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Relationship between triglyceride-glucose index and intravenous thrombolysis outcomes for acute ischemic stroke

Selcen Duran, Aysu Yetiş
Department of Neurology, Faculty of Medicine, Kırşehir Ahi Evran University, Kırşehir, Turkiye

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ABSTRACT

Aims: The aim of this study was to investigate the effect of triglyceride glucose index, a marker of insulin resistance, on early neurological deterioration (END), development of intracerebral hemorrhage and hemorrhagic transformation and mortality in patients receiving intravenous thrombolytic therapy for acute ischemic stroke.

Methods: This retrospective study included 71 patients with acute ischemic stroke who received intravenous tissue plasminogen activator. Demographic data, clinical and radiological findings, fasting glucose and lipid profile, END, hemorrhage development and mortality rates were analyzed. We also calculated the triglyceride glucose (TyG) index and examined its correlation with early neurological deterioration, hemorrhage development and mortality.

Results: The median age was 74 years (41-88), with a female predominance of 54.9%. The incidence of intracerebral hemorrhage was 9.6%, while END occurred in 39.6% of cases, and the 30-day mortality rate was 28.2%. The mean TyG index was 7.8 (2.8-27.6). The receiver operating characteristic curve analysis indicated that the TyG index predicted mortality with an area under the curve of 84.4%, a sensitivity of 85%, and a specificity of 82.35% in patients with a TyG index above 10.01 ($p<0.01$). According to univariate analyse, the admission NIHSS score was associated with a 1.46-fold increase in the odds of mortality (odds ratio [OR]: 1.459), while a TyG index greater than 10.01 was associated with a 1763.9-fold increase in mortality risk (OR: 1763.9) ($p=0.005$; $p=0.009$, respectively). Patients with higher TyG index also exhibited significantly increased rates of mortality and END ($p<0.001$ for both). There was no association between development of hemorrhage and TyG index ($p>0.05$).

Conclusion: This study supports that a high TyG index is associated with END and mortality but not with the development of hemorrhage. Multicenter studies with larger sample size are needed.

Keywords: Triglyceride glucose index, insulin resistance, intravenous thrombolytic therapy, acute ischemic stroke, hemorrhagic transformation

INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity globally, with ischemic stroke constituting approximately 85% of all stroke cases.[1] In the management of acute ischemic stroke, both mechanical thrombectomy and intravenous thrombolytic therapy can yield favorable outcomes in patients who present within the appropriate time window for intravenous thrombolysis.[2] Intravenous thrombolysis results in an average absolute increase in disability-free survival of approximately 5-10%.[3] Despite encouraging results, the development of hemorrhagic transformation and intracerebral hemorrhage in patients receiving intravenous tissue plasminogen activator (IV tPA) may lead to a significant increase in mortality and morbidity associated with the disease.[3-5]

Insulin resistance (IR) plays a major role in the pathophysiology of diabetes mellitus and metabolic syndrome.[5,6] Also IR is closely associated with obesity and is an independent risk factor for mortality and major disability after stroke.[7] The presence of hyperglycemia (consequence of IR), which can have a negative impact on brain function, has been shown to adversely affect the prognosis of individuals with ischemic stroke, regardless of their diabetic status.[8] IR plays a predisposing role for stroke through the formation of atherosclerosis by promoting thrombosis, but also induces inflammatory response, oxidative stress and neuronal damage, leading to poor prognosis.[8] Although IR has been detected by methods such as hyperinsulinemic-euglycemic clamp, Homeostasis Model Assessment of IR (HOMA-IR), these methods are not practical enough.[5,7] The triglyceride-glucose (TyG) index is a biomarker of IR that is calculated using fasting triglycerides and fasting blood glucose levels, making it easily accessible.[9] The TyG index has been shown to be at least as good as or even superior to the HOMA-IR in detecting IR.[10] Thus, the TyG index has been verified as a simple surrogate marker of IR and is cost-effective and replicable.[6,11]

Corresponding Author: Selcen Duran, drselcenduran@gmail.com

Factors that may predict the development of early neurological deterioration and hemorrhage after IV tPA therapy in ischemic stroke have recently become popular areas of research.[3] Studies on the effect of TyG index on early neurological deterioration (END), hemorrhage development and mortality after IV tPA are quite limited and there is no study from our country. The aim of this study is to investigate the effect of TyG index on hemorrhage development and mortality after IV tPA.

