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Triglyceride glucose index as a novel biomarker to identify severity of acute pancreatitis

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Abstract

Background: Reduced morbidity and mortality may be achieved with prompt detection of severe acute pancreatitis (AP). The purpose of this research is to demonstrate a connection between AP severity and the Triglyceride glucose (TYG) index.

Methods: This research included 60 individuals who met the clinical criteria for AP and was an observational prospective cohort. Two categories of patients were identified: the severe group (n = 17) and the non-severe group (n = 43). For each patient, the TYG index was computed as follows: $\ln [\text{fasting plasma glucose (mg (dL)} \times \text{fasting TG (mg/dL)})]^2$.

Results: TYG index was significantly higher in severe group. TYG index can significantly predict severity of AP (P=0.002 and AUC = 0.741) at cut-off >5.16 with 76.47% sensitivity, 72.09% specificity, 68.9% PPV and 78.2% NPV.

Conclusions: The results of this research indicate that the TYG index exhibits independent prognostic value in individuals diagnosed with AP. Furthermore, we propose that the TYG index serve as a prognostic tool for SAP when a cut-off value of >5.16 is used. The sensitivity of this cut-off value is determined to be 76.47%, while the specificity is 72.09%. Additionally, the positive predictive value (PPV) is calculated to be 68.9%, and the negative predictive value (NPV) is determined to be 78.2%. There is a direct link between the frequency of SAP and AP-related problems and a high TYG index.

Keywords: TYG index, novel biomarker, AP

Introduction

Acute pancreatitis (AP) is a disorder defined by the abrupt inflammation of the pancreas, which has the ability to cause localized damage to the pancreas, spread to other tissues, or trigger systemic inflammation by activating cascades of cytokines [1]. AP is characterized by the autodigestion of the pancreatic parenchyma, necrosis of the interstitial fat, and necrotizing vasculitis. This condition arises due to the inappropriate intracellular activation of proteolytic pancreatic enzymes. The inflammatory process has the potential to be localized inside the pancreas, it may extend to the tissues surrounding the pancreas, or it may even affect the distant organs, which may lead to the failure of several organs and even death [2].

The number of people diagnosed with AP continues to rise all over the globe, and it is now one of the most prevalent gastrointestinal conditions that result in hospitalization in the United States.

The use of alcohol (30-35%) and gallstones (30-45%) are the two most prominent risk factors that lead to AP [3], Hypertriglyceridemia, hypercalcemia, and endoscopic retrograde cholangiopancreatography (ERCP) are examples of less prevalent causes. Idiopathic AP accounts for up to 20% of all occurrences of the condition [4, 5]. When there is persistent or recurrent abdominal pain, a subsequent rise in serum pancreatic enzymes, the development of fever or leukocytosis, and increasing organ dysfunction, the possibility of local consequences of AP should be considered. Associated pancreatic fluid collections and pancreatic pseudocysts are also examples of local complications [6].

The inflammation may proceed to cause: systemic complication such as organ failure and its consequences are well recognized in AP. Several scoring systems to assess the severity of AP and the prognosis of patients are used such as (Ranson, Acute Physiology and Health Care Evaluation (APACHE) techniques has been shown to possess some limitations in terms

of time consumption, complexity, and inadequate sensitivity in accurately forecasting the progression of severe Acute pancreatitis [7].

The Atlanta Classification, established in 1992, has been widely recognized as the prevailing international standard for evaluating the severity of AP [8]. The Atlanta classification was revised in 2012, with a particular focus on the enduring occurrence of organ failure [6].

Recent researches have shown that there is a significant correlation between insulin resistance and the prognosis and severity of AP. Insulin resistance is a persistent, mild inflammatory condition that is believed to contribute to the development of several inflammatory disorders, such as AP. The TYG index is an emerging surrogate measure of insulin resistance and its associated metabolic problems, which is gradually becoming recognized in academic circles [9]. The TyG index has been discovered in the literature as a possible predictor of diabetes, hypertension, nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease [10].

The purpose of work to assess TYG index as an effective marker to identify severity of AP.

Patients and Methods

This prospective cohort observational research was done on 60 patients recruited from Tanta University Hospitals.

Inclusion criteria

The individual presents with: persistent upper abdominal pain, with elevated levels of serum amylase and/or lipase that exceed the normal threshold by at least thrice. Additionally, abnormal imaging results indicate a potential diagnosis of AP.

