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ASSOCIATION OF TRIGLYCERIDE GLUCOSE INDEX WITH CLINICAL OUTCOMES IN ISCHEMIC STROKE

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ABSTRACT:

Background: Stroke, a significant global health concern, ranks among the leading causes of morbidity, mortality, and long-term disability. Insulin resistance(IR) is a hallmark of metabolic syndrome and is considered to be one of the important risk factors of stroke. Insulin resistance (IR) is prevalent in patients with stroke. The triglyceride-glucose (TyG) index has been proposed as the alternative indicator of IR due to its relevance to lipotoxicity and glucotoxicity.

Aim: The study aimed to evaluate the association of triglyceride glucose with clinical outcomes in ischemic stroke. The Primary Objective is to evaluate the relationship between high TyG indexes and adverse clinical outcomes in patients with Ischemic stroke. The Secondary objective is to identify the prevalence of adverse outcomes (Recurrence and all-cause mortality) in patients with ischemic stroke.

Method: This is a retrospective observational study which was carried out for a period of 6 months in patients admitted to Dr. pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation which is a 850 bedded tertiary care teaching hospital at Chinnaoutpalli, Gannavaram Mandal, Krishna district, Andhra Pradesh (India). A total of 95 patients who met the inclusion criteria were recruited into the study

Results: In this study, the plasma lipid profile of patients, that is Total cholesterol was found to be 165.01 ± 51.5 mg/dL; Triglycerides was 157.031 ± 98.9 mg/dL; HDL-c was 37.253 ± 5.52mg/dl; LDL-c was 107 ± 48.3mg/Dl; and FBS was 153.74 ± 71.52 mg/dL.

Conclusion: Few studies showed that there is a significant association between TyG Index and cardiovascular outcomes, but according to our study, we conclude that there may be no significant association between and clinical outcomes in ischemic stroke patients.

Keywords: Triglyceride Glucose, TyG Index,Ischemic stroke.

Impact statements:

- The association of triglyceride glucose index (TyG index) with clinical outcomes in ischemic stroke patients highlights its potential whether it acts as a valuable prognostic marker or not to predict patient outcomes and guide personalized treatment strategies.
- This study investigated the relationship between the triglyceride glucose index and clinical outcomes in ischemic strokeby using SPSS software.
- The findings from this research underscore the clinical significance of monitoring triglyceride glucose index in ischemic stroke patients and concluded that there may not be

a substantial correlation between TyG Index and clinical results in ischemic stroke patients.

- This study's identification of association between triglyceride glucose index and clinical outcomes in ischemic stroke emphasizes the importance of a holistic approach to stroke management, where triglyceride glucose index can be eliminated from the marker role.

