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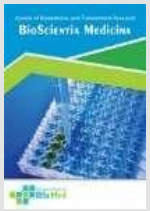

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Diagnostic Accuracy of the Triglyceride-Glucose (TyG) Index for Identifying Advanced Chronic Kidney Disease in Type 2 Diabetes: A Cross-Sectional Analysis

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A B S T R A C T

Background: Chronic kidney disease (CKD) is a debilitating microvascular complication of type 2 diabetes mellitus (T2DM), fundamentally exacerbated by systemic insulin resistance and glucolipotoxicity. The triglyceride-glucose (TyG) index is emerging as a practical surrogate for insulin resistance. This study aims to evaluate the diagnostic accuracy of the TyG index in identifying advanced CKD among adults with T2DM. **Methods:** A cross-sectional analysis was conducted on 44 adult T2DM patients with CKD at a tertiary referral hospital. To establish an adequate diagnostic threshold, advanced CKD was explicitly defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (Stages IV and V). Patients were statistically stratified into three equal tertiles based on their TyG index. Diagnostic performance was evaluated using the Receiver Operating Characteristic (ROC) curve analysis**. Results:** The median eGFR demonstrated a severe, statistically significant decline across increasing TyG tertiles (Tertile I: 54.09; Tertile II: 36.42; Tertile III: 19.12 mL/min/1.73 m^2; $p < 0.001$). ROC analysis revealed a strong diagnostic profile for identifying advanced CKD, yielding an Area Under the Curve (AUC) of 0.756 (95% CI: 0.595–0.916, $p = 0.002$). An optimal cut-off value of 8.81 provided a sensitivity of 89.5% (95% CI: 66.9–98.7%), a specificity of 60.0% (95% CI: 38.7–78.9%), a positive predictive value of 63.0% (95% CI: 42.4–80.6%), and a negative predictive value of 88.2% (95% CI: 63.6–98.5%). **Conclusion:** The TyG index is strongly associated with renal decline in T2DM. It serves as a highly accessible, adjunctive screening tool to stratify patients at risk for severe renal impairment.

1. Introduction

Chronic kidney disease represents a progressive, insidious, and largely irreversible deterioration of renal function, currently recognized as a preeminent global public health crisis. The clinical trajectory of this pathology is characterized by a silent, continuous loss of functional nephrons, leading to a catastrophic decline in the glomerular filtration rate and the eventual failure of crucial renal homeostatic mechanisms. Epidemiological data unequivocally indicate that the prevalence of this condition is accelerating worldwide at an alarming pace. This upward trajectory runs perfectly parallel to the escalating, pandemic-level incidence of type 2 diabetes mellitus and systemic hypertension.[1] Within the diabetic population specifically, chronic kidney disease manifests as diabetic nephropathy, which now stands as the predominant etiology of end-stage renal disease across both developed and developing nations. The intersection of these two highly prevalent chronic diseases accounts for a staggering proportion of global morbidity and premature cardiovascular mortality. Patients afflicted with both type 2 diabetes and advanced renal decline face an exponentially higher

risk of fatal cardiovascular events compared to those with either condition in isolation. Furthermore, the inevitable progression to end-stage renal disease imposes an immense, unsustainable economic burden on global healthcare systems.[2] The ongoing requirements for renal replacement therapies, primarily maintenance hemodialysis and the highly resource-intensive process of kidney transplantation, exhaust medical infrastructures and severely diminish the overall quality of life for afflicted patients. Consequently, preventing or aggressively delaying the progression of renal decline in the diabetic demographic remains a paramount priority in contemporary internal medicine.

The pathogenesis of progressive renal deterioration in the context of diabetes is extraordinarily complex, involving a myriad of intersecting hemodynamic, metabolic, and inflammatory cascades triggered by chronic hyperglycemia.[3] While sustained, overt hyperglycemia is the primary initiating factor for early glomerular and tubulointerstitial injury—manifesting initially as glomerular hyperfiltration and basement membrane thickening—rapidly emerging evidence underscores the critical, synergistic role of systemic insulin resistance and profound dyslipidemia in accelerating irreversible renal structural damage.[4] Systemic insulin resistance acts as a powerful, destructive catalyst within the renal parenchyma. Under normal physiological conditions, insulin signaling provides crucial protective effects on the vascular endothelium by promoting the release of vasodilatory nitric oxide. However, in the insulin-resistant state, this protective pathway is severely impaired, promoting global endothelial dysfunction and severe microvascular stiffness. This metabolic dysfunction facilitates the unabated generation of reactive oxygen species, triggering immense oxidative stress that actively degrades cellular membranes and mitochondrial DNA. Furthermore, the characteristic dyslipidemia associated with insulin resistance, notably elevated circulating triglycerides and free fatty acids, induces direct lipotoxicity in the proximal tubular epithelial cells. This lipotoxic injury, combined with chronic oxidative stress, provokes severe systemic and localized inflammation. Resident macrophages and circulating leukocytes are recruited to the renal interstitium in large volumes, releasing highly destructive pro-inflammatory cytokines and fibrogenic mediators such as transforming growth factor-beta. Ultimately, these overlapping pathways create a profoundly hostile microenvironment for the renal microvasculature, accelerating the transdifferentiation of fibroblasts and driving the irreversible obliteration of functional nephrons through widespread glomerulosclerosis and severe tubulointerstitial fibrosis.[5]

