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Association Between TyG Index, Liver Steatosis and Immunosenescence in People Living with HIV

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Background: Metabolic disorders and immunosenescence increase the risk of complications in people living with HIV (PLWH), affecting mortality and quality of life. However, their relationship remains unclear.

Methods: Participants were grouped by median TyG index, and logistic regression identified baseline independent factors of a high TyG index at Week 24. The association of the TyG index for hepatic steatosis was determined using ROC curves. We also explored correlations between the TyG index and aging markers, including CD4/CD8 ratio and CD8+ T cells and evaluated health-related quality of life (HRQoL).

Results: A total of 203 PLWH were included in the study. We observed that PLWH in high TyG group tended to be older (P<0.001), have greater body weight (P<0.001), higher ALT levels (P=0.021), and increased low-density lipoprotein levels (P=0.001). ROC analysis revealed that TyG index was closely associated with hepatic steatosis at Week 52 (AUC=0.743) and Week 104 (AUC=0.728). Moreover, a higher TyG index was positively correlated with CD8+ T cell counts, while patients in the high TyG group had lower CD4/CD8 ratios at Week 52 and Week 104. Poorer mental health was observed in patients with CD8+ T cell counts ≥1000 and a high TyG index. Multivariate analysis further identified baseline older age (OR=1.108, P=0.002), elevated cholesterol (OR=3.407, P<0.001), and low HDL (OR=0.003, P<0.001) as factors associated with a high TyG index at Week 24.

Conclusion: The TyG index is closely linked to metabolic disorders and immunosenescence in PLWH. It offers a basis for personalized treatment strategies, improving physical and mental health and reducing complication risks.

Keywords: HIV/AIDS, triglyceride-glucose index, metabolic disorders, immunosenescence, hepatic steatosis

Introduction

HIV/AIDS continues to be one of the most significant global health challenges.[1] While the introduction of highly effective antiretroviral therapy (ART) has significantly extended the life expectancy of people living with HIV (PLWH), increasing evidence suggests that PLWH are at a higher risk of developing premature aging-related complications compared to age-matched healthy individuals, such as cardiovascular diseases, cancer, osteoporosis, and metabolic disorders.[2–4] These complications have a profound impact on both mortality risk and quality of life in PLWH.[5] Consequently, the issues of metabolic disorders and aging in PLWH have received increasing attention.[6]

Aging, especially immunosenescence, in this population is characterized by progressive immune dysfunction, leading to increased susceptibility to opportunistic infection and cancer, as well as reduced vaccine efficacy.[7] Although current technologies are limited in accurately evaluating immunosenescence, it is widely recognized that its key manifestations include: (1) a reduction in the number of naive T and B cells in peripheral blood; (2) an increased proportion of terminally differentiated memory (CD28-) T cells; (3) a decreased CD4+/CD8+ ratio; and (4) reduced diversity in T-cell

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receptors (TCR) and B-cell receptors (BCR).[8,9] Recent studies have also highlighted the close relationship between immunosenescence and metabolic disorders, both of which are common chronic complications.[10–12]

It is important to note that metabolic disorders and immunosenescence, two chronic long-term complications in PLWH, are closely interrelated.[13] HIV infection often leads to persistent immune activation and chronic inflammation. This inflammatory state continues even after viral control has been achieved.[14] Such chronic inflammation not only accelerates the process of immunosenescence but is also closely linked to metabolic disorders.[15] This link may contribute to complications such as hepatic steatosis, insulin resistance, and dyslipidemia, which are common in PLWH and are gaining increased attention.[16]

Given the interrelationship between immunosenescence and metabolic disorders, early identification of high-risk individuals is crucial for improving long-term prognoses. However, there is currently a lack of reliable indicators associated with immunosenescence and metabolic disorders in PLWH, posing challenges for clinicians in managing and mitigating the long-term impacts of HIV. While previous studies have demonstrated a close link between CD8+ T cells and immunosenescence in PLWH during antiretroviral therapy,[17] there is no evidence to suggest a close relationship between CD8+ T cells and metabolic disorders in this population. The triglyceride-glucose (TyG) index, a simple and cost-effective measure calculated using fasting triglyceride and glucose levels, has emerged as a promising marker for identifying insulin resistance and metabolic syndrome in the general population.[18–20] Despite its potential, the utility of the TyG index in predicting metabolic disorders in PLWH and its association with immunosenescence has not been extensively studied.

Therefore, this study aims to analyze the levels of the TyG index and CD8+ T cells in an HIV-infected cohort and to explore their relationship with immunosenescence and metabolic disorders. The primary objective of this study is to determine whether the TyG index can serve as a reliable marker for these conditions, thereby facilitating early identification and intervention.