1. INTRODUCTION:

The World Health Organisation describes a stroke as a clinical illness with rapidly emerging clinical indications of a focal (or global, in the case of a coma) impairment of brain function that lasts for more than 24 hours or results in death with no other underlying known cause save a vascular origin.Ischemic stroke, haemorrhagic stroke, and subarachnoid haemorrhage are the three main types of stroke. Ischemic stroke is caused by a blood vessel blockage that reduces blood flow to the brain, whereas haemorrhagic stroke is caused by a blood vessel rupture that causes blood to flood into the cerebral cavity.The haemorrhagic stroke may be characterised as an intracerebral haemorrhage or a subarachnoid haemorrhage depending on where the blood was spilled. Ischemic strokes account for 60–80% of all strokes.[1-4]
The haemorrhagic stroke may be characterised as an intracerebral haemorrhage or a subarachnoid haemorrhage depending on where the blood was spilled. Ischemic strokes account for 60–80% of all strokes. [5].The statistics from the USA are slightly different, with 87% of strokes being ischemic, 10% being haemorrhagic, and only approximately 3% being subarachnoid haemorrhage. [6,7]. Although there is a paucity of information regarding the occurrence of stroke in India, data from the West can be extrapolated. In a research conducted in 2001 by Banerjee et al., the yearly incidence rate and crude prevalence rate of stroke in India were both measured at 36/100,000. Age-adjusted prevalence rates for women were much higher than those for men (564/100,000 vs. 196/100,000), as were incidence rates (204/100,000 vs. 36/100,000) [8,9]. According to several research, the overall prevalence of stroke ranges between 147-922/100,000[10,11].
Acute coronary syndrome (ACS) is the leading cause of death worldwide, and the three leading risk factors for ACS are smoking (40%), high blood pressure (38%), and diabetes (30%)[12].We may fairly presume that India has a very high incidence of stroke given the facts above and the fact that ACS and stroke both share a number of risk factors..
One of the major risk factors for stroke, insulin resistance is a defining feature of the metabolic syndrome.Patients who have had a stroke frequently have insulin resistance (IR). Previous research showed that IR promotes atherosclerosis, causes hemodynamic disturbances, and accelerates platelet adhesion, activation, and aggregation, which may lead to stroke recurrence in people who have already experienced an ischemic stroke (IS)[13].
The most often used technique for measurementThere are two methods for performing IR glucose clamp testing: Using the hyperglycaemic clamp technique, one may measure the sensitivity of beta cells to glucoseandthe euglycemic insulin clamp technique for measuring the insulin sensitivity of peripheral cells.These methods, which are considered as the gold standard for quantifying IR, depend on continuous insulin infusion and steady-state measurements of glucose disposal.[14] However, because of the time and financial costs, this strategy is only partially applicable.Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is a different assessment strategy, but it is equally pricey because it involves measuring insulin.Previous research has shown that glucotoxicity and lipotoxicity are crucial elements in IR modulation.The relevance of the triglyceride-glucose (TyG) index to lipotoxicity and glucotoxicity has led to its proposal as a substitute for the IR indication.
The triglyceride-glucose (TyG) index, which was computed as ln (fasting triglyceride [mg/dL] fasting glucose [mg/dL]/2), was proposed as a viable proxy marker of insulin

resistance.TyG index's typical range was 4.080 to 4.808.[15] There are few current studies linking the TyG index to stroke.A recent cross-sectional investigation revealed that in the general population, greater values of the TyG index were linked to a higher risk of ischemic stroke.

2. METHODS

- This study was conducted over the course of six months in retrospect and is an observational study in patients admitted to the 850-bed tertiary care teaching hospital Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation Chinnaoutpalli, Krishna district in Andhra Pradesh, Gannavaram Mandal. 95 patients in all who met the eligibility requirements were enrolled in the trial.
- Patients > 18 years of age. Patient diagnosed with Ischemic stroke confirmed by brain imaging. Estimated glomerular filtration rate eGFR > 60ml/min*173m2 at admission.
- Patients taking statins and triglycerides-lowering medication before the onset of stroke were excluded. Patients with severe physical disability, inability to give written informed consent, and reduced life expectancy (<1 year).
- 95 patients in all who satisfied the inclusion requirements were enrolled in the trial. An appropriate data collecting from (Annexure) was created to be used in the research. The required information, including the patient's demographics (age, sex), social history (smoking, alcohol consumption), family history, co-morbidites, lab investigations were collected from clinical records. Then Triglyceride Glucose index is calculated and subsequent data will can be discovered via hospital records or through interviewing (by telephone) patients and their families for identifying the major clinical outcomes.
- Gender, Age, Smoking, Alcohol Comorbidities, Modified ranking scale (disability score) Lipid profile Fasting blood glucose levels Triglyceride glucose index
- Modified ranking scale is used to analyse the results
- Triglyceride glucose Index(TyG) formula: ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2].
- Data obtained from Patient case reports, Laboratory reports and from the data collection forms.
- Clinical outcomes: Recurrent stroke, All-cause mortality.
- For continuous variables, the values were reported as the mean standard deviation (SD), and for categorical variables, as a number (%). Whenever necessary, Student t-tests and 2-tests were used to analyse how clinical features varied between groups. Pearson The TyG Index was correlated with clinical factors and results using correlation analysis. Univariate Cox regression analysis was performed to estimate the association TyG index with Clinical outcomes. A simple Scatter plot was obtained to determine the relation between TGI and outcomes. Kaplan–Meier survival analysis was done for 2 groups of TyG Indexes (No risk and Risk) using SPSS software.

