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Total cholesterol/high-density lipoprotein cholesterol ratio is a significant predictor of metabolic syndrome among people on dolutegravir-based antiretroviral therapy: A cross-sectional study in southwestern Uganda

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Abstract

Objective: The total cholesterol/high-density lipoprotein cholesterol ratio is a predictor of nonalcoholic fatty liver disease—a hepatic manifestation of metabolic syndrome. This study investigated the association between total cholesterol/high-density lipoprotein cholesterol ratio and metabolic syndrome among people living with human immunodeficiency virus on dolutegravir-based antiretroviral therapy in southwestern Uganda.

Methods: We conducted a secondary analysis of data obtained from a cross-sectional study of 377 adults who had been on dolutegravir-based antiretroviral therapy for at least 1 year at Ruhoko Health Centre IV, southwestern Uganda.

Results: The median total cholesterol/high-density lipoprotein cholesterol ratio was significantly higher in individuals with metabolic syndrome (3.92) than in those without (2.96, $p < 0.001$). A statistically significant association was observed between high total cholesterol/high-density lipoprotein cholesterol ratio and metabolic syndrome (adjusted odds ratios: 2.06, 95% confidence interval: 1.08–3.91, $p = 0.028$). The total cholesterol/high-density lipoprotein cholesterol ratio at an optimal cutoff of 3.30 had a significant ability (area under the curve $= 0.696$, 95% confidence interval: 0.642–0.750) to differentiate participants with metabolic syndrome from those without at a sensitivity of 73% and specificity of 60%.

Conclusion: The total cholesterol/high-density lipoprotein cholesterol ratio is a significant predictor of metabolic syndrome and serves as a potential blood-based biomarker.

Keywords

Total cholesterol/high-density lipoprotein cholesterol, metabolic syndrome, blood-based biomarker, predictor, dolutegravir

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Introduction

With the increasing availability of antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection is no longer a death sentence but has become a manageable chronic illness.[1] However, patients on ART seem to exhibit an increased prevalence of noncommunicable disorders such as metabolic syndrome (MetS).[2] MetS is associated with an increased risk of cardiovascular disease (CVD), type 2 diabetes mellitus, and nonalcoholic fatty liver disease (NAFLD)[3–5] and is characterized by a cluster of metabolic disorders, including central obesity, dyslipidemia, and hypertension, along with insulin resistance.[6]

Increased use of dolutegravir (DTG)-based ART among HIV-infected patients seems to have a strong association with a higher prevalence of MetS and its components.[7] Studies have documented the prevalence of MetS among HIV-infected populations on ART in sub-Saharan Africa to be within the range of 16.9%–50.3% based on the International Diabetes Federation (IDF) criteria.[8] Notably, higher prevalence rates have been observed among individuals on DTG-based regimens.[9] In Ethiopia, a cross-sectional study among people living with HIV (PLWH) on DTG-based ART reported a MetS prevalence of 25.6%.[10] Similarly, a study conducted in northern Tanzania found a MetS prevalence of 42.3% in the PLWH population.[11] In southwestern Uganda, Nzaramba et al.[12] reported a prevalence of 35.3% among PLWH on DTG-based ART.

In PLWH, undiagnosed or untreated MetS can lead to significant clinical problems. Gupta et al.[5] noted that uncontrolled MetS can increase mortality, cause NAFLD, and accelerate CVD. NAFLD, which is increasingly problematic as a component of MetS, is a major hepatic manifestation in HIV infection and is often associated with liver cirrhosis and fibrosis, complicating the clinical management of HIV-infected patients.[13] Due to these risks, early detection of MetS is critical to avert irreversible complications, particularly in resource-limited settings such as Uganda.