Methods

Study Cohort and Participant Selection

This was a retrospective cohort study. All participants who were regularly followed up at the Department of Infectious Diseases, Nanfang Hospital between January 2018 and December 2021 were consecutively enrolled. Participants were included if they met the following criteria: 1) diagnosed with HIV infection, 2) received ART therapy with regular follow-up, 3) did not receive steroids or cytotoxic agents, 4) had no history of organ transplantation, autoimmune diseases, severe cardiovascular disease, liver or kidney renal failure and active malignancies, and 5) had no missing key data. It is noteworthy that regular follow-up was defined as visits at least once every 3 months, during which viral load, CD4/CD8+ T cell count, complete blood count, liver and kidney function, lipid and glucose levels were monitored. HIV suppression was defined as a viral load of fewer than 100 copies/mL during these visits.[21]

This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation, the Declaration of Helsinki, and the principles of good clinical practice. It was approved by the Ethics Committee of Nanfang Hospital (NFEC-2021-448). All enrolled patients were provided with sufficient information, and written informed consent was obtained from all participants.

Transient Elastography Assessment

Liver stiffness (LS) and the Controlled Attenuation Parameter (CAP) were assessed using transient elastography, performed by a professionally trained technician following the manufacturer's instructions. Ultrasonic attenuation was measured at 3.5 MHz using signals provided by the elastography device. The median CAP value was reported in decibels per meter (dB/m), while LS was expressed in kilopascals (Kpa). A CAP value was deemed reliable if the interquartile range/median ratio was <0.3 and the success rate exceeded 60%. We considered CAP values >238 dB/m as indicative of liver steatosis.[22]

Laboratory Assays and TyG Index Calculation

CD4+ and CD8+ T cell counts were determined by flow cytometry and analyzed automatically using mULTI-SET software (BD, New Jersey, USA). HIV-1 viral loads were measured using the Gen Probe assay and expressed as log10 copies/mL. Blood cell counts were analyzed with a Sysmex SE9000 automatic blood cell analyzer. Serum biochemical parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin (ALB), were measured using an Olympus AU5400 automatic biochemical analyzer. The above data was sourced from medical records or databases. Additionally, the TyG index is calculated using the following formula,[23] where TG represents fasting triglycerides (TG) concentration (mg/dL) and fasting blood glucose (FBG) represents fasting blood glucose concentration (mg/dL).

$$\text{TyG Index} = \ln\left(\frac{\text{TG} \times \text{FBG}}{2}\right)$$

Questionnaire Assessments

The SF-36 questionnaire comprises eight multi-item dimensions:[24] physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items). Scores for each dimension range from 0 to 100, with higher scores indicating better HRQoL in the respective domain. The SF-36 has demonstrated good internal consistency, with Cronbach's alpha values greater than 0.85.[25] The Self-Rating Depression Scale (SDS) is a psychological assessment tool used to measure the severity of depressive symptoms.[26] The scale consists of 20 items, each rated on a 4-point Likert scale, resulting in a total score ranging from 20 to 80, with higher scores indicating more severe depressive symptoms. A score of 50 or above is indicative of clinically significant depression. The SDS has shown good reliability, with a Cronbach's alpha of 0.87,[27] and has been validated in various clinical settings.[28] Similarly, the Self-Rating Anxiety Scale (SAS) evaluates the intensity of anxiety symptoms.[29] The SAS also consists of 20 items, rated on a 4-point Likert scale, with total scores ranging from 20 to 80, where higher scores indicate more severe anxiety. A score of 50 or above suggests clinically significant anxiety. The SAS has demonstrated good reliability (Cronbach's alpha = 0.78).[30] All enrolled participants completed the SF-36, SDS, and SAS questionnaires at Week 24.

Statistical Analysis

Statistical analysis were conducted using Statistical Product and Service Solutions (SPSS, version 20.0, Chicago, IL, USA) and GraphPad Prism (version 8.0.2). Data are presented as mean ± SD. Comparisons between two groups were performed using Student's *t*-test, while comparisons among three or more groups were conducted using ANOVA. A P value < 0.05 was considered statistically significant. To examine the relationship between pre-ART clinical variables and elevated TyG index levels at week 24 post-ART, we performed a binary logistic regression analysis. Given that the calculation of the TyG index incorporates TG and FBG, these two variables were excluded from the logistic regression analysis, while all other relevant variables were included. We performed both univariate analysis and multivariate stepwise backward regression to identify independent factors.

Results

Clinical Characteristics Associated with TyG Index Levels

A total of 203 PLWH were included in the study. Considering that these participants might have been in an acute inflammatory state before initiating ART, we analyzed the TyG index and serum indicators at 24 weeks post-ART when their condition had stabilized. The TyG index among the 203 PLWH ranged from 7.46 to 10.54. Based on the median TyG value of 8.5, these participants were categorized into two groups: TyG < 8.5 (Low TyG group) and TyG ≥ 8.5 (High TyG group). As shown in Table 1, we observed that among PLWH with stable condition, the high TyG group tended to be older (P<0.001), have greater body weight (P<0.001), higher ALT levels (P=0.021), and increased low-density lipoprotein levels (P=0.001), while exhibiting lower high-density lipoprotein levels (P<0.001).