3. RESULTS AND DISCUSSION

- A total of 95 patients are taken into the study. The sample is predominantly male are 63.2% and females are 36.8%. The study's participants' average age was 59.28 ± 12.54 years.
- Various patient characteristics like co-morbidities, smoking, alcohol, laboratory parameters (Table 1) were considered. Predictive variables like Triglyceride glucose index were analysed. The entire accordance with the values of these variables, the research population was divided.

- The mean FBS in low TGI was found to be 107.026 ± 19.26 mg/dL whereas in high TGI it is 186.25 ± 76.564 (P-value <0.001). The differences in the values of TGI among males & females and in patients with Diabetes, Hypertension, Smokers, and Alcoholics were found to be statistically significant (P-value <0.0001). The mean TG in low TGI was found to be 94.718 ± 27.56 mg/dL whereas in high TGI it is 200.43±107.4 mg/dL (P-value <0.001). The mean T. cholesterol in low TGI was found to be148.077 ± 41.984 mg/dL whereas in high TGI it is176.803 ± 54.452 mg/dL (P-value <0.001).

TABLE1: Patient Characteristics and Laboratory Parameters

VARIABLES	ALL	TGI ≤4.808 (NO RISK) N= 39	TGI >4.808 (RISK) N= 56	P VALUE
Age	59.28 ± 12.54	59.74 ± 14.85	58.964 ± 10.7	0.187
Male (%)	63.2	28.4	34.7	**<0.001**
Female (%)	36.8	12.6	24.2	**<0.001**
Diabetes (%)	49.5	11.6	64.3	**<0.001**
Hypertension (%)	65.3	33.9	76.8	**<0.001**
Smoking (%)	42.1	30.4	41.1	**<0.001**
Alcohol (%)	37.9	26.8	37.5	**<0.001**
FBS	153.74 ± 71.52	107.026 ± 19.26	186.25 ± 76.564	**<0.001**
LDL	107 ± 48.3	94.57 ± 41.89	115.7 ± 50.9	0.808
HDL	37.25 ± 5.52	36.54 ± 3.824	37.75 ± 6.44	0.361
TG	157.03 ± 98.92	94.718 ± 27.56	200.43 ± 107.4	**<0.001**
T. CHOLESTROL	165.01 ± 51.47	148.077 ± 41.984	176.803 ± 54.452	**<0.001**

TABLE2: Frequencies of Medications taken by the Patients at the Discharge

VARIABLES	ALL	TGI ≤4.808 (NO RISK)	TGI>4.808 (RISK)
Aspirin	87	35	52
Atorvastatin	92	37	55
Pantoprazole	47	25	22
Ondansetron	2	2	0

Multi-vitamin	52	19	33
Telmisartan	20	5	15
Betahistine	8	2	6
Insulin	27	5	22
Metformin	23	8	15
CCB's	32	6	26
Levetriacetam	11	8	3
Lactulose	24	10	14
Clonazepam	5	2	3
Beta blockers	6	1	5
Clopidogrel	11	3	8

- Illustration of the frequencies of medications taken by the patients at the discharge (Table 2) Predominantly Aspirin, Atorvastatin, Pantoprazole, Multivitamin, calcium channel blockers were taken by most of the patients. Aspirin, Atorvastatin, Multivitamin, telmisartan, insulin, Metformin Hydrochloride, CCB, are taken by patients with abnormal TGI>4.808 (Risk).

TABLE 3: **Correlation between the triglyceride glucose index and outcomes**

VARIABLES	**TyG INDEX**	**PVALUE**
Age	-0.137	0.187
FBS	0.719	**<0.001**
Triglyceride	0.812	**<0.001**
LDL	0.025	0.808
HDL	0.095	0.361
TotalCholesterol	0.420	**<0.001**
OUTCOMES	0.119	0.252

- **Correlation between the triglyceride glucose index and outcomes**:

Pearson Correlation analysis was done to correlate the TyG Index with clinical variables and outcomes. TGI was significantly correlated with, Total cholesterol, Triglycerides, and FBS, TG/HDL, LDL/HDL Total cholesterol, Triglycerides, and FBS. (Table 3)

TABLE 4: Association of triglyceride glucose index with outcomes

VARIABLES	**HR**	**95%CI**	**P-VALUE**
TyG INDEX	1.454	0.829-2.552	0.192

- **Association of triglyceride glucose index with outcomes:**

The Cox proportional hazards model was used to investigate the link between the TyG Index and outcomes related to stroke (Table 4). There is no significant relationship between the TyG Index and results.

