulting in persistent hyperglycemia, as well as modify lipid metabolism, suggesting that such metabolic abnormalities may lead to cardiovascular damage. Finally, the TyG index is related to arterial stiffness as measured by pulse pressure and brachial-ankle pulse wave velocity, all of which are key risk factors for adverse cardiovascular outcomes[18].

Limitations

Our study may, however, have major limitations. First, our study was a retrospective assessment of a limited database that based on single-center experience. Second, we only examined the baseline TYG index upon admission, and the alterations revealed by serial measurements may have an incremental prognostic value. Third, we did not collect data about plasma insulin levels, HbA1c, Homeostatic Model Assessment-IR, and brain natriuretic peptide. More multicenter prospective investigations including more participants are required to assess the TyG index's predictive accuracy in detecting poor cardiovascular outcome in the nondiabetic COVID-19 cohort.

CONCLUSIONS

We believe that TyG could be part of cardiovascular evaluation to identify nondiabetic COVID-19 patients with myocardial injury who are at high risk of having worse prognosis.

AUTHORS' CONTRIBUTIONS

HIB: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **MK:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **ART:** Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. **SÇ:** Funding acquisition, Writing – review & editing. **ZA:** Data curation, Funding acquisition, Writing – review & editing. **AG:** Data curation, Funding acquisition, Writing – review & editing. **TÇ:** Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **FE:** Validation, Visualization, Writing – original draft, Writing – review & editing. **EB:** Project administration, Resources, Supervision, Validation, Writing – review & editing. **MMC:** Project administration, Resources, Supervision, Validation, Writing – review & editing.

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