Table 1 Demographics of the Two Groups Week 24 Post-ART

Characteristic	People Living with HIV		P value
	TyG Index < 8.5	TyG Index ≥ 8.5	
Sample size	104	99	
Age, year	29.58±6.46	33.66±9.46	<0.001*
Gender,			0.691
Male	101 (97.1)	97 (98.0)	
Female	3 (2.9)	2 (2.0)	
Weight, kg	58.93±9.54	65.41±11.69	<0.001*
Height, cm	169.17±6.12	169.78±6.29	0.493
WBC, 10^9/L	5.72±1.36	6.09±1.55	0.074
LYM, 10^9/L	1.94±0.57	2.14±0.69	0.028*
NEU, 10^9/L	3.21±1.17	3.33±1.12	0.464
HGB, g/L	149.96±13.52	151.05±14.59	0.583
PLT, 109/L	243.52±56.83	234.78±57.75	0.280
ALT, U/L	28.13±18.25	41.43±53.36	0.021*
AST, U/L	24.23±11.95	31.91±42.74	0.089
ALB, g/L	46.85±3.03	46.82±3.37	0.952
Globulin, g/L	29.41±4.98	29.79±5.31	0.594
ALP, U/L	100.36±24.05	102.86±27.47	0.624
GGT, U/L	35.04±26.81	51.70±41.58	0.014*
BUN, mmol/L	4.24±1.11	4.36±1.18	0.465
Creatinine, μmol/L	76.41±14.05	81.19±16.20	0.026*
UA, μmol/L	369.84±89.43	402.47±87.65	0.010*
Total Cholesterol, mmol/L	3.98±0.74	4.48±0.93	<0.001*
HDL, mmol/L	1.18±0.23	1.02±0.24	<0.001*
LDL, mmol/L	2.46±0.58	2.76±0.69	0.001*
VLDL, mmol/L	0.34±0.15	0.70±0.69	<0.001*
TG, mmol/L	0.849±0.197	2.156±1.245	<0.001*
Glucose, mmol/L	5.17±0.42	5.64±0.98	<0.001*

Notes: *indicates P value < 0.05.

Abbreviations: WBC, White Blood Cell count; LYM, Lymphocytes; NEU, Neutrophils; HGB, Hemoglobin; PLT, Platelets; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALB, Albumin; ALP, Alkaline Phosphatase; GGT, Gamma-Glutamyl Transferase; BUN, Blood Urea Nitrogen; UA, Uric Acid; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; VLDL, Very-Low-Density Lipoprotein; TG, Triglycerides.

Association of TyG Index and Hepatic Steatosis at Week 52 and 104 Post-ART

The Fibroscan assessments conducted during PLWH follow-up facilitated the analysis of the relationship between TyG index and hepatic steatosis. We found significant differences in CAP values at Week 52 and Week 104 in PLWH, stratified by TyG index at Week 24 post-ART (Figure 1A and B). However, the TyG index was not able to differentiate liver stiffness values at week 52 although a higher liver stiffness value at week 104 observed in patients with high TyG index (Figure 1C and D). Moreover, there was a positive correlation between the TyG index and CAP values at Week 52 and Week 104 ($p < 0.001$, Figure 1E and F). Subsequently, we found that the TyG index at Week 24 post-ART was associated with the presence of hepatic steatosis at Week 52 and Week 104 (Figure 1G and H). The areas under the ROC curves for these predictions were 0.743 and 0.728, respectively.

Association Between TyG Index and Immunosenescence-Related Markers

We next explored the relationship between the aging-related indicators and TyG index as well as CD8+ T cells, which are known as a marker of immune senescence in PLWH. The participants were divided into three groups based on CD8+ T cell counts at Week 24 post-ART: <500, 500–1000, and ≥1000 cells/μL. The analysis revealed significant differences in CD4/CD8 ratios among these three groups, which persisted with continued antiretroviral therapy (Figure 2A).