An increasing number of researchers have highlighted the potential importance of using the total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio as a simple, cost-effective biomarker for estimating MetS and other metabolic disorders.[14,15] Increased TC/HDL-C ratios are related to insulin resistance, cardiovascular dysregulation, and dyslipidemia, which are all indicative of MetS.[16] In addition, studies from other parts of the world, including eastern parts of Africa, have highlighted the TC/HDL-C ratio's predictive value for NAFLD, thereby reinforcing the notion of its role as a marker of metabolic derangement.[17,18]

Uganda, similar to many sub-Saharan African countries, faces a dual burden of infectious and noncommunicable diseases.[19] Southwestern Uganda, in particular, has one of the highest HIV prevalence rates in the country,[20] coupled with a rapidly expanding rollout of DTG-based ART.[21,22] However, despite these trends, there are limited local data assessing the relationship between TC/HDL-C ratio and MetS among this population. The region's high HIV burden, increasing use of newer ART regimens, and constrained health resources make it an important setting for evaluating simple biomarkers that can aid in early MetS detection and improve long-term outcomes in PLWH.

Therefore, our study aimed to assess the association between the TC/HDL-C ratio and MetS and determine the optimal TC/HDL−C cutoff for discriminating individuals with and without MetS among PLWH on DTG-based ART in southwestern Uganda.

Material and methods

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.[23]

Study design, population, and variables

We conducted a secondary data analysis using a dataset generated from a cross-sectional study[12] that investigated the association between low aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and MetS among 377 PLWH on DTG-based ART in southwestern Uganda. The secondary study was conducted between 20 January 2025 and 20 March 2025. In the primary study, patients aged 18 years and above who had been on DTG-based ART for at least 12 months and had provided informed consent were systematically enrolled. Individuals with missing clinical records, pregnant women, those on interrupted treatment, and those who visited due to an acute illness, including hepatitis, were excluded. Those who were on diabetes treatment, lipid-lowering medication, corticosteroids, or oral contraceptive pills were also excluded from the study. This primary study explored many independent variables, including anthropometric measurements (waist circumference (WC), hip circumference, neck circumference, mid-upper arm circumference (MUAC), weight, and height), liver enzymes (AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)), and lipid profile (TC, triglycerides

(TG), low-density lipoprotein (LDL)-cholesterol (LDL-C), and HDL-C)—some of which were used to calculate the TC/HDL-C ratio in our secondary study.

In the secondary analysis, the primary dependent variable of interest was MetS, which was defined based on the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria as fulfilling three or more of the following conditions: (a) WC >102 cm for men and >88 cm for women; (b) TG level ≥150 mg/dL; (c) HDL-C level <40 mg/dL for men and <50 mg/dL for women; (d) blood pressure (BP) >130/85 mmHg or hypertension treatment; and (e) fasting plasma glucose (FPG) level ≥110 mg/dL or being on diabetes treatment.[24] However, the TC/HDL-C ratio was the main independent variable in the secondary analysis.

Other independent variables considered in this secondary analysis included sociodemographic variables (such as sex, age, marital status, educational level, residence, religion, employment status, and having a ventilated kitchen), lifestyle factors (such as smoking status, alcohol consumption, and vegetable and fruit intake), medical history (reported comorbidities such as hypertension, family history of dementia, and other chronic conditions such as hypertension, kidney disease, CVDs, and dyslipidemias), biochemical parameters (such as FPG; TC; TG; LDL; liver enzymes such as serum AST, ALT, ALP, and GGT; and serum electrolytes such as sodium, potassium, and chloride), sleep-related factors (such as poor sleep quality, obstructive sleep apnea (OSA), and sleep duration); anthropometric parameters (such as BP, body mass index (BMI), and WC), and ART-related variables (such as DTG-based ART duration).