All patients provided informed written permission. The research was granted clearance by the Ethics Committee of the Faculty of Medicine at Tanta University, spanning from November 2021 to December 2022, with the approval; number 35062/11/21.

Our Exclusion criteria was patients with idiopathic pancreatitis.

All patients in this research were exposed to:

- History taking.
- Vital signs measurement.
- Through clinical examination with emphasis on jaundice and posture.
- Abdominal examination with special emphasis on haemorrhagic discoloration of flanks or umbilicus tenderness or rigidity.
- The laboratory investigation comprises several tests, namely the complete blood count (CBC), renal function assessment through serum urea and creatinine levels, liver function evaluation using aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin measurements, serum amylase and lipase analysis conducted at the time of diagnosis, C-reactive protein (CRP) testing, and arterial blood gas (ABG) analysis.
- Fasting glucose level and fasting triglyceride.

All patients' TYG indices are determined by taking the

natural logarithm of their fasting triglyceride and fasting glucose levels./2. [11].

Imaging by any of the following modality:

- a) Pelvi abdominal U/S.
- b) CT abdominal and pelvis.
- c) Magnetic resonance cholangiopancreatography (MRCP).
- d) Assessing disease severity.

Determination of severity of AP by Atlanta score:

Revised Atlanta criteria

The Atlanta classification was revised in 2012 in order to categorize people with pancreatitis into mild, moderate, and severe classifications. The latter condition is characterized by the occurrence of organ failure and/or the development of local problems [12].

Revised Atlanta classification

Mild AP

- There is an absence of organ failure.
- There are no local or systemic difficulties.

Moderately sever AP

- Transient organ failure refers to a condition characterized by the temporary occurrence of organ failure, which often resolves over a period of 48 hours.
- Adverse effects occurring at the local or systemic level in the absence of sustained organ dysfunction.

Severe AP: Persistent organ failure (> 48 h)

- Single organ failure.
- Multiple organ failure.

Statistical analysis

IBM Inc. of Chicago, Illinois, USA created the statistical analysis program SPSS v26, which was used. Quantitative variables were represented by mean and standard deviation (SD), and a Student's t-test was performed to compare the two groups. Analyses of the qualitative variables were performed using the Chi-square test or Fisher's exact test, as appropriate, and results were reported in terms of frequency and percentage (%). Diagnostic accuracy was determined by calculating the test's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with the use of ROC curve analysis. A perfect test would have a ROC curve that went from the bottom left to the top left, and then to the top right. Where an AUC higher than 50% denotes acceptable performance and an AUC value around 100% signifies excellent performance for the test, the area under the curve (AUC) is used to evaluate overall test efficacy. Statistical significance was defined as a two-tailed P value of less than 0.05.

Results

43 patients of our study population had non-sever pancreatitis while 17 patients had sever pancreatitis. The highest cause of sever pancreatitis was post-ERCP while in non-severe pancreatitis was gallstones.

Table 1: Demographic data and cause of pancreatitis of the studied groups

		Severe group (n=17)	Non-severe group (n=43)	P value
Age (Years)		52.47 ± 18.61	60.16 ± 19.08	0.162
Sex	Male	9 (52.94%)	23 (53.49%)	0.969

	Female	8 (47.06%)	20 (46.51%)	
Etiology of AP	Gall stone	3 (17.65%)	18 (41.86%)	0.223
	Hypertriglyceridemia	5 (29.41%)	13 (30.23%)	
	Hypercalcemia	1 (5.56%)	2 (4.65%)	
	Post ERCP	8 (47.06%)	10 (23.26%)	
Special Habits	Smoking	9 (52.94%)	20 (46.51%)	0.653
Past medical history	Hypertension	8 (47.06%)	21 (48.84%)	0.901
	DM	7 (41.18%)	18 (41.86%)	0.961

Data presented by Mean ± SD or number (%) ERCP: Endoscopic retrograde cholangiopancreatography, DM: Diabetes mellitus.