TABLE 5: Association of triglyceride glucose index with modified ranking scale (mRS)

mRS / TGI	0	1	2	3	4	5	6
TGI ≤ 4.808(41.1%) N=39	3.2	4.2	10.5	7.4	3.2	6.3	6.3
TGI > 4.808(58.9%) N=56	11.6	14.7	13.7	7.4	2.1	5.3	4.2

- **Association of triglyceride glucose index with modified ranking scale (mRS):** The percentage of disability score with TGI in no risk and risk patients were shown in (Table 5)

TABLE 6: Percentage of outcomes

OUTCOME / TyG INDEX	NO OUTCOME N=56 (58.9%)	REOCCURENCE N=25(26.3%)	DEATH N=14(14.7%)
TGI ≤ 4.808 (NO RISK)	21(22.09%)	10(10.52%)	8(8.4%)
TGI >4.808 (RISK)	35(36.81%)	15(15.78%)	6(6.3%)

- **Percentage of outcomes:** The percentage of outcomes in TGI (no risk and risk) was given below. In TGI ≤ 4.808(no risk), 22.09% of patients has no outcome, 10.52% of patients has suffered with recurrence, and 8.4% have undergone death whereas in TGI >4.808 (risk), 36.81% of patients has no outcome, 15.78% of patients has reoccurrence, 6.3% of patients has death. (TABLE-6)

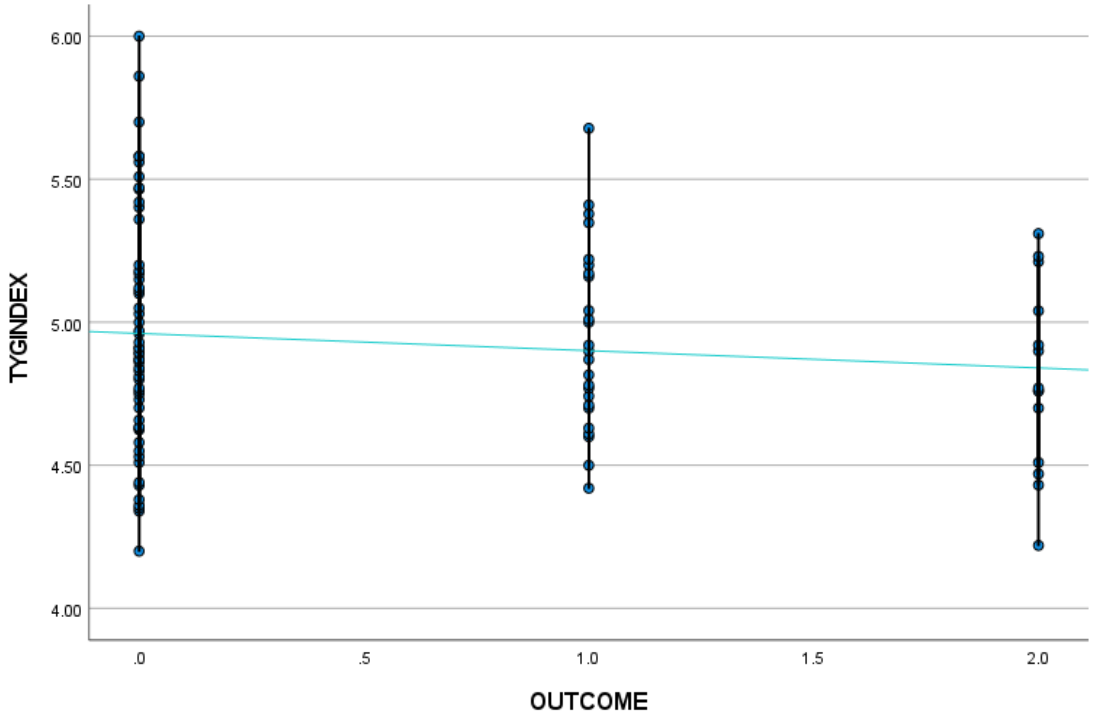

FIGURE 1: Relation between triglyceride glucose index and outcome

The above graph shows negative deviation, which indicates thatTyG Index and clinical outcomes in ischemic stroke patients do not significantly correlate.(Fig 1)