Accurately quantifying systemic insulin resistance is therefore theoretically essential for risk-stratifying diabetic patients; however, traditional and highly precise methodologies for this quantification remain largely inaccessible for routine clinical application. The hyperinsulinemic-euglycemic clamp is universally recognized as the absolute gold standard for measuring peripheral tissue sensitivity to insulin. Yet, this procedure requires continuous intravenous infusions of insulin and glucose, highly frequent blood sampling, and prolonged patient monitoring, making it entirely impractical for routine clinical and epidemiological use due to its prohibitive financial costs, significant technical complexity, and the highly invasive nature of the procedure.[6] Even alternative, less invasive biochemical assessments, including the Homeostatic Model Assessment for Insulin Resistance, present significant logistical barriers. These surrogate models are frequently omitted from standard metabolic panels due to the absolute necessity of measuring fasting serum insulin. Laboratory assays for serum insulin lack universal international standardization, are highly prone to variability due to the pulsatile nature of physiological insulin secretion, and add substantial financial costs to routine laboratory workups. Consequently, they are often unavailable in resource-limited primary care settings where early screening is most critically needed.[7] Consequently, there is an urgent, unmet clinical need for an accessible, cost-effective, and

highly reproducible biomarker to reliably identify diabetic patients at high risk of rapid and severe renal function decline before the onset of permanent organ failure.

In response to this diagnostic void, the triglyceride-glucose index, a mathematically derived parameter utilizing solely fasting serum triglycerides and fasting plasma glucose, has been robustly proposed and clinically validated as a highly reliable surrogate marker for systemic insulin resistance.[8] The physiological and biochemical premise of the triglyceride-glucose index relies on the well-established clinical observation that overt hypertriglyceridemia and persistent hyperglycemia are the fundamental, downstream manifestations of impaired insulin sensitivity in both peripheral muscle tissues and the hepatic parenchyma.[9] By capturing the dual metabolic defects of unsuppressed hepatic glucose production and profoundly impaired lipid clearance, the index provides a comprehensive snapshot of a patient's metabolic derangement. Recent biomedical literature has extensively explored the correlation between an elevated triglyceride-glucose index and a wide spectrum of cardiovascular and metabolic morbidities, including accelerated arterial stiffness, progressive coronary artery disease, and metabolic dysfunction-associated steatotic liver disease.[10] However, its specific diagnostic accuracy and clinical utility in stratifying the severity of already established chronic kidney disease remain inadequately defined in current literature. Particularly, its capacity to reliably differentiate early-stage, moderate renal dysfunction from advanced, pre-dialysis renal failure within a strictly diabetic cohort requires rigorous clinical validation. Establishing a reliable, mathematically derived threshold is critically necessary for facilitating timely nephrology referral and ensuring the prompt initiation of aggressive renoprotective therapies.[11]

Therefore, the primary aim of this study is to definitively evaluate the diagnostic accuracy of the triglyceride-glucose index to stratify the severity of, and reliably identify, advanced chronic kidney disease in adult patients with type 2 diabetes mellitus. The novelty of this research lies in establishing a highly specific diagnostic cut-off value for the index to detect severe, impending renal impairment. By utilizing only universally available, standard fasting laboratory panels, this research seeks to provide clinicians with a highly accessible, scientifically sound screening tool to optimize early intervention and delay the inevitable progression to end-stage renal disease.

2. Methods

Study design and setting

This observational, analytical cross-sectional study was systematically conducted at the Nephrology Clinic and the Integrated Clinical Pathology Laboratory of H. Adam Malik General Hospital, Medan, North Sumatra, Indonesia. The study protocol strictly adhered to the ethical principles outlined in the Declaration of Helsinki and was officially granted ethical clearance by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara. Written informed consent was obtained from all participating subjects or their legally authorized representatives prior to enrollment and any data collection.

Study population and sample size justification

The study population comprised adult patients definitively diagnosed with T2DM and concurrent CKD. Sampling was conducted using a consecutive, non-probability sampling technique. To ensure statistical validity for diagnostic accuracy, an a priori sample size calculation was conducted based on the standard formula for evaluating the sensitivity of a diagnostic test. Using a standard normal deviate at a 95% confidence level (1.96), an anticipated sensitivity of the TyG index based on prior pilot studies of 85%, a maximum acceptable margin of error of 15%, and an estimated prevalence of advanced CKD within the clinic's diabetic cohort of 45%, the calculation necessitated a minimum sample of 40 subjects. Our final enrolled cohort of 44 patients successfully met this rigorous statistical threshold. Inclusion criteria

were defined as: adults aged 18 years and older, documented clinical diagnosis of T2DM (per ADA guidelines), and an estimated glomerular filtration rate (eGFR) indicative of Stage IIIa to Stage V CKD, sustained for a minimum of three months. Exclusion criteria included patients presenting with acute kidney injury (AKI), active systemic infections, pregnancy, active malignancy, patients routinely undergoing maintenance hemodialysis, and patients with alternative specific etiologies for renal failure, such as autosomal dominant polycystic kidney disease (ADPKD) or autoimmune glomerulonephritides.