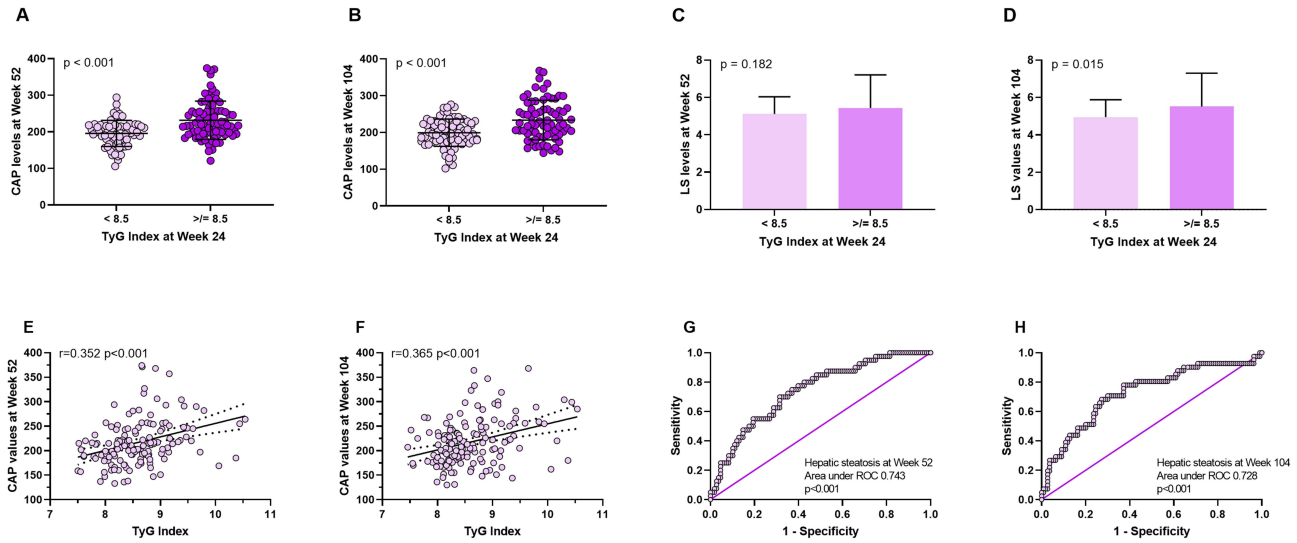

Figure 1 Association between TyG index and hepatic steatosis. (**A**) The CAP values at Week 52 in relation to TyG index (<8.5 and ≥8.5) at Week 24 (195.94±35.63 vs 231.82±52.30 dB/m, p<0.001). (**B**) The CAP values at Week 104 in relation to TyG index (<8.5 and ≥8.5) at Week 24 (199.26±37.16 vs 233.60±53.85 dB/m, p<0.001). (**C**) The LS values at Week 52 by TyG index groups (<8.5 and ≥8.5) at Week 24 (5.12±0.92 vs 5.43±1.78 Kpa, p=0.182). (**D**) The LS values at Week 104 by TyG index groups (<8.5 and ≥8.5) at Week 24 (4.95±0.93 vs 5.51±1.79 Kpa, p=0.015). (**E**) The Correlation between TyG index and CAP values at Week 52 (r=0.352). (**F**) The Correlation between TyG index and CAP values at Week 104 (r=0.365). (**G**) The ROC curve for predicting hepatic steatosis at Week 52 based on TyG index at Week 24 (AUC=0.743, p<0.001). (**H**) The ROC curve for predicting hepatic steatosis at Week 104 based on TyG index at Week 24 (AUC=0.728, p<0.001).
Abbreviations: CAP, Controlled Attenuation Parameter; LS, Liver Stiffness.

Specifically, PLWH with CD8+ T cell counts ≥ 1000 cells/ul at Week 24 exhibited the lowest CD4/CD8 ratio during ART. Similarly, patients in the high TyG index group had lower CD4/CD8 ratios at Week 52 and Week 104 compared to those in the low TyG index group (Figure 2B).

We then assessed changes in CD4+ T cells to determine whether immune reconstitution was related to CD8+ T cell counts and the TyG index (Figure 2C and D). We observed no significant correlation between changes in CD4+ T cells and either CD8+ T cell counts or the TyG index at Week 24 post-ART.

Finally, we further analyzed the correlation between the TyG index and aging-related markers (Figure 3). We found that the TyG index was positively correlated with age and CD8+ T cell counts, and negatively correlated with CD4/CD8 ratios at baseline, and at Week 24, 52, and 104.

Impact of Immunosenescence and Metabolic Disorders on HRQoL

Aging and metabolic disorders are closely linked to quality of life. Therefore, we evaluated the relationship between HRQoL and levels of depression and anxiety in PLWH, categorized by CD8+ T cell count and TyG index. We found that PLWH with CD8+ T cell counts ≥ 1000 had poorer mental health (p = 0.043). However, there were no significant differences in anxiety and depression levels across different CD8+ T cell count groups (Figure 4A–C). A similar pattern was observed with the TyG index. Patients with a high TyG index exhibited poorer mental health (p = 0.041) and general health (p = 0.009). Despite these findings, no significant association was found between the TyG index and levels of depression and anxiety (Figure 4D–F).

Baseline Risk Factors Associated with High TyG Index at Week 24 After ART

To improve risk stratification prior to antiretroviral therapy (ART), we conducted logistics regression analysis to examine the relationship between pre-ART variables and high TyG index levels at Week 24 post-ART (Table 2). Univariate analysis indicated that factors including older age, increased body weight, elevated ALT, AST, GGT levels, lower HDL, and higher VLDL levels were associated with high TyG index levels at week 24 post-ART. However, multivariate analysis revealed that older age (OR=1.108, P=0.002), elevated total cholesterol (OR=3.407, P<0.001), and low HDL (OR=0.003, P<0.001) were independent factors associated with high TyG index at Week 24 post-ART. Additionally, we