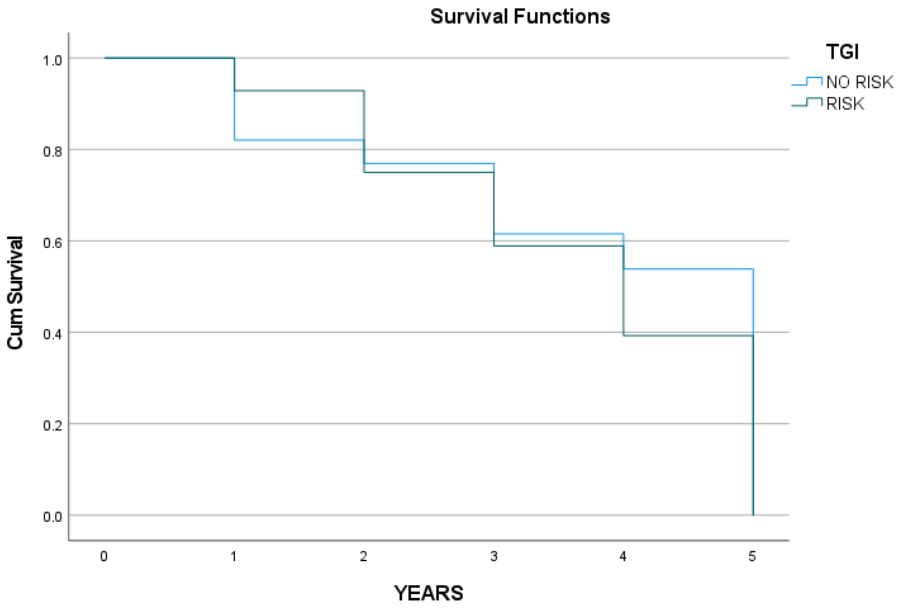

FIGURE – 2(a)

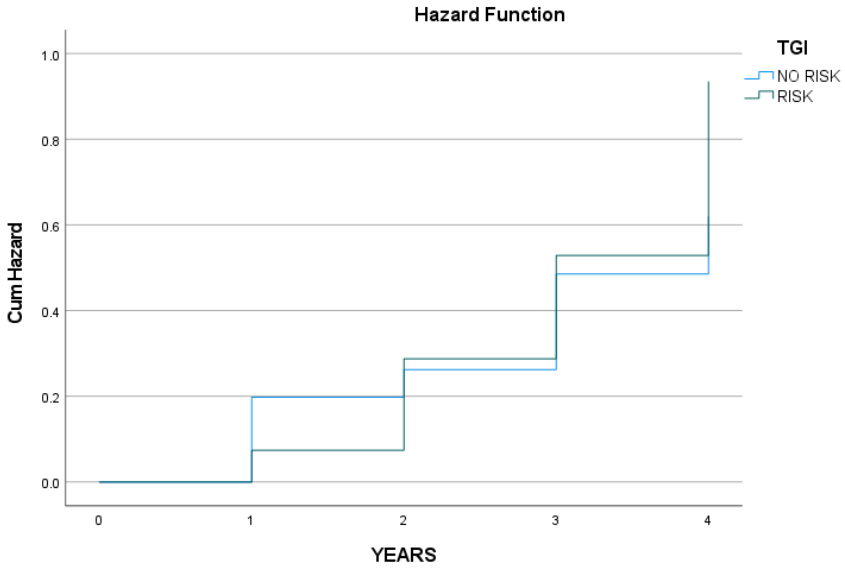

FIGURE – 2(b)

FIGURE 2(a) & 2(b): Kaplan–meier survival analysis

The above figures **2(a) & 2(b)** indicates Kaplan–meier survival analysis for 2 groups of TyG Index using SPSS software. There was no significant difference between the low and high score survival curves. (Fig 2(a) and Fig2(b))