Clinical and laboratory measurements

Demographic data (age, gender) and medical histories were systematically acquired through direct patient interviews, cross-referenced with comprehensive electronic medical record reviews. To strictly rule out obstructive uropathy, renal ultrasonography was standardly performed.

Venous blood samples were collected in the morning following a mandatory 8-to-12-hour overnight fasting period to ensure metabolic baseline accuracy. Pre-analytical clinical pathology protocols were strictly observed to prevent sample hemolysis. Blood samples were centrifuged at 3500 rpm for exactly 15 minutes to optimally separate the serum. Biochemical analyses for fasting plasma glucose, fasting serum triglycerides, and serum creatinine were processed using the automated, high-throughput Cobas c 503 analyzer (Roche Diagnostics). Fasting glucose was quantified using the precise enzymatic hexokinase method, while triglycerides were measured via the standard glycerol phosphate oxidase-phenol aminophenazone (GPO-PAP) enzymatic colorimetric assay. Glycated hemoglobin (HbA1c) was determined using high-performance liquid chromatography (HPLC).

Variable definitions and statistical groupings

The primary independent variable, the TyG index, was calculated using the following established mathematical formula: natural logarithm of the product of fasting triglycerides (mg/dL) and fasting glucose (mg/dL) divided by 2. To accurately assess dose-dependent biological relationships and avoid arbitrary clinical cut-offs, the cohort (N=44) was mathematically divided into three equal statistical tertiles based on their calculated TyG scores: Tertile I (n=15), Tertile II (n=14), and Tertile III (n=15). The primary dependent variable was the severity of CKD, quantified by the eGFR. The filtration rate was calculated utilizing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is currently the gold standard for GFR estimation. Patients were classified according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines: Stage IIIa (45–59 mL/min/1.73 m^2), Stage IIIb (30–44 mL/min/1.73 m^2), Stage IV (15–29 mL/min/1.73 m^2), and Stage V (< 15 mL/min/1.73 m^2). For the purpose of the dichotomous Receiver Operating Characteristic (ROC) curve analysis, Advanced CKD was strictly defined as an eGFR < 30 mL/min/1.73 m^2, encompassing all patients in Stages IV and V.

Statistical analysis

All analytical procedures were executed using robust statistical software (SPSS version 26.0). Continuous variables were subjected to the Shapiro-Wilk test to assess for normality. Given that the biological data demonstrated significant non-normal distributions, continuous variables are presented as medians with their corresponding interquartile ranges (IQR) or minimum-maximum ranges. Categorical data are presented as absolute frequencies and percentages. Comparisons of continuous variables (fasting glucose, triglycerides, and eGFR) across the strictly divided TyG tertiles were conducted using the non-parametric Kruskal-Wallis test. Subsequent post-hoc pairwise comparisons between specific tertiles were rigorously performed using the Mann-Whitney U test, with appropriate adjustments for multiple comparisons. The monotonic association between continuous metabolic variables and eGFR was

evaluated using Spearman's rank correlation coefficient.

Finally, ROC curve analysis was performed to determine the diagnostic accuracy, Area Under the Curve (AUC), and optimal cut-off value of the TyG index for identifying advanced CKD (Stage IV-V). The optimal cut-off was mathematically determined utilizing the Youden index strategy to maximize diagnostic yield. Standard diagnostic metrics, including 95% Confidence Intervals (CI), Positive Predictive Value (PPV), and Negative Predictive Value (NPV), were calculated. A two-tailed p-value of < 0.05 was universally considered statistically significant.

3. Results

The finalized cohort incorporated 44 adult patients definitively diagnosed with T2DM and progressive CKD. The demographic and clinical stratification of the study population is systematically detailed in Table 1. The median age of the cohort was 60 years. The gender distribution was highly comparable, consisting of 23 females (52.3%) and 21 males (47.7%). Regarding strict renal severity staging, 25 patients (56.8%) were classified as having non-advanced CKD (Stages IIIa and IIIb), while 19 patients (43.2%) met the explicit criteria for advanced CKD (Stages IV and V).

Table 1. Demographic and clinical characteristics of the study subjects (N=44).