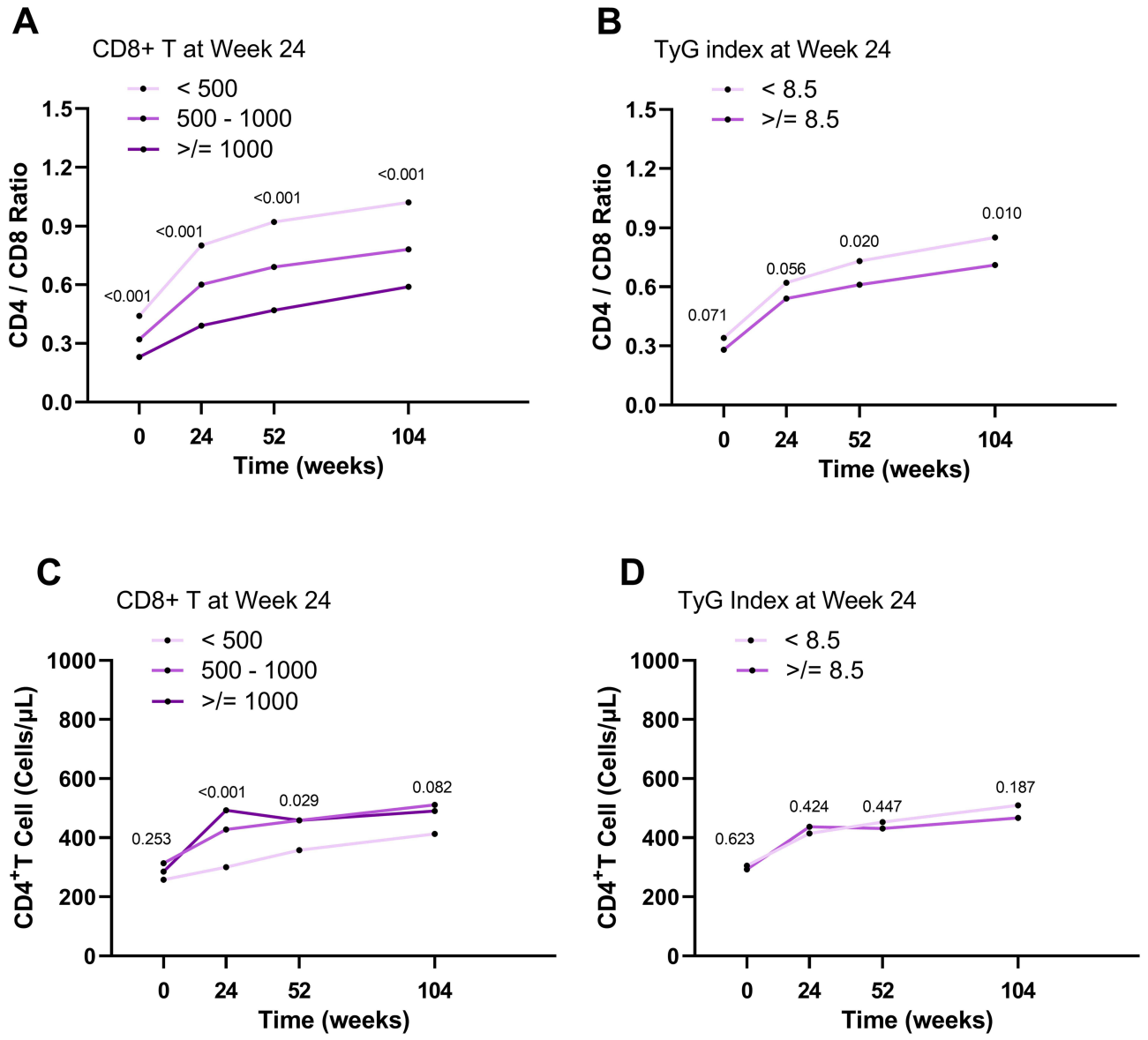

Figure 2 Association between the TyG index and immunosenescence markers. (**A**) Longitudinal changes in the CD4/CD8 ratio across different CD8+ T cell count groups (<500, 500–1000, and ≥1000 cells/μL) over a 104-week period (p<0.001 for all time points). (**B**) Longitudinal changes in the CD4/CD8 ratio across different TyG index groups (<8.5 and ≥8.5) over a 104-week period (p=0.071, 0.056, 0.020, and 0.010 at Week 0, 24, 52, and 104, respectively). (**C**) Longitudinal changes in CD4+ T cell counts across different CD8+ T cell count groups (<500, 500–1000, and ≥1000 cells/μL) over a 104-week period (p=0.253, <0.001, 0.029 and 0.082 at Week 0, 24, 52, and 104, respectively). (**D**) Longitudinal changes in CD4+ T cell counts across different TyG index groups (<8.5 and ≥8.5) over a 104-week period (p=0.623, 0.424, 0.447 and 0.187 at Week 0, 24, 52, and 104, respectively).

performed logistics regression analysis between variables at week 24 post-ART and high TyG index (Supplementary Table 1), and found that weight (OR=1.081, P=0.001) and CD8+T cells (OR=1.001, P=0.054) were identified as factors associated with high TyG index.