The TC/HDL-C ratio was calculated by dividing the TC levels in mg/dL by the HDL-C levels in mg/dL, and a high ratio was defined as ≥5 according to the NCEP ATP III criteria.[14,17,25,26] OSA is a condition characterized by recurrent episodes of respiratory pause with durations greater than or equal to 10 s. OSA was evaluated using the Stop Bang scoring model tool.[27] Sleep quality is defined as an individual's self-satisfaction with all aspects of sleep experience and was determined by the Pittsburgh Sleep Quality Index (PSQI), which encompasses factors such as prolonged sleep latency, frequent awakenings, insufficient sleep duration, daytime sleepiness, and overall dissatisfaction with sleep. A good sleep quality is defined as a global PSQI score ≤5, and a poor sleep quality is defined as a global PSQI score ≥6.[28] Sleep duration was categorized as <5, 5–6, 6–7, and >7 h.[29] BMI, which is the ratio of weight to the square of height in kg/m^2, was categorized as <25, 25–29.9 (overweight), and ≥30 (obesity).[30] Low fruit and vegetable intake was defined as consuming less than five servings of fruit and vegetables per day.[31]

Sample size determination

For the secondary analysis, a sample size calculation was based on the prevalence (35.3%) of MetS[12] among PLWH on DTG-based ART in a study conducted in southwestern Uganda. We used the Kish Leslie formula (1965) with a 5% margin of error and a 95% confidence interval (CI).

$$N = 1.96^2 \times 0.353(1 - 0.353)/0.05^2 = 351$$

Since the primary study enrolled 377 participants, this sample size was adequate for the secondary data analysis.

Statistical analysis

Data were analyzed using STATA version 17. Categorical variables were summarized using frequencies and proportions. Median (interquartile range (IQR)) was utilized to summarize the continuous variable "age" as it was not normally distributed across the study participants. The median TC/HDL-C ratio was compared between participants with and without MetS using Mann–Whitney U test. The prevalence of MetS was also compared between participants with a high TC/HDL-C ratio and those with a low TC/HDL-C ratio using chi-square test. A p-value <0.05 was considered to indicate statistical significance.

Logistic regression was used to assess the association between the TC/HDL-C ratio and MetS. MetS was the binary dependent variable ($1 = \text{present}$, $0 = \text{absent}$). At the bivariate level, crude associations between MetS and each independent variable, including the TC/HDL-C ratio, were evaluated. Associations were quantified using crude odds ratios (cORs), with corresponding 95% CIs, and statistical significance was determined at a p-value <0.05. The primary exposure and other variables that were clinically and/or statistically significant at this level were included in the multivariable model to adjust for potential confounding. Adjusted ORs (aORs) with 95% CIs and p values were reported. The model's goodness of fit was assessed using the Hosmer–Lemeshow test, with a p-value >0.05 indicating a good fit ($p = 0.6617$ in our final model). In the final multivariable model, associations were considered significant at a p value <0.05.