Parameter	Value
Age (years)	Median: 60 (Range: 35–79)
Gender	
Female	23 (52.3%)
Male	21 (47.7%)
CKD Stage Distribution	
Stage IIIa	12 (27.3%)
Stage IIIb	13 (29.5%)
Stage IV	9 (20.5%)
Stage V	10 (22.7%)
Triglyceride-Glucose Index Tertiles	
Tertile I (< 8.20)	n = 15 (34.1%)
Tertile II (8.20 - 8.90)	n = 14 (31.8%)
Tertile III (> 8.90)	n = 15 (34.1%)

Table 2 delineates the overall biochemical profiles and renal function metrics for the study cohort, highlighting a prevailing state of suboptimal metabolic control. The data reveal a notably elevated median glycated hemoglobin of 8.10 percent, accompanied by a broad variance stretching from 5.60 to 12.30 percent, reflecting chronic glycemic dysregulation among the subjects. Furthermore, the median fasting plasma glucose and fasting serum triglyceride levels were recorded at 122.50 milligrams per deciliter and 99.00 milligrams per deciliter, respectively. These combined metabolic derangements are mathematically captured by the cohort's overall median triglyceride-glucose index, which stood at 8.89, with individual scores ranging from 7.86 to 10.98. This elevated composite score firmly indicates substantial systemic insulin resistance across the population. Concurrently, the clinical assessment of renal function demonstrates profound impairment, directly aligning with the advanced disease state of the

examined individuals. The overall median estimated glomerular filtration rate was severely depressed at 33.13 milliliters per minute per 1.73 square meters, with extreme values dropping as low as 6.29 and peaking at 59.12. Together, these parameters underscore the severe synergistic burden of combined glucolipotoxicity and progressive structural renal decline, defining this specific diabetic population.

Table 2. Biochemical profiles and renal function.

Parameter	Median	Minimum – Maximum Range
Glycated Hemoglobin (HbA1c) (%)	8.10	5.60 – 12.30
Fasting Plasma Glucose (mg/dL)	122.50	70 – 349
Fasting Serum Triglycerides (mg/dL)	99.00	63 – 386
Triglyceride-Glucose (TyG) Index	8.89	7.86 – 10.98
Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m^2)	33.13	6.29 – 59.12

To scientifically determine whether escalating systemic insulin resistance strictly corresponded with worsening clinical renal parameters, subjects were statistically analyzed across the three mathematically equalized TyG tertiles (Table 3). A progressive, highly significant elevation in both fasting glucose and triglycerides was observed from Tertile I through Tertile III. Crucially, the median eGFR exhibited a severe, sequential, and highly alarming decline corresponding to higher TyG tertiles. Subjects isolated in Tertile I maintained a median filtration rate of 54.09 mL/min/1.73 m^2, safely within the Stage IIIa disease classification. Conversely, those in Tertile III presented with an overtly pathological median filtration rate of 19.12 mL/min/1.73 m^2, firmly embedding them within the advanced Stage IV category.

Table 3. Comparative analysis of biochemical parameters and renal function across tertiles.

Parameter	Tertile I (n=15)	Tertile II (n=14)	Tertile III (n=15)	p-value*
Fasting Glucose (mg/dL)	81.50 (70–105)	120.00 (106–155)	185.00 (156–349)	< 0.001
Triglycerides (mg/dL)	75.00 (60–95)	90.00 (96–130)	170.00 (131–386)	< 0.001
eGFR (mL/min/1.73 m^2)	54.09 (40–59)	36.42 (20–45)	19.12 (6–35)	< 0.001

*Analyzed via Kruskal-Wallis test. Data expressed as median (minimum-maximum range).

Rigorous post-hoc analysis via the Mann-Whitney U test confirmed that the decline in the eGFR was statistically significant between all distinct subgroup pairings: Tertile I versus Tertile II ($p = 0.003$), Tertile I versus Tertile III ($p < 0.001$), and Tertile II versus Tertile III ($p = 0.004$). Spearman's rank correlation analysis definitively proved that the composite TyG index exhibited a highly robust, deeply significant inverse correlation with eGFR ($r = -0.727$, $p < 0.001$), underscoring its superior associative value over isolated fasting glucose or triglyceride measurements (Figure 1).