Discussion

This study included 203 hIV-infected individuals and conducted a longitudinal analysis of clinical data to explore the relationship between the TyG index, markers of immunosenescence and metabolic disorders. On the one hand, the results indicated that a high TyG index was closely associated with hepatic steatosis at weeks 52 and 104 post-antiretroviral therapy, indicating a close association between the TyG index and adverse metabolic disorders. On the other hand, the strong correlation between the TyG index, CD8+ T cell counts, and the CD4/CD8 ratio further supports its ability as

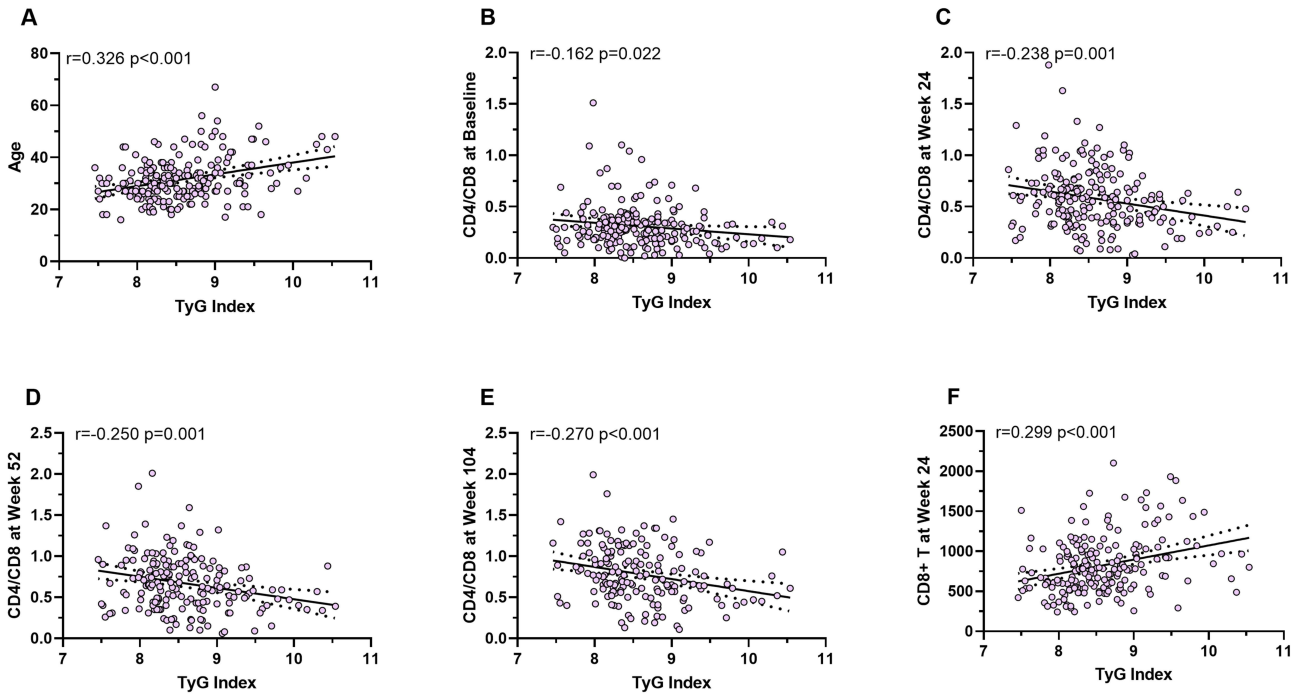

Figure 3 Correlation analysis between TyG index and immunosenescence markers. The Scatter plots of TyG index and age (r=0.326, p<0.001) (**A**), CD4/CD8 ratio at baseline (r=−0.162, p=0.022) (**B**), CD4/CD8 ratio at Week 24 (r=−0.238, p=0.001) (**C**), CD4/CD8 ratio at Week 52 (r=−0.250, p=0.001) (**D**), CD4/CD8 ratio at Week 104 (r=−0.270, p<0.001) (**E**), and CD8+ T cell counts at Week 24 (r=0.299, p<0.001) (**F**).