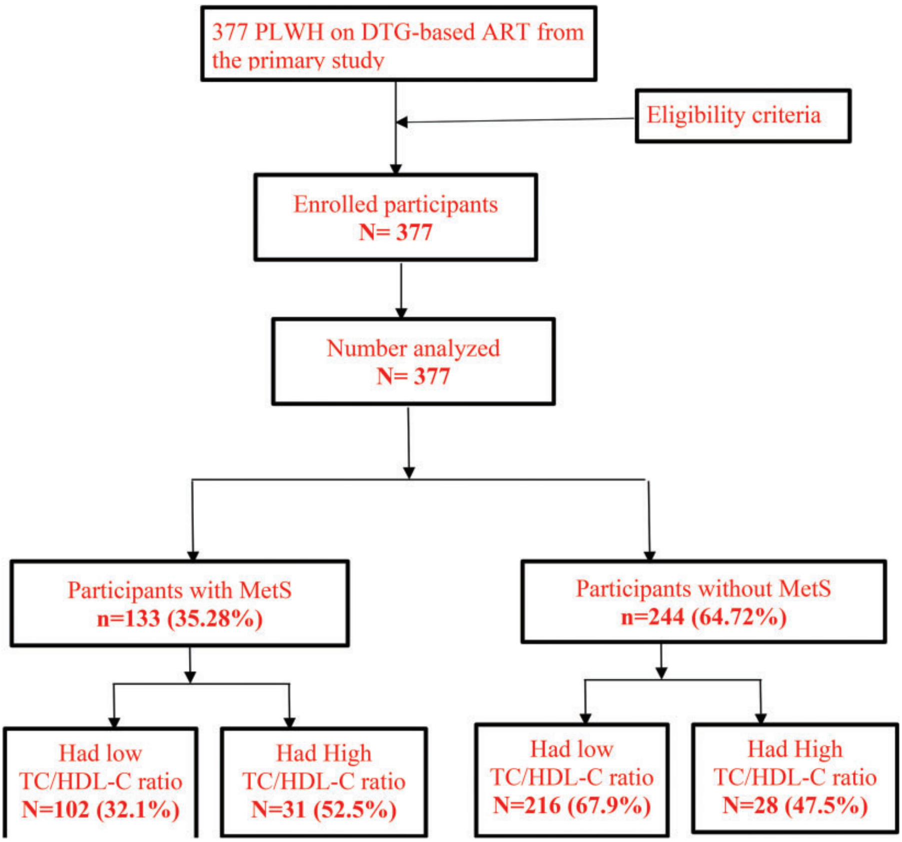
To evaluate the predictive ability of the TC/HDL-C ratio for identifying participants with MetS, we conducted a receiver operating characteristic (ROC) curve analysis. ROC analysis was selected because it is an established method for evaluating the diagnostic or discriminative performance of a continuous biomarker in classifying a binary outcome. The area under the curve (AUC) was computed to quantify the overall discriminative performance of the TC/HDL-C ratio. An AUC value closer to 1.0 indicates better predictive power, whereas an AUC of 0.5 indicates that the predictive performance is due to chance. Predictive performance was considered statistically significant if the 95% CI for the AUC did not include the null value of 0.5. Additionally, the interpretation of AUC values is summarized as follows: AUC of 0.90–1.00 = excellent; 0.80–0.89 = good; 0.70–0.79 = fair; 0.60–0.69 = poor; and 0.50–0.59 = failure.[32]

Ethical approvals and consent to participate

Ethical clearance was obtained from the Research Ethics Committee (REC) of the Mbarara University of Science and Technology (REC number, MUST-2024-1575) on 10 June 2024 to conduct the primary study.[12] All participants provided written informed consent prior to enrollment. The consent forms were translated into the local language (Runyankore) to ensure comprehension. Formally educated participants gave consent by signing the written forms. For participants with no formal education, the written informed consent form was read aloud in Runyankore, followed by administration of the comprehension screening tool approved by the MUST REC. Only participants who demonstrated understanding were allowed to consent by placing a thumbprint on the informed consent form. Participants were also explicitly asked to provide consent for the use of their data in the secondary analysis, for which they approved. This study was conducted in accordance with the Declaration of Helsinki (1975) as revised in 2024. Confidentiality of the study participants was observed by giving each participant a study code that was not traceable to them. To protect patient privacy, all personal identifiers were removed, and the data were fully deidentified before analysis. Permission to perform secondary analysis was also obtained from the principal investigator of the primary study.

Results

Study flowchart



Narrative of the study flowchart

Data from all 377 PLWH on DTG-based ART from the primary study, who met the eligibility criteria, were included in this study. Of these, a significant number of patients (133 (35.28%)) were diagnosed with MetS. Among those with MetS, more than half (31 (52.5%)) had a high TC/HDL-C ratio.