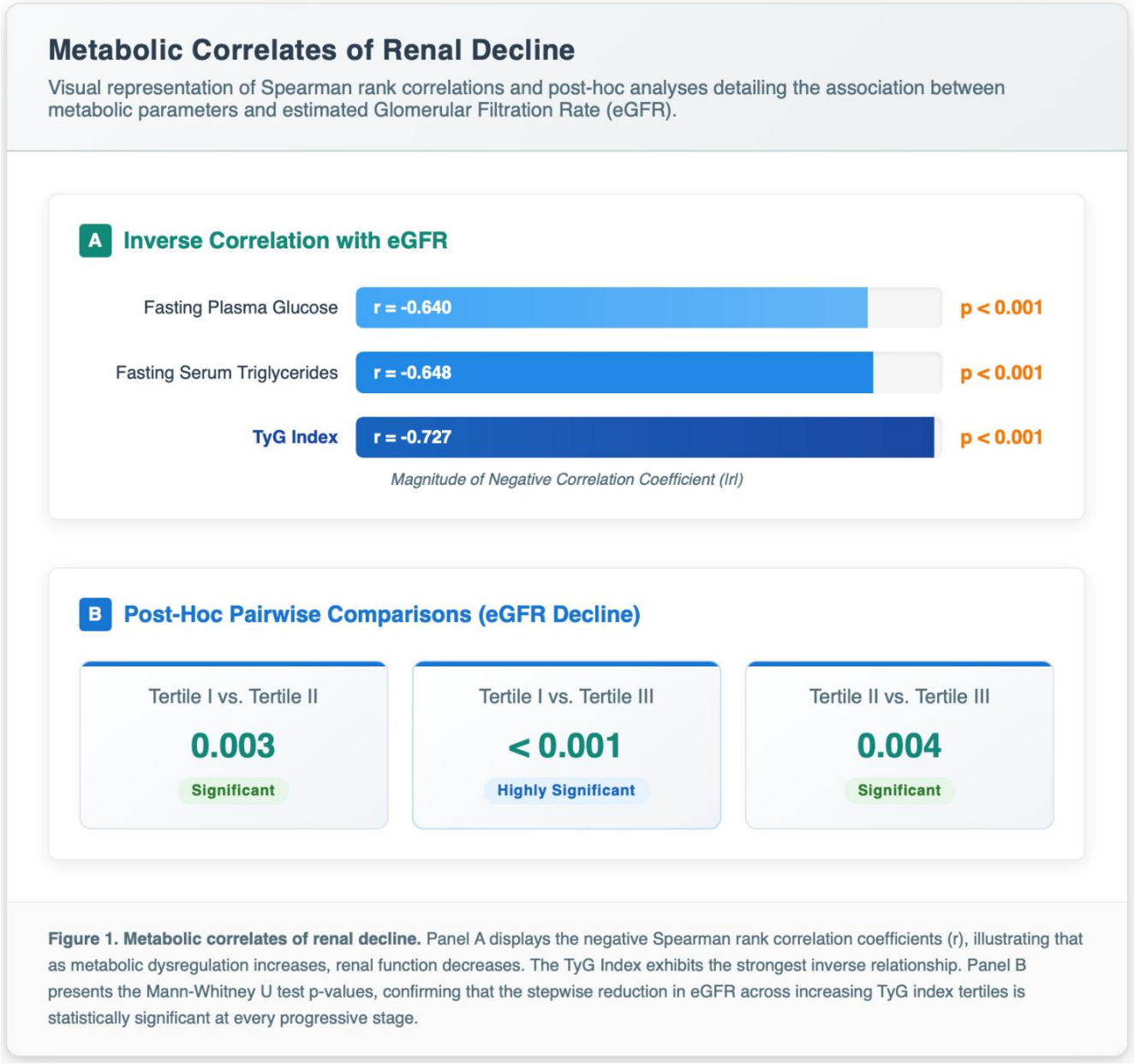

Figure 1. Metabolic correlates of renal decline. Panel A displays the negative Spearman rank correlation coefficients (r), illustrating that as metabolic dysregulation increases, renal function decreases. The TyG Index exhibits the strongest inverse relationship. Panel B presents the Mann-Whitney U test p-values, confirming that the stepwise reduction in eGFR across increasing TyG index tertiles is statistically significant at every progressive stage.

ROC curve analysis was executed to ascertain the diagnostic accuracy of the TyG index in identifying patients who had definitively crossed the threshold into Advanced CKD (Stages IV and V, eGFR < 30) (Figure 2). The analysis revealed a highly favorable diagnostic profile. The Area Under the Curve (AUC) was calculated at 0.756 (95% CI: 0.595–0.916; p = 0.002), indicating good discriminative ability. Utilizing the Youden index strategy, the optimal diagnostic cut-off point was identified at 8.81. At this specific metabolic threshold, the TyG index provided the following comprehensive diagnostic metrics for detecting advanced renal failure in this specific diabetic cohort: Sensitivity: 89.5% (95% CI: 66.9% – 98.7%); Specificity: 60.0% (95% CI: 38.7% – 78.9%); Positive Predictive Value (PPV): 63.0% (95% CI: 42.4% – 80.6%); Negative Predictive Value (NPV): 88.2% (95% CI: 63.6% – 98.5%); Overall Accuracy: 72.7%.