METHODS

Study Design

This retrospective study involved patients diagnosed with acute ischemic stroke who received intravenous thrombolysis with alteplase at Kırşehir Training and Research Hospital from 2020 to 2024. The study was approved by the Kırşehir Ahi Evran University Health Sciences Scientific Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024-07/46). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Thrombolytic treatment involves the administration of recombinant tissue plasminogen activator (r-tPA) at a dosage of 0.9 mg/kg up to a maximum of 90 mg, with 10% of the dose given as a bolus and the remaining amount infused over 60 minutes, ideally within 4.5 hours of the onset of a stroke. Patients diagnosed with acute ischemic stroke who did not undergo thrombolytic therapy, patients with transient ischemic attack were excluded from the study. Additionally, patients who underwent interventional procedures, such as thrombectomy, were also excluded. Patients with incomplete data in their medical records were excluded as well. Of the 87 patients who underwent thrombolytic therapy, 5 were referred to an advanced center for thrombectomy and lipid profile was not studied in 11 patients; therefore, 71 patients were included in the study.

Demographic data, comorbidities, medications, and clinical data including admission blood pressures, National Institute of Health Stroke Scale (NIHSS) score, number of hemorrhage developing and mortality, NIHSS score prior to discharge were recorded. Body-mass index (BMI) was calculated as weight (kg) ratio to height squared (m^2). Fasting glucose, fasting triglycerides, fasting cholesterol, fasting low density lipoprotein (LDL) cholesterol and fasting high density lipoprotein (HDL) cholesterol levels were assessed based on laboratory data. Blood samples were examined after 8 hours of fasting after admission to the hospital. TyG index was calculated by the formula: fasting TG (mg/dl) × glucose (mg/dl)/2.[9] END was considered as a decrease of ≥4 points in the total baseline NIHSS score in the first 72 hours, development of intracerebral hemorrhage or resulting in mortality.[12] Hemorrhage detected on computed tomography examination of the brain routinely performed 24 hours after thrombolytic therapy or in case of neurological deterioration. Hemorrhagic transformation and hematoma formation in the infarct area or distant area in the intracranial region until discharge were considered as hemorrhage development. The definitions of hemorrhagic transformation and inracerebral hemorrhage were based on the safe implementation of thrombolysis in stroke-monitoring study study criteria.[13]

Statistical Evaluation

Statistical package for the social sciences (SPSS) version 25.0 was utilized for the statistical analysis of the data. Categorical variables were summarized as counts and percentages, while continuous variables were summarized using the mean, standard deviation, median, minimum-maximum range, and the 25th to 75th percentiles when appropriate. The Chi-square test was employed to compare categorical variables. The Shapiro-Wilk test was conducted to assess whether the study parameters followed a normal distribution. For normally distributed parameters, the independent Student's t-test was applied, whereas the Mann-Whitney U test was used for non-normally distributed parameters. The sensitivity and specificity values of the TyG index were calculated, and the cutoff value was determined by analyzing the area under the receiver operating characteristic (ROC) curve. Spearman's rho correlation coefficient was used to evaluate the relationship between continuous variables. Univariate and multivariate logistic regression models were used to analyze the factors influencing mortality and the development of hemorrhage. A statistical significance level of $p<0.05$ was established for all tests.

RESULTS

In this study involving 71 patients, the median age was 74 years (41-88), with a female predominance of 54.9%. Hypertension was the most prevalent predisposing factor, affecting 69% of the participants. The incidence of intracerebral hemorrhage was recorded at 9.6%, while the occurrence of END was noted in 39.6% of cases. The 30-day mortality rate was found to be 28.2%. The mean TyG index was 7.8 (2.8-27.6). A summary of the demographic, clinical, and laboratory data is presented in Table 1.