Demographic characteristics of the study participants

A total of 377 participants were analyzed in the study, with a median age of 44 (IQR: 30–59) years. The study predominantly comprised women, constituting 56.2% of the study population. Married (57.3%) and single (27.9%) participants were identified with regard to marital status; 14.9% of the participants were separated. Overall, 40.1% of the participants had tertiary education, 19.9% secondary education, 18.0% primary education, and 22.0% had no formal education. A significant proportion (57.3%) of the participants resided in urban areas, whereas 42.7% were from rural regions. Religious affiliation was diverse, with Protestants forming the largest group (36.6%), followed by Catholics

(29.7%), other religious groups (25.2%), and Muslims (8.5%). Employment status indicated that a majority of the participants (84.1%) were employed, whereas 15.9% were unemployed, as shown in Table 1.

Clinical characteristics of the participants

The majority of the participants were non-smokers (88.1%) and had a history of alcohol consumption (62.1%). Most participants reported low fruit and vegetable intake, with 97.3% consuming fewer than five servings per day. Only 16.4% had been diagnosed with hypertension, while 19.9% were at high risk of OSA. Sleep duration varied, with most participants (66.6%) reporting 6–7 h of sleep per night. Family history data revealed that 24.4% of the participants had a history of diabetes, 16.7% had a history of hypertension, and 16.4% had a history of kidney disease. Histories of CVD (2.4%) and dyslipidemia (4.2%) were less common. The majority had been on ART for more than 5 years (69.5%), with a similar proportion on DTG-based ART for more than 2 years (70.3%). The median values for the anthropometric and biochemical markers were as follows: BMI, 22.72 kg/m^2; MUAC, 28 cm; and TC level, 168 mg/dL; with liver enzymes remaining within normal limits.

MetS and its components and biomarkers

MetS was identified in 35.3% of the participants, indicating a notable prevalence within the cohort. Among its components, elevated TG level was the most common abnormality, affecting 70.3% of the participants. Low HDL levels were observed in 48.0%, while high BP was noted in 61.5% of the participants, further underscoring the metabolic risks within this population. Central obesity, defined by a high WC, was found in 26.3%, and elevated FPG level was detected in 14.6% of the participants. These findings reflect a clustering of cardiovascular and metabolic risk factors. Biomarker evaluation showed a median TC level of 168 mg/dL and a TC/HDL-C ratio of 3.36, with 15.6% of the participants exhibiting a high TC/HDL-C ratio (>5), a marker of atherogenic risk. Liver function markers (AST, ALT, ALP, and GGT) were largely within normal limits, with an AST/ALT ratio median of 0.90, suggesting no overt hepatic dysfunction. Electrolyte balance was maintained, with the median sodium, potassium, and chloride levels within physiological ranges.

Association of high TC/HDL-C ratio with MetS

The median TC/HDL-C ratio was significantly higher in individuals with MetS (3.92, IQR: 3.15–4.87) than in those without (2.96, IQR: 2.29–3.87; $p < 0.001$). Additionally, the prevalence of MetS differed significantly by TC/HDL-C status ($p = 0.003$); more than half (31/59 (52.5%)) of the individuals with a high TC/HDL-C ratio had MetS, compared with only 102/318 (32.1%) individuals showing MetS among those with a low TC/HDL-C ratio (Table 2).

At the bivariate level (Table 3), participants with a high TC/HDL-C ratio were more likely to have MetS (cOR: 2.34, 95% CI: 1.34–4.12, $p = 0.003$) compared with those with a low TC/HDL-C ratio. Several other factors were also significantly associated with MetS at this level. Female sex was associated with higher odds of MetS than male sex (cOR: 2.44, 95% CI: 1.56–3.82, $p < 0.001$). Advancing age showed a positive association with MetS (cOR: 1.03, 95% CI: 1.01–1.04, $p < 0.001$). Those with a BMI of 25–29 kg/m^2 (cOR: 1.72, $p = 0.033$) and $\geq$30 kg/m^2 (cOR: 4.52, $p < 0.001$) were more likely to have MetS than those with a BMI of <25 kg/m^2. Ever smoking (cOR: 1.90, $p = 0.044$),

Table 1. Characteristics of the study participants.