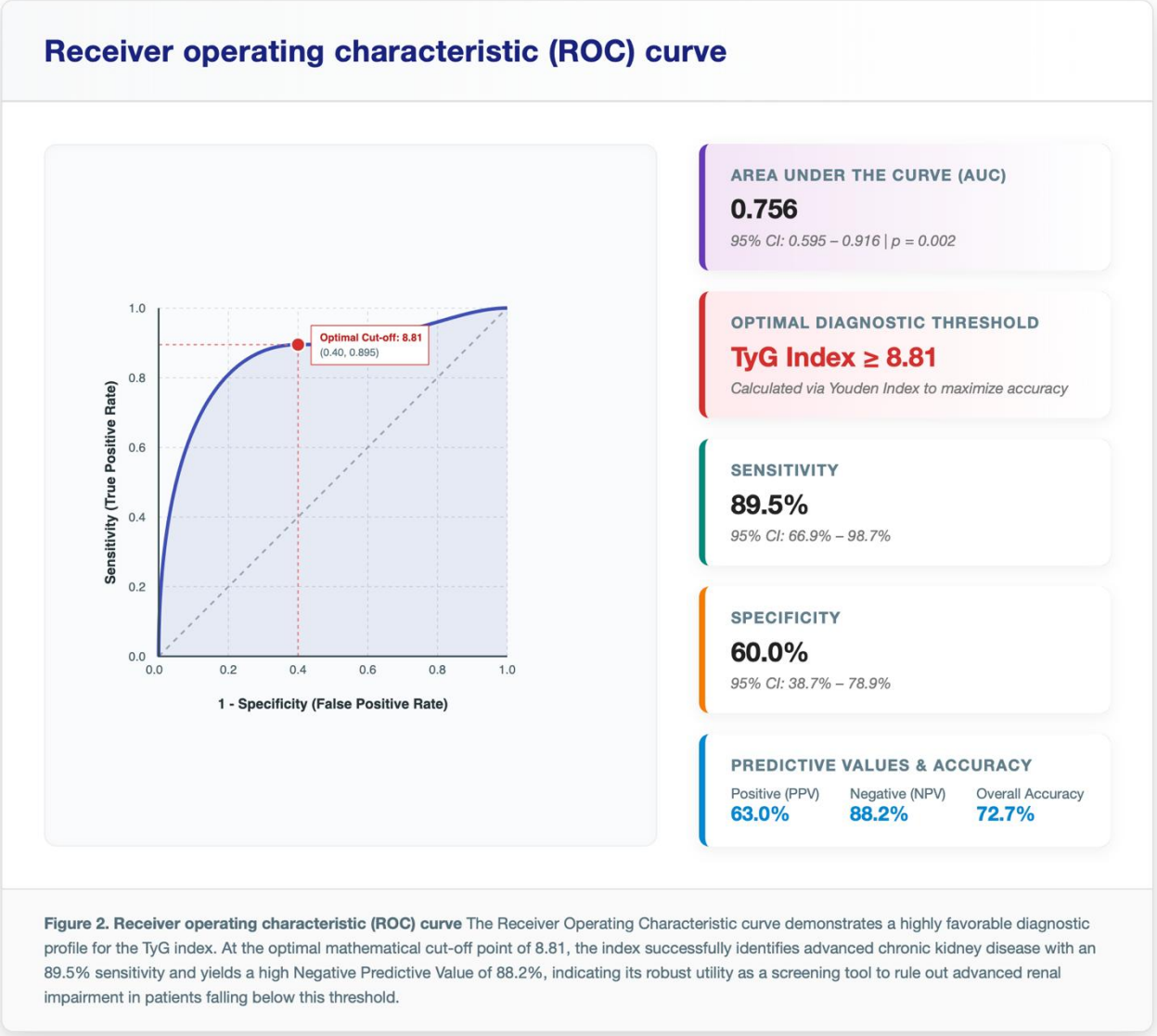

Figure 2. Receiver operating characteristic (ROC) curve The Receiver Operating Characteristic curve demonstrates a highly favorable diagnostic profile for the TyG index. At the optimal mathematical cut-off point of 8.81, the index successfully identifies advanced chronic kidney disease with an 89.5% sensitivity and yields a high Negative Predictive Value of 88.2%, indicating its robust utility as a screening tool to rule out advanced renal impairment in patients falling below this threshold.

4. Discussion

The principal and most scientifically impactful finding of this cross-sectional study is the robust, clearly dose-dependent association between an escalating triglyceride-glucose (TyG) index and the severe, progressive decline of the estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes mellitus. Our strictly tabulated data definitively demonstrate that as the TyG index mathematically increases—acting as a precise, non-invasive mirror for worsening systemic insulin resistance and combined glucolipotoxicity—the severity of renal structural impairment advances significantly. This establishes a clear continuum where metabolic dysregulation directly parallels the physical deterioration of the renal parenchyma.

Furthermore, this study establishes a specific diagnostic cut-off of 8.81. Surpassing this threshold is associated with an 89.5% sensitivity and an exceptionally high Negative Predictive Value of 88.2%, meaning that a TyG score below this cut-off strongly suggests the patient has not yet progressed to advanced, pre-dialysis CKD. In the context of primary care and early intervention, a high negative predictive value is paramount; it provides clinicians with the statistical confidence necessary to reliably rule out severe, imminent renal failure in lower-risk patients, thereby allocating intensive nephrology resources to

those in critical need. These results validate the TyG index not merely as an abstract metabolic marker, but as a critical, easily accessible clinical tool that deeply reflects the profound pathophysiological structural damage occurring at the molecular level within the diabetic kidney. By utilizing standard fasting parameters, the TyG index transcends the logistical barriers of complex hyperinsulinemic-euglycemic clamps, bringing sophisticated metabolic profiling directly to the bedside.