Regarding laboratory data, comparison between both groups was statistically significant in platelets count, TLC, serum creatinine, urea, total serum calcium level, lipase, CRP,

fasting glucose and LDL. While non-significant as regard to HB level, AST, ALT levels, total bilirubin, serum amylase, Hba1c level, triglycerides level and HDL

Table 2: Laboratory investigations of the studied groups

	Severe group (n=17)	Non-severe group (n=43)	P value
Hb (g/dL)	14.15 ± 1.68	12.73 ± 2.86	0.062
Platelets (*10 ³ /uL)	192.94 ± 14.58	265.58 ± 43.68	<0.001*
TLC (*10 ³ /uL)	17.38 ± 5.17	12.75 ± 6.91	0.015*
AST (U/L)	174.29 ± 93.72	144.05 ± 72.09	0.185
ALT (U/L)	147.06 ± 88.79	135.33 ± 92.74	0.657
Total bilirubin (mg/dL)	2.45 ± 0.51	2.09 ± 0.78	0.079
Creatinine (mg/dL)	1.73 ± 0.28	1.46 ± 0.2	<0.001*
Urea (mg/dL)	57.25 ± 22.84	28.38 ± 4.24	<0.001*
Total serum calcium (mg/dL)	7.97 ± 0.27	9.19 ± 0.3	<0.001*
Amylase (U/L)	1128.29 ± 325.63	1076.07 ± 329.54	0.581
Lipase (U/L)	116.24 ± 20	67.56 ± 26.17	<0.001*
C-reactive protein (mg/dL)	27.41 ± 8.57	14.58 ± 6.46	<0.001*
Fasting glucose (mg/dL)	203.71 ± 109.01	130.84 ± 53.51	<0.001*
HbA1c (%)	7.26 ± 1.28	6.32 ± 1.88	0.061
Triglyceride (mg/dL)	377.53 ± 138.12	285.58 ± 180.09	0.063
HDL (mg/dL)	30.06 ± 14.93	36.28 ± 10.32	0.070
LDL (mg/dL)	143.65 ± 18.24	77.86 ± 8.57	<0.001*

Data presented by Mean ± SD, CBC: complete blood cell, Hb: hemoglobin, TLC: total Leukocyte Count AST: aspartate aminotransferase, ALT: alanine transaminase, data is presented by Mean ± SD, HDL: High density lipoprotein, LDL: Low density lipoprotein, *: significant P value as <0.05.

Hospital stays, ICU stay, and mortality were significantly higher in the severe group.

TYG index as well as Atlanta score was significantly higher in severe group.

Table 3: Hospital stays, ICU stay and Mortality of the studied groups.

	Severe group (n=17)	Non-severe group (n=43)	P value
Hospital stays (days)	12.82 ± 4.82	4.67 ± 1.27	<0.001*
ICU stay	17 (100%)	9 (20.93%)	<0.001*
Mortality	11 (64.71%)	2 (4.65%)	<0.001*

Data presented by Mean ± SD, ICU: Intensive care unit, *: significant P value as <0.05.

Table 4: TY Gindex and Atlanta score of the studied groups.

	Severe group (n=17)	Non-severe group (n=43)	P value
TYG index	5.47 ± 0.47	5.1 ± 0.32	<0.001*
Atlanta score	2.94 ± 0.24	1.42 ± 0.5	<0.001*

Data is presented by Mean ± SD, TyG index: triglyceride glucose index, *: significant P value as <0.05.