Variables	Total ($N = 377$), frequency (%)
Sociodemographic characteristics	
Age in years, median (IQR)	44 (30–59)
Sex	
Male	165 (43.8%)
Female	212 (56.2%)
Marital status	
Single	105 (27.9%)
Married	216 (57.3%)
Separated	56 (14.9%)
Educational level	
No education	83 (22.0%)
Primary	68 (18.0%)
Secondary	75 (19.9%)
Tertiary	151 (40.1%)
Residence	
Urban	216 (57.3%)
Rural	161 (42.7%)
Religion	
Catholic	112 (29.7%)
Protestant	138 (36.6%)
Muslim	32 (8.5%)
Others	95 (25.2%)
Employment status	
Unemployed	60 (15.9%)
Employed	317 (84.1%)
MetS and its components	
MetS	
Absent	244 (64.7%)
Present	133 (35.3%)
High fasting plasma glucose	
Absent ($<$110 mg/dL)	322 (85.4%)
Present ($\geq$110 mg/dL)	55 (14.6%)
Central obesity (high waist circumference)	
Absent ($<$88 cm for females and $<$102 cm for males)	278 (73.7%)
Present ($\geq$88 cm for females and $\geq$102 cm for males)	99 (26.3%)
Elevated triglycerides	
Absent ($<$150 mg/dL)	112 (29.7%)
Present ($\geq$150 mg/dL)	265 (70.3%)
Low high-density lipoprotein levels	
Absent ($\geq$50 mg/dL for females and $\geq$40 mg/dL for males)	196 (52.0%)
Present ($<$50 mg/dL for females and $<$40 mg/dL for males)	181 (48.0%)
High blood pressure (SBP $\geq$ 130 mmHg and DBP $\geq$ 85 mmHg)	
Absent	145 (38.5%)
Present	232 (61.5%)

(continued)

Table 1. Continued.

Variables	Total ($N = 377$), frequency (%)
Clinical characteristics and biomarkers	
Smoking	
Nonsmoker	332 (88.1%)
Ever smoked	45 (11.9%)
Alcohol status	
Never consumed	143 (37.9%)
Ever consumed	234 (62.1%)
Diagnosed hypertension	
No	315 (83.6%)
Yes	62 (16.4%)
Vegetable and fruit intake	
$<$5 servings per day	367 (97.3%)
$\geq$5 servings per day	10 (2.7%)
Global PSQL score, median (IQR)	4 (2–6)
OSA	
Low risk of OSA	302 (80.1%)
High risk of OSA	75 (19.9%)
Sleep duration	
$>$7 h	72 (19.1%)
6–7 h	251 (66.6%)
5–6 h	38 (10.1%)
$<$5 h	16 (4.2%)
Family history of hypertension	
No	314 (83.3%)
Yes	63 (16.7%)
Family history of diabetes mellitus	
No	285 (75.6%)
Yes	92 (24.4%)
Family history of CVD	
No	368 (97.6%)
Yes	9 (2.4%)
Family history of dyslipidemia	
No	361 (95.8%)
Yes	16 (4.2%)
Family history of kidney disease	
No	315 (83.6%)
Yes	62 (16.4%)
ART duration	
$\leq$5 years	115 (30.5%)
$>$5 years	262 (69.5%)
DTG-based ART duration	
$\leq$2 years	112 (29.7%)
$>$2 years	265 (70.3%)
MUAC (cm)	28 (27–29)
BMI (kg/m^2)	22.72 (20.32–25.86)

(continued)

Table 1. Continued.