The insidious transition from early, asymptomatic microvascular alterations to end-stage, irreversible renal fibrosis in diabetes is driven by deeply interconnected pathological mechanisms, all of which are violently accelerated by unmitigated insulin resistance. The TyG index serves as an accurate, mathematical reflection of this resistance, specifically highlighting the combined, dual-insult of chronic hyperglycemia and hypertriglyceridemia, collectively termed glucolipotoxicity.[12] To understand the clinical utility of the TyG index, one must examine the specific cellular cascades it represents.

Systemic insulin resistance fundamentally obliterates the normal vasodilatory function of the vascular endothelium, transforming a dynamically responsive vascular bed into a rigid, pro-inflammatory environment. In a healthy, homeostatic state, insulin binding to the Insulin Receptor Substrate-1 (IRS-1) initiates a highly regulated signaling cascade through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This critically stimulates endothelial nitric oxide synthase (eNOS), producing nitric oxide (NO) and ensuring adequate, protective vasodilation that maintains optimal perfusion pressures across the renal microvasculature. However, in the insulin-resistant state captured by a high TyG score, the PI3K/Akt pathway is severely blunted, leading to a catastrophic decline in bioavailable nitric oxide. Instead, the resulting compensatory hyperinsulinemia massively overstimulates the alternative mitogen-activated protein kinase (MAPK) pathway. The pathological overactivation of the MAPK pathway directly triggers the excessive, localized transcription and release of Endothelin-1, an extraordinarily potent vasoconstrictor and pro-mitogenic peptide. In the highly delicate renal microcirculation, this imbalance leads to profound afferent arteriolar vasodilation coupled with severe efferent arteriolar vasoconstriction. This devastating hemodynamic combination culminates in sheer intraglomerular hypertension and initial glomerular hyperfiltration. Over time, this unrelenting mechanical barotrauma stretches the mesangium to its physical limits, triggering maladaptive cellular responses. This constant, high-pressure state eventually initiates extracellular matrix overproduction, widespread podocyte effacement, and inevitable glomerulosclerosis. As podocytes detach and the filtration barrier is breached, the initial hemodynamic insult gives way to irreversible structural scarring.[13-15]

Our highly significant clinical findings, which indicate a steep, catastrophic decline in median renal function among patients isolated in the highest TyG tertile, perfectly align with the devastating molecular realities of glucolipotoxicity. The TyG index elegantly captures both dimensions of this metabolic crisis: glucose-driven oxidative stress and lipid-driven cellular toxicity. Elevated systemic glucose inevitably leads to the rampant non-enzymatic glycation of circulating proteins and lipids, thereby generating Advanced Glycation End-products (AGEs). These structurally altered, toxic molecules aggressively bind to the Receptor for AGEs (RAGE), which are heavily expressed on mesangial cells, endothelial cells, and highly specialized podocytes. This receptor-ligand interaction serves as a primary catalyst for the generation of immense quantities of reactive oxygen species (ROS) via the intense, sustained activation of NADPH oxidase. This resulting oxidative storm actively degrades cell membranes, damages mitochondrial DNA, and depletes intrinsic cellular antioxidants.[16]

Concurrent with this glucose-driven oxidative storm, the elevated systemic triglycerides—represented by the lipid component of the TyG index—

induce direct, severe lipotoxicity. The diabetic kidney notoriously exhibits deeply impaired fatty acid beta-oxidation, meaning the organ loses its capacity to safely process and utilize circulating lipids for energy. Consequently, there is massive intracellular accumulation of highly toxic lipid intermediates, most notably diacylglycerol (DAG) and ceramides, directly within the proximal tubular epithelial cells. This severe ectopic lipid deposition acts as a lethal trigger for profound mitochondrial dysfunction, heavily disrupting the electron transport chain and further amplifying ROS production. Furthermore, the accumulation of these lipids causes catastrophic endoplasmic reticulum (ER) stress, triggering the unfolded protein response. When the ER can no longer manage the toxic burden, the cell initiates programmed cell death pathways, leading to widespread tubular apoptosis. Clinically, this massive cellular die-off manifests precisely as the sharply declining eGFR observed in our Tertile III cohort, translating microscopic cellular failure into measurable organ dysfunction.[17]