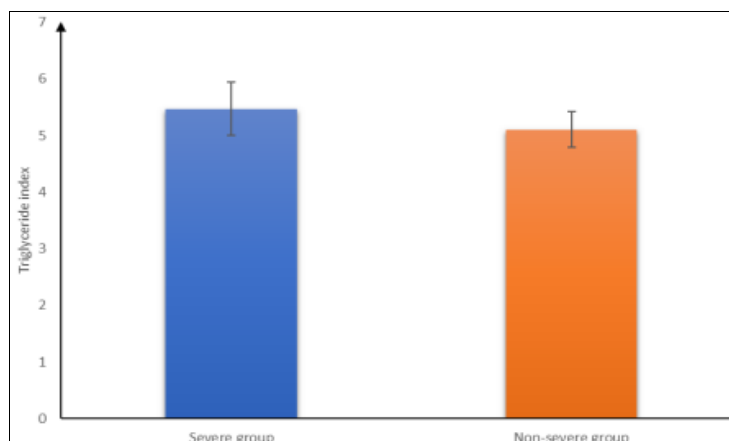


Fig 1: TyG index of the studied groups

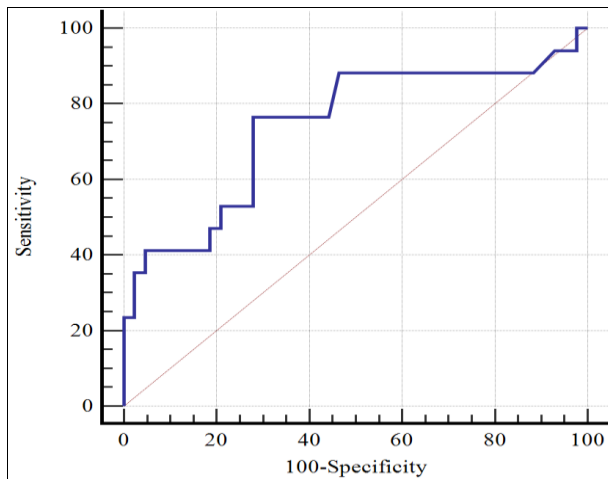


Fig 2: Role of TyG index in prediction of severity of AP of the studied groups

Discussion

AP is predominantly a self-limiting condition that resolves with minimal complications with proper management. Nevertheless, around 15% of AP cases develop into more severe conditions. Notwithstanding advancements in the comprehension of the disease, severe acute pancreatitis (SAP) continues to entail a mortality rate ranging from 2% to 9% [13].

Skeletal muscle triglyceride levels are inversely related to both skeletal muscle insulin sensitivity and whole-body insulin action, which led to the development of the TYG index [10].

Our prospective cohort research intended to determine whether the TYG index is a reliable indicator of AP severity.

In this work, age, sex and etiology of AP were statistically non-significant different between both groups.

This agrees with Pokharel *et al.* [14] who reported that the severity of AP was not related to the age or sex of the patient. Similarly, there was no association between etiology and severity of AP.

However, Kong *et al.* [15] investigated an analysis of the prognostic factors and clinical characteristics of a consecutive series of patients diagnosed with SAP. They reported that SAP patients are characterized by advanced age.

This study showed that, Creatinine and Urea were significantly higher in severe group.

This agrees with Thong *et al.* [16] this research aimed to investigate the biochemical and clinical features of individuals with hyper-triglyceridemic pancreatitis (HTGP) and to determine the variables linked to the severity of HTGP. They found that, with $P = .006$, $P = .004$, and $P < 0.001$, respectively, the severe AP group had greater creatinine than the non-severe AP group.

The precise pathophysiological pathway behind renal failure in pancreatitis remains incompletely elucidated. However, empirical evidence has shown the involvement of systemic inflammation, cytokine generation, free radical production, and other variables that impact microcirculatory function [17].

We found that CRP was significantly higher in the severe group than in the non-severe group ($p < 0.001$).

This agrees with Stirling *et al.* [18] in order to compare exact CRP readings with changes in CRP over time in order to

classify the seriousness of AP. The mean CRP was much higher in the group with serious AP.

In contrary, the findings of a prior investigation did not support the use of laboratory markers upon admission as having prognostic significance. Instead, it was seen that the CRP/albumin ratio at the 48-hour mark of hospitalization exhibited a substantial association with problems arising from AP [19].

The findings of this research indicate a statistically significant elevation in lipase levels among those in the severe category.

Similar to our results, Chang *et al.* [20] assessed the efficacy of the L/A ratio and computed tomography (CT) severity index in the evaluation of the prognosis of different etiologies of AP. They reported that there is no significant difference in amylase between mild, moderate and severe pancreatitis. However, they differed from our results regarding the lipase level as it was comparable between normal to mild, moderate and severe pancreatitis.

On the other hand, Devanath *et al.* [21] It has been observed that the use of the serum lipase to amylase ratio, using a cut off of 3.0 or above, lacks utility in distinguishing between severe AP and less severe cases of AP.

We found fasting glucose was significantly higher in severe group.

This agrees with Sun *et al.* [22] who found that the incidence of fasting hyperglycaemia was significantly higher in patients with severe AP.

In contrast, Lankisch *et al.* [23] found that there was no significant difference in fasting glucose levels between patients with severe AP and those with non-severe AP.

In this study, triglyceride and HDL were insignificantly different between both groups. LDL was significantly higher in the severe group.

On the other hand, Wu *et al.* [24]. It has been found that a modest increase in triglyceride levels has little influence on the severity of AP. However, it should be noted that severe hypertriglyceridemia may enhance the extent of acute kidney injury in individuals with AP. This suggests that the degree of hypertriglyceridemia might potentially contribute to the occurrence of complications, such as acute kidney injury in AP.