The ROC curve demonstrated that the TyG index is a significant predictor of mortality, exhibiting an area under the curve (AUC) of 84.4%, a sensitivity of 85%, and a specificity of 82.35% in patients with a TyG index above 10.01 ($p<0.01$) (Figure).

The comparison of demographic, clinical, and laboratory data between the two groups based on the TyG index is presented in Table 2. The mean values for admission NIHSS, final NIHSS, glucose, triglycerides, LDL, and total cholesterol were significantly elevated in patients exhibiting a high TyG index in comparison to those with a low TyG index ($p=0.002$; $p<0.001$; $p<0.001$; $p<0.001$; $p<0.001$; $p=0.037$; $p=0.006$, respectively). Patients with a higher TyG index demonstrated significantly elevated rates of mortality and END ($p<0.001$ for both). No significant differences were noted for the other parameters ($p>0.05$).

Univariate analysis indicated a significant difference in mortality outcomes among patients based on various factors, including diabetes mellitus, END, admission NIHSS, final NIHSS, glucose levels, triglycerides, LDL and TyG index identified as significant in the univariate analysis, were subsequently incorporated into the multivariate model. According to this model, the admission NIHSS score was associated with a 1.46-fold increase in the odds of mortality

Table 1. Demographic, clinical and laboratory data of patients with acute ischemic stroke who received intravenous thrombolysis (n=71)	
Age	74 (41-88)
Female gender	39 (54.9)
BMI	28.2±4.8
Comorbidities	
Hypertension	49 (69)
Diabetes mellitus	28 (39.4)
Coronary heart disease	26 (36.6)
Atrial fibrillation	9 (12.7)
Chronic obstructive pulmonary disease	8 (11.3)
Congestive heart failure	14 (19.7)
Prior stroke	7 (9.9)
Localization of stroke	
Right middle cerebral artery	33 (46.5)
Left middle cerebral artery	19 (26.8)
Brainstem	2 (2.8)
Cerebellar	5 (7)
Striatocapsular infarct	10 (14.1)
Posterior cerebral artery	2 (2.8)
Carotid and vertebral system examination	
Normal	56 (78.8)
≤49% stenosis	3 (4.2)
50-69% stenosis	6 (8.5)
70%≥ stenosis	6 (8.5)
Clinical data	
Admission SBP (mmHg)	169.9±19.4
Admission DBP (mmHg)	90 (65-130)
Admission NIHSS	14 (4-37)
Final NIHSS	7 (0-42)
Development of hemorrhage	
Hemorrhagic transformation	11 (15.5)
Intracerebral hemorrhage	7 (9.6)
Early neurological deterioration	19 (26.7)
Mortality	20 (28.2)
Symptom/door time	90 (15-180)
Symptom/needle time	180 (45-240)
Laboratory data	
Glucose	133 (71-329)
Triglyceride	122 (53-309)
Low density lipoprotein	110.8±31.1
High density lipoprotein	41 (25-71)
Cholesterol	176.9±38.5
TyGI	7.8 (2.8-27.6)

BMI: Body-mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NIHSS: National Institute of Health Stroke Scale, TyGI: Triglyceride-glucose index

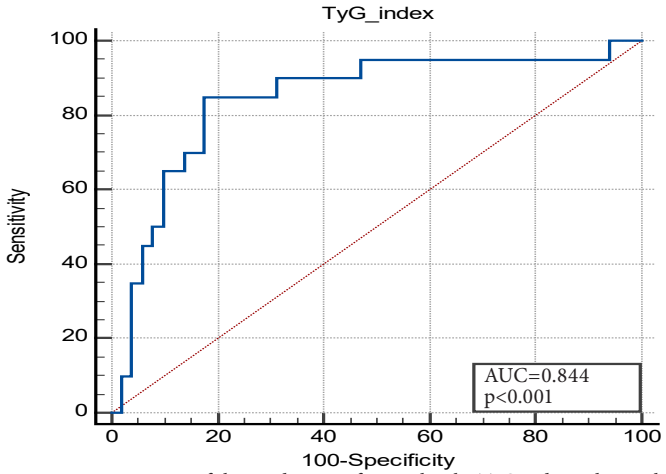

Figure. Investigation of the prediction of mortality by TyG index value with ROC curve test