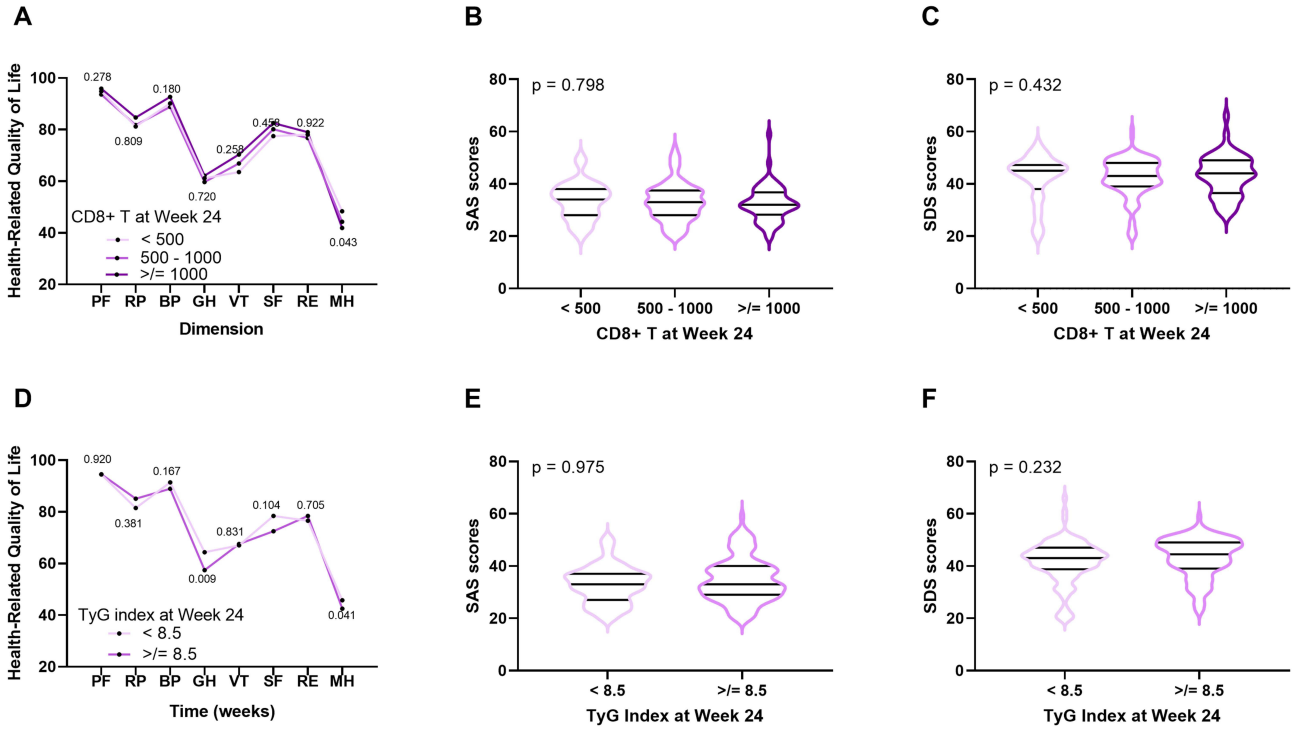

Figure 4 Association between CD8+T cells and TyG index on Physical and Mental Health. (**A**) Health-related quality of life across different dimensions in relation to CD8+ T cell counts (<500, 500–1000, and ≥1000 cells/μL) at Week 24. (**B**) SAS scores across different CD8+ T cell count groups (<500, 500–1000, and ≥1000 cells/μL) at Week 24 (p=0.798). (**C**) SDS scores across different CD8+ T cell count groups (<500, 500–1000, and ≥1000 cells/μL) at Week 24 (p=0.432). (**D**) Health-related quality of life across different dimensions in relation to TyG index (<8.5 and ≥8.5) at Week 24. (**E**) SAS scores across different TyG index groups (<8.5 and ≥8.5) at Week 24 (p=0.975). (**F**) SDS scores across different TyG index groups (<8.5 and ≥8.5) at Week 24 (p=0.232).

Abbreviations: PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; MH, Mental Health; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

Table 2 Univariate and Multivariate Analysis of Baseline Variables Associated with High TyG Index at Week 24 Post-ART

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.066	1.027–1.107	0.001*	1.108	1.037–1.184	0.002*
Gender, male	1.441	0.236–8.809	0.693			
Weight	1.048	1.019–1.077	0.001*			
Height	1.016	0.971–1.063	0.491			
WBC	0.999	0.832–1.201	0.995			
LYM	1.030	0.696–1.525	0.881			
NEU	0.945	0.743–1.201	0.641			
HGB	0.993	0.977–1.010	0.420			
PLT	0.996	0.992–1.001	0.105			
ALT	1.025	1.008–1.043	0.005*			
AST	1.042	1.007–1.077	0.017*			
ALB	0.965	0.908–1.025	0.246			
Globulin	0.993	0.953–1.035	0.731			
ALP	1.006	0.986–1.026	0.557			
GGT	1.024	1.000–1.047	0.047*			
BUN	1.177	0.945–1.465	0.145			
Creatinine	1.007	0.987–1.027	0.504			
UA	1.001	0.999–1.004	0.365			
Total Cholesterol	1.275	0.887–1.834	0.189	3.407	1.605–7.229	0.001*
HDL	0.109	0.029–0.407	0.001*	0.003	0.000–0.041	<0.001*
LDL	1.216	0.779–1.897	0.389			
VLDL	39.549	8.233–189.98	<0.001*			

Notes: *indicates P value < 0.05.
Abbreviations: WBC, White Blood Cell count; LYM, Lymphocytes; NEU, Neutrophils; HGB, Hemoglobin; PLT, Platelets; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALB, Albumin; ALP, Alkaline Phosphatase; GGT, Gamma-Glutamyl Transferase; BUN, Blood Urea Nitrogen; UA, Uric Acid; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; VLDL, Very-Low-Density Lipoprotein.

a marker of immunosenescence. In summary, the TyG index may serve as a potential marker for the early identification of high-risk individuals with immunosenescence and metabolic disorders among PLWH, providing a basis for developing personalized intervention strategies.