In study done by Hidalgo *et al.* [25]. The objective of the study was to investigate the relationship between high blood triglyceride (TG) levels at admission and the development of pancreatic necrosis. The researchers discovered that the trend analysis revealed a statistically significant correlation between elevated levels of pancreatic necrosis and high triglyceride (TG) levels.

The current research revealed that the TYG index was significantly higher in the severe group.

Our results are supported by Park *et al.* [26]. The individual(s) responsible for the discovery observed that the TyG index exhibited a greater value in the SAP group compared to the non-SAP group, despite there being no significant differences in TG and glucose levels between the two groups. This also agrees with Wei and Guo [27]. The objective of this study was to investigate the correlation between the TyG index and the prognosis of AP. The researchers observed that the TyG index was considerably elevated in the SAP group compared to the non-SAP group (10.44 ± 1.55 vs 9.33 ± 1.44 , $p < 0.001$).

The strong correlation between the TyG index and SAP may be explained by a physiologically reasonable mechanism.

There is a robust association between SAP and ectopic fat (such as NAFLD or fatty pancreas). Wu *et al.* [28]. Ectopic fat, which is linked to insulin resistance, activates pro-inflammatory molecules such nuclear factor κ B, tumor necrosis factor α , leptin, and interleukin 6; these molecules may play a critical role in the pathogenesis of AP in insulin-resistant patients [29].

In a pediatric study on NAFLD, Ye *et al.* [30] reported that, a notable association was observed between the TyG index and various factors including body mass index, triglyceride levels, low-density lipoprotein cholesterol, uric acid, and the homeostasis model assessment of insulin resistance (HOMA-IR). This suggests that the TyG index holds potential as a tool for investigating blood lipid metabolism and insulin resistance levels in children diagnosed with non-alcoholic fatty liver disease (NAFLD).

In this study, hospital stays, ICU stay, and mortality were significantly higher in the severe group.

Mortality and morbidity increased with disease severity across the studies. In three of these studies, the risk of death for patients with non-SAP was 0% compared with 21%-40% for patients with SAP (126-128). Although the morbidity of non-SAP was not found to be as high as in patients with SAP, evidence showed that the condition was often still associated with poor outcomes. For instance, 48% (Koutroumpakis *et al.* [31] had systemic inflammatory response syndrome (SIRS), 26.1% had organ failure (OF) and up to 23% were admitted to the ICU [32].

In this work, Atlanta score was significantly higher in severe group than non-severe group Venkatesh *et al.* [33] in their study looked at 164 patients with AP and found that the Atlanta score was the best predictor of severity, with a sensitivity of 85% and a specificity of 82%. The mean Atlanta score in the severe AP group was 12.5, while the mean Atlanta score in the non-severe AP group was 4.5.

In this study, TyG index can significantly predict severity of AP ($P=0.002$ and $AUC = 0.741$) at cut-off >5.16 with 76.47% sensitivity, 72.09% specificity, 68.9% PPV and 78.2% NPV. This agrees with Park *et al.* [26]. They found that the TyG index was a decent predictor of AP severity. Incorporating the TyG index into conventional models for SAP greatly improved their predictive value. Using many statistical approaches, including a comparison of AUCs and model fitness statistics, they looked at TyG's prediction capacity for SAP in depth. This discovery suggests that established prognostic markers of AP, which need many clinical assessments, may be reliably compensated by a simple, single test of serum chemistry at clinical baseline. They found that the TyG index was significantly predictive of survival in AP patients. After including the TyG index into a model consisting of conventional SAP risk variables, the AUC of the ROC for SAP prediction rose from 0.738 to 0.830 ($p = 0.033$). Moreover, Wei and Guo [27]. The researchers determined that the TyG index served as an independent risk factor for SAP, with an odds ratio of 1.835 (95% confidence interval: 1.380-2.442, $p < 0.001$), using ROC curve cutoff values of 8.76 for non-HTG/AAP and 11.81 for HTG/AAP.

Conclusions

The findings of this study indicate that the TYG index exhibits independent prognostic value in individuals diagnosed with AP. Furthermore, we propose that the TYG index serve as a prognostic marker for SAP when a cut-off

value of >5.16 is used. The sensitivity of this cut-off value is determined to be 76.47%, while the specificity is 72.09%. Additionally, the positive predictive value (PPV) is calculated to be 68.9%, and the negative predictive value (NPV) is determined to be 78.2%. There exists a strong correlation between a high TYG index and the occurrence of issues associated with SAP and AP.

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Conflict of Interest: Nil

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