AUC: Area under the curve, TyG: Triglyceride glucose, ROC: Receiver operating characteristic

Table 2. Comparison of demographic, clinical, and laboratory data of the two groups based on the triglyceride glucose index in patients with intracerebral hemorrhages (n=71)			
	TyGI score <10.01 (n=45)	**TyGI score of >10.01 (n=26)**	**p**
Age	74 (60-78.5)	77 (67-80)	0.364µ
Female gender	23/22	16/10	0.395†
Localization of stroke			
Right middle cerebral artery	22 (48.9)	11 (42.3)	0.343†
Left middle cerebral artery	10 (22.2)	9 (34.6)	
Brainstem	1 (2.2)	1 (3.8)	
Cerebellar	2 (4.4)	3 (11.5)	
Striatocapsular infarct	9 (20)	1 (3.8)	
Posterior cerebral artery	1 (2.2)	1 (3.8)	
Admission NIHSS	11 (8-16)	19 (13.25-23.25)	0.002**µ
Development of hemorrhage	6 (17.7)	10 (38.5)	0.054†
Mortality	3 (6.7)	17 (65.4)	<0.001**†
Final NIHSS	5 (2.5-11)	42 (5.5-42)	<0.001**µ
Early neurological deterioration	5 (17.2)	14 (73.7)	<0.001**†
Carotid and vertebral system examination			
Normal	38 (84.4)	18 (69.2)	0.260†
≤49% stenosis	1 (2.2)	2 (7.7)	
50-69% stenosis	2 (4.4)	4 (15.4)	
70%≥ stenosis	4 (8.9)	2 (7.7)	
Laboratory data			
Glucose	116 (90-138.5)	162 (134-214)	<0.001**µ
Triglyceride	105 (83.5-128)	180.5 (157-207)	<0.001**µ
Low density lipoprotein	104.9±31.2	120.9±28.8	0.037*‡
High density lipoprotein	41 (38-46.5)	41.5 (36.75-47)	0.872µ
Cholesterol	167.3±38.7	193.7±32.7	0.006**‡

TyGI: Triglyceride-glucose index, NIHSS: National Institute of Health Stroke Scale, †: Chi-square, ‡: Independent student t-test, µ: Mann-Whitney U test

[odds ratio (OR): 1.459], while a TyG index greater than 10.01 was linked to a 1763.9-fold increase in mortality risk (OR: 1763.9) (p=0.005; p=0.009, respectively).

Univariate analysis indicated a statistically significant difference in the occurrence of hemorrhage and END, as well as in the final NIHSS, admission systolic blood pressure,

and admission diastolic blood pressure (p=0.004; p=0.028; p<0.001; p<0.001, respectively). The parameters identified as significant in the univariate analysis were included in the multivariate model. According to this model, it was determined that the parameters deemed significant in the univariate analysis had no statistically significant effect on the development of hemorrhage (p>0.05).

DISCUSSION

Several studies have shown that IR is a risk factor for stroke[14] and a poor prognostic marker for stroke.[6,7] It has been proposed that IR may serve as a poor prognostic indicator following thrombolytic therapy in cases of acute ischemic stroke.[4,5,11,15] There are several theories suggesting that IR is linked to a poor prognosis following a stroke. Firstly, IR in adipocytes leads to the production of chemokines, which in turn recruit monocytes and activate pro-inflammatory macrophages.[16] Inflammation, recognized as a negative prognostic indicator in stroke patients undergoing thrombolytic therapy,[17-19] exacerbate worse outcomes in the presence IR. Secondly, it inhibits the membrane translocation of glucose transporter type 4 in insulin receptors, resulting in insufficient glucose uptake and subsequently contributing to neuronal apoptosis.[5] The adverse effects of IR are not only on stroke prognosis but also on thrombolytic therapy. Patients with high IR have elevated blood levels of fibrinolysis inhibitors such as plasminogen activator inhibitors, which may be associated with an impairment in endogenous fibrinolytic capacity and IR may also be associated with a worsened response to intravenous thrombolysis.[4,20] IR can make the structure of the clot denser and more resistant to lysis, making it resistant to IV tPA.[4] Vascular alterations observed in diabetic patients, including cerebral vascular endothelial dysfunction, increased arterial stiffness, and thickening of the capillary basement membrane, as well as hyperglycemia-induced overproduction of reactive oxygen species, significantly contribute to the diminished efficacy of thrombolytic therapy.[12]