The chronic hypertriglyceridemia and hyperglycemia accurately captured by a high TyG index act as perpetual, unyielding stimuli for the innate immune system. Consequently, insulin resistance is now unequivocally categorized in internal medicine not merely as a metabolic defect, but as a state of chronic, low-grade systemic inflammation. This inflammatory state acts as the definitive bridge between initial metabolic injury and ultimate fibrotic destruction. Within the dense renal parenchyma, toxic lipid peroxidation products trigger the rapid activation of crucial intracellular transcription factors, particularly Nuclear Factor-kappa B (NF-kappa B). This master switch orchestrates a massive immunological response, resulting in the prolific local renal synthesis of highly destructive, pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-alpha) and Interleukin-6 (IL-6), alongside powerful chemokines such as Monocyte Chemoattractant Protein-1 (MCP-1). MCP-1 forcefully facilitates the aggressive, unrelenting infiltration of circulating, M1-polarized macrophages directly into the delicate tubulointerstitium, effectively turning the kidney into an active inflammatory battleground.[18]

Once localized and activated within the renal tissue, these macrophages incessantly secrete Transforming Growth Factor-beta 1 (TGF-beta 1). In clinical pathology, TGF-beta 1 is universally recognized as the central, master regulator of irreversible renal fibrosis. It aggressively drives the transdifferentiation of resident renal fibroblasts and surviving tubular epithelial cells into highly active, pathological myofibroblasts, characterized by their heavy expression of alpha-smooth muscle actin (alpha-SMA). These newly formed myofibroblasts act as pathological factories, rapidly and uncontrollably depositing impossibly thick, rigid layers of Type I and Type III collagen, alongside dense networks of fibronectin. This extracellular matrix overproduction literally obliterates the delicate peritubular capillaries. As the capillary networks are crushed, the resulting local tissue hypoxia further drives the fibrotic cascade, creating a vicious, self-sustaining cycle of destruction. Ultimately, this process suffocates the surrounding tissue and permanently replaces functional, filtering nephrons with non-functioning, avascular fibrotic scar tissue. Our clinical findings, demonstrating advanced renal failure in patients with the highest TyG indices, provide a stark, direct macroscopic reflection of this microscopic fibrotic destruction.[19,20]

While this study provides highly compelling clinical insights and robust statistical associations that deepen our understanding of diabetic nephropathy, several critical limitations must be explicitly addressed to properly contextualize the scope and applicability of the findings. First and foremost, the study's severely restricted sample size (N=44) represents a significant methodological limitation. While the sample size mathematically satisfied the minimum a priori requirements for preliminary diagnostic accuracy testing, a cohort of 44 patients inherently increases the margin of error and elevates the risk of statistical overfitting within the Receiver Operating Characteristic curve analysis. Because the

cohort is small, the mathematical modeling is highly sensitive to individual outliers. Consequently, the generalizability of the 8.81 diagnostic cut-off point is heavily restricted; it must be viewed as highly indicative rather than universally definitive. External validation in vastly larger, independent, and multicenter cohorts is absolutely mandatory before this specific numerical threshold can be safely implemented into routine, standardized clinical guidelines. Secondly, the cross-sectional design inherently and fundamentally restricts any ability to establish definitive causal pathways between the temporal rise in the TyG index and the longitudinal timeline of actual renal decline. We can clearly establish that high index scores and advanced kidney disease exist simultaneously within this patient population, highlighting a powerful correlation. However, we cannot mathematically prove that one directly predicts the future onset of the other within this dataset. Longitudinal cohort studies tracking the intra-individual variance of the TyG index over several years are necessary to confirm its true predictive, rather than purely associative, capabilities. Finally, as this study was executed in a resource-limited setting, advanced immunological and molecular evaluations could not be performed. The diagnostic framework relied upon standard biochemical assays and ultrasound imaging. The absence of specific, advanced markers—such as antinuclear antibodies, anti-double-stranded DNA, specific complement profiles, or direct tissue biopsies to confirm specific histological fibrosis staging—limits the ability to conclusively exclude ultra-rare, overlapping autoimmune pathologies that may have synergistically contributed to the observed renal decline. Future research incorporating detailed histopathological correlations with the TyG index would significantly strengthen the clinical narrative.

5. Conclusion

In conclusion, this cross-sectional analysis demonstrates a profound, statistically significant association between an escalating Triglyceride-Glucose (TyG) index and the presence of advanced-stage chronic kidney disease in adult patients with type 2 diabetes mellitus. The data clearly illustrate that systemic insulin resistance, heavily compounded by concurrent glucolipotoxicity, serves as a primary driver of renal decline. The TyG index possesses robust diagnostic accuracy, with an optimized cut-off of 8.81 offering exceptional sensitivity and high negative predictive value for identifying severe renal impairment. As a highly accessible, radically inexpensive parameter derived entirely from standard, universally available fasting lipid and glucose panels, the index serves as a powerful, practical reflection of the underlying insulin resistance and glucolipotoxicity driving diabetic renal decline. While it cannot independently predict longitudinal outcomes due to the constraints of the study design, integrating this straightforward mathematical calculation into routine internal medicine and primary care practice can substantially optimize clinical risk stratification. It provides clinicians with a vital, early-warning metric to facilitate timely nephrology referrals and initiate aggressive renoprotective interventions, ultimately aiming to disrupt the fibrotic cascade and delay the catastrophic onset of end-stage renal disease.

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