4. DISCUSSION

- In this research, the average age of the sample was found to be 59.28± 12.54 years whereas the mean age was found to be 47.1 ± 19.3 years in a study conducted by Xiao-cong Liu et al., and 64.83 ± 11.9 years in a research project by Yimo Zhou et al. Males were predominant in the current study which has similarities with other studies.
- According to the findings of our research, 49.5% of patients have diabetes whereas in a research project by Mengyuan Miao et al., 26.1% of patients had diabetes mellitus. In our study, 65.3% of patients have hypertension this is similar to the study conducted by Yimo Zhou et al., 65% of patients has hypertension. Comorbidities of the patients were hypertension, diabetes mellitus, indicates that these are the diseases that may contribute to the development of Stroke.
- In this study, the plasma lipid profile of patients, that is Total cholesterol was found to be 165.01 ± 51.5 mg/dL; Triglycerides was 157.031 ± 98.9 mg/dL; HDL-c was 37.253 ± 5.52mg/dl ; LDL-c was 107 ± 48.3mg/Dl; and FBS was 153.74 ± 71.52 mg/dL, whereas in a study conducted by Xiao-cong Liu et al., the Total cholesterol was found to be 194.9 ± 42.9 mg/dL; Triglycerides was 135.9 ± 118.7 mg/dL; HDL-c was 53.4± 15.8 mg/dL; LDL-c was 114.9 ± 35.9 mg/dL, and FBS was 105.6 34.6 mg/dL.
- In this study, the stroke medications prescribed was predominantly Aspirin (91.56%), Atorvastatin (96.84%), Clopidogrel (11.58%), Beta-blockers (6.31%), Telmisartan (21.05%), Hypoglycemics (24.21%) whereas in a study conducted by Xiao-cong Liu et al., Anti-platlets (1.9%), lipid-lowering medications (13%), Hypotensives (25.4%), Hypoglycemics (8.3%) Also, in a study by B.E. Stähli et al., Aspirin (99.3%), Clopidogrel (45.2%), Statins (98.2%), Beta-blockers (81.3%), ACE inhibitor(77.1%) were predominantly given. Overall, the use of guideline-recommended medication was found in this study.
- According to our study, Triglyceride glucose index less than or equal to 4.808 was considered to be normal, and greater than 4.808 was considered to be high. In our study, 39

patients have no risk and 56 patients have high/abnormal triglyceride glucose index. Pearson correlation analysis showed that Triglyceride glucose index was significantly correlated with FBS (Fasting blood sugar), Triglycerides, and Total cholesterol. Cox regression didn't show any statistically significant association between the score and the outcomes.

- In this study, Kaplan–Meier analysis showed no significant difference between normal and high/abnormal TyG Index values whereas, in the study conducted by Xiao-cong Liu et al., elevated TyG Index due to all-cause and CVD was significantly related to cumulative incidence of death (log-rank, $P < 0.001$). However, Xiao-cong Liu et al., study included recruitment of large sample and follow up was done for a longer duration.

5. CONCLUSION

- In our study, we included 95 patients of >18 years of age with confirmed ischemic CVA. Utilising a formula, the triglyceride glucose index was calculated: ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2]. A simple modified ranking scale was used to observe disability score in stroke patients. Few studies showed that TyG Index and cardiovascular outcomes are significantly correlated, but our research suggests that there may not be a substantial correlation between TyG Index and clinical results in ischemic stroke patients.
- First, the retrospective single-center design of this study is a drawback. Second, due to limitations imposed by the study design of a retrospective investigation at a single Centre, our study had a limited study sample. Third, the clinical follow-up duration was short and may have chances of follow-up errors, which might influence the reliability of results. More large-scale research will be needed to assess the implications of these findings.
- Due to these drawbacks, the association between the TyG Index and clinical outcomes in ischemic stroke patients that has been reported may not be statistically connected and may instead be influenced by the constraints of the study. But these results need to be verified in a wider patient group.

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- **Conflicts of Interest:** The authors have no conflicts of interest to declare.

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