TyG index is a biomarker indicative of IR, derived from the values of triglycerides and glucose. It is considered superior to other IR parameters due to its straightforward calculation [9]. Although numerous studies indicate that both hyperglycemia and hypercholesterolemia serve as unfavorable prognostic markers following an acute stroke, research has demonstrated that the TyG index, which is derived from these two parameters, provides a more accurate reflection of prognosis after cardiovascular and cerebrovascular events than either of the individual values alone.[12] A meta-analysis encompassing 18 studies and a total of 592,635 patients revealed that a higher TyG index is correlated with an increased risk of ischemic stroke. Furthermore, a significant association was identified between an increased TyG index and various adverse outcomes related to stroke, particularly with respect to stroke recurrence and heightened mortality rates.[6] Studies on TyG index as a prognostic marker in acute stroke patients receiving thrombolytics are more limited. A study conducted by Zhang et al.,[4] which involved 676 participants, demonstrated that a high TyG index is correlated with END in patients treated with IV tPA. In a study conducted by Toh et al.[12] involving 698 patients who received IV tPA, a high TyG index was found to be associated with increased mortality and poor functional outcomes; however, it was not associated with symptomatic intracerebral hemorrhage. In a study conducted by Calleja et al.,[15] which included 109 patients who underwent thrombolytic therapy, it was found that IR was associated with a poor prognosis; however, it did not have an effect on the development of hemorrhagic transformation. Another study conducted by Bas et al.[21] found that IR had no significant effect on the development of hemorrhage or mortality; however, it was associated with a poor prognosis at the three-month mark. In our study, we similarly observed that the TyG index was correlated with END and mortality; however, it did not demonstrate an association with the occurrence of hemorrhage. In the ROC curve analysis of patients TyG index predicting mortality, it was determined that patients with TyG index above 10.01 predicted mortality with 84.4% AUC, 85% sensitivity, 82.35% specificity.

One of the most important reservations when administering IV tPA to a patient with acute ischemic stroke is the risk of intracerebral hemorrhage.[22] In a meta-analysis of 52,610 patients, the rate of patients who developed only intracerebral hematoma excluding hemorrhagic transformation was 3.2% and more in the female sex and those with higher diastolic blood pressure and higher rates of previous stroke, chronic heart failure and cardioembolism.[3] Our study identified an intracerebral hemorrhage rate of 8.5%. The observed slightly elevated rate of hemorrhage in our research may be due to the relatively higher NIHSS and elevated blood pressure at the time of admission. It is important to note that some studies define intracerebral hematoma as hemorrhage occurring outside the infarct area; however, our methodology included intracerebral hemorrhage within the infarct region. This methodological distinction may have resulted in an increased rate of hemorrhage development in our findings.

Limitations

This study presents several limitations. Firstly, the sample size was limited, and the research design was retrospective and observational in nature. Secondly, the analysis was restricted to the initial 30 days of patient data, thereby lacking long-term follow-up. Thirdly, smoking, a significant risk factor for stroke, was not incorporated into the study due to the unavailability of this information in the patient records. Lastly, the homeostasis model assessment of insulin resistance (HOMA-IR) and the hyperinsulinemic-euglycemic clamp were not included in the study, as these assessments are not routinely conducted for stroke patients at our institution.

CONCLUSION

This study supports that a high TyG index is associated with END and mortality but not with the development of hemorrhage. A high TyG index, which encompasses readily accessible parameters and serves as a biomarker for IR, may provide clinicians with insights into END and mortality risk.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of the Kırşehir Ahi Evran University Health Sciences Scientific Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024-07/46).

Informed Consent
Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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