The TyG index, derived from triglycerides and fasting glucose, has been widely used in recent years as a biomarker for coronary artery disease.[31] Its advantages include simplicity, cost-effectiveness, and high sensitivity and specificity in assessing metabolic syndrome and insulin resistance.[32] In this study, we found that the TyG index at Week 24 post-ART effectively was associated with the occurrence of hepatic steatosis at Week 52 and 104. Previous research has confirmed the TyG index as a reliable predictor of cardiovascular disease (CVD) risk in PLWH.[33,34] Our findings further demonstrate its value in predicting hepatic steatosis in this population. However, the lack of hepatic steatosis data at week 24 in this study may have introduced some bias into the analysis. Furthermore, the TyG index showed limited ability to differentiate liver stiffness, indicating that it may primarily reflect lipid metabolism-related processes, with less sensitivity to liver fibrosis. Overall, the TyG index serves as a simple and practical biomarker, providing clinicians with a valuable tool for early identification of hepatic steatosis risk in PLWH.

Immunosenescence is characterized by a decline in T cell function, a reduction in the CD4/CD8 ratio, an expansion of CD8+ T cells, and a loss of T cell and B cell diversity.[35] Among these, CD8+ T cells have been widely recognized as a key marker of immunosenescence in PLWH and are predictive of various complications following long-term antiretroviral therapy.[36,37] Our correlation analysis revealed a significant positive association between the TyG index and CD8+ T cells. Additionally, we found that PLWH with a high TyG index exhibited a significant reduction in the CD4/CD8 ratio during treatment, suggesting the potential of the TyG index as a marker of immunosenescence and further

supporting the close link between metabolic disorders and immunosenescence. Insulin resistance is commonly observed in individuals with a high TyG index,[38] and metabolic disorders may lead to an increased production of pro-inflammatory cytokines and oxidative stress,[39,40] both of which are known drivers of immunosenescence.[35] These processes may further exacerbate systemic inflammation and trigger immune cell exhaustion, thereby accelerating immune system aging.[41] Future studies should aim to explore the potential mechanisms underlying the relationship between the TyG index and immunosenescence, and evaluate its potential role as a clinical marker for both metabolic and immunological health in PLWH.

In recent years, the relationship between the TyG index and mental health issues has garnered considerable attention. Several studies have pointed out that a higher TyG index is closely associated with the prevalence of depression.[42,43] Furthermore, recent research has also reported a significant association between the TyG index and suicidal ideation.[44,45] However, we did not observe a significant increase in anxiety or depression among participants with higher TyG indices in our study. Our results showed that PLWH with higher TyG index had a generally lower quality of life, particularly in the domain of mental health. An elevated TyG index indicates metabolic disorders, such as insulin resistance, which may lead to systemic inflammation and neuroinflammation,[46] and could be involved in the pathogenesis of mood disorders and suicidal ideation.[47,48] On the other hand, the study also demonstrated that participants with higher CD8+ T cell counts exhibited poorer mental health. CD8+ T cell counts is a marker of immune senescence and challenges in immune reconstitution, and senescence may lead to increased psychological stress and anxiety,[49,50] which may be more pronounced in PLWH with a higher risk of suicide.[51] These findings also underscore the importance of comprehensively evaluating the potential role of the TyG index in managing HIV-infected individuals, not only in its association with metabolic abnormalities but also in assessing immunosenescence and its impact on quality of life. Therefore, monitoring the quality of life and physical health of PLWH with a high TyG index is crucial. Regular assessment of the TyG index can help identify high-risk patients who may require more proactive interventions at an earlier stage.

This study provides important insights, particularly in understanding the role of the TyG index in its association with hepatic steatosis and immunosenescence in PLWH. Although previous studies have indicated an association between elevated CD8+ T cells and immunosenescence in PLWH, there is still limited direct evidence linking CD8+ T cells to metabolic disorders. This study seeks to bridge this gap, offering a new perspective on the interplay between metabolic disorders and immunosenescence. However, this study also has some limitations. First, as a retrospective single-center study, the generalizability and external validity of the findings may be limited. Additionally, the lack of comprehensive aging biomarkers hinders a more complete understanding of the relationship between the TyG index and immunosenescence. Future research should consider multicenter, large-scale prospective studies to enhance the generalizability and external validity of the results. Additionally, potential interventions, such as lifestyle changes and pharmacotherapy, should be explored to address TyG index-related immunosenescence and metabolic disorders, providing stronger evidence for personalized treatment in PLWH.

Conclusion

Our findings reveal that a high TyG index is not only closely associated with hepatic steatosis at 52 and 104 weeks post-antiretroviral therapy but is also strongly related to immunosenescence markers such as CD8+ T cells and the CD4/CD8 ratio. Assessing the TyG index can inform personalized treatment strategies for PLWH, helping to improve their HRQoL and reduce the risk of adverse outcomes.

Data Sharing Statement

The authors confirm that all relevant data are included in the article, and the materials are available upon reasonable request from the authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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