Variables	Total ($N = 377$), frequency (%)
Total cholesterol (mg/dL), median (IQR)	168 (144–208.8)
AST (IU/L), median (IQR)	21 (15–30)
ALT (IU/L), median (IQR)	23 (17–31)
AST/ALT ratio, median (IQR)	0.90 (0.66–1.28)
ALP (IU/L), median (IQR)	101 (82–119)
GGT (IU/L), median (IQR)	19 (13–29)
Na^{+} (mmol/L), median (IQR)	137.8 (135.40–141)
K^{+} (mmol/L), median (IQR)	4.03 (3.81–4.41)
Cl^{-} (mmol/L), median (IQR)	99.40 (97.30–102.7)
TC/HDL-C ratio, median (IQR)	3.36 (2.55–4.34)
TC/HDL-C ratio	
Low (<5)	318 (84.4%)
High (≥5)	59 (15.6%)

This table presents the sociodemographic, MetS and it is components, and clinical characteristics of the study participants, including age, sex, marital status, educational level, residence, religion, and employment status. Data are expressed as median (IQR) for continuous variables and as frequencies (percentages) for categorical variables.
ALT: alanine aminotransferase; ALP: alkaline phosphatase; ART: antiretroviral therapy; AST: aspartate aminotransferase; BMI: body mass index; Cl^{-}: chloride ion; DBP: diastolic blood pressure; DTG: dolutegravir; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; K^{+}: potassium ion; MUAC: mid-upper arm circumference; Na^{+}: sodium ion; N: number of participants; OSA: obstructive sleep apnea; PSQI: Pittsburgh sleep quality index; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; MetS; metabolic syndrome.

Table 2. Distribution of MetS by TC/HDL-C status.

Variable	Total 377	MetS Absent ($N = 244$)	MetS Present ($N = 133$)	p value
TC/HDL-C ratio: median (IQR)	3.36 (2.55–4.34)	2.96 (2.29–3.87)	3.92 (3.15–4.87)	**<0.001**
TC/HDL-C ratio				**0.003**
Low (<5)	318 (84.4%)	216 (67.9%)	102 (32.1%)	
High (≥5)	59 (15.6%)	28 (47.5%)	31 (52.5%)	

This table presents the distribution of MetS across participants with low and high TC/HDL-C ratios. Results are stratified by MetS presence, with medians (IQR) and frequency distributions reported. Statistical significance (indicated by bold values) is determined using appropriate tests at $p < 0.05$.
HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; N: number of participants; TC: total cholesterol; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; MetS; metabolic syndrome.

high MUAC (cOR: 1.17, $p < 0.001$), high risk of OSA (cOR: 2.24, $p = 0.002$), family history of hypertension (cOR: 2.18, $p = 0.005$), duration of DTG-based ART >2 years (cOR: 2.24, $p = 0.002$), and lower AST levels (cOR: 0.97, $p = 0.013$) were also significantly associated with MetS.

After adjustment for confounding variables, a high TC/HDL-C ratio was significantly associated with MetS, with an aOR

Table 3. Association between high TC/HDL-C ratio and MetS.

Variable	Bivariate analysis		Multivariate analysis	
	cOR (95% CI)	p value	aOR (95% CI)	p value
TC/HDL-C ratio				
Low (<5)	1.00		1.00	
High (≥5)	**2.34 (1.34–4.12)**	**0.003**	**2.06 (1.08–3.91)**	**0.028**
Age (years)	**1.03 (1.01–1.04)**	**<0.001**	1.01 (0.99–1.03)	0.161
Sex				
Male	1.00		1.00	
Female	**2.44 (1.56–3.82)**	**<0.001**	**3.18 (1.83–5.55)**	**<0.001**
Educational level				
No education	1.00			
Primary	0.72 (0.38–1.37)	0.314		
Secondary	0.61 (0.32–1.15)	0.128		
Tertiary	**0.32 (0.18–0.57)**	**<0.001**		
Residence				
Urban	1.00			
Rural	1.16 (0.76–1.78)	0.486		
Religion				
Catholic	1.00			
Protestant	1.06 (0.63–1.79)	0.817		
Muslim	1.46 (0.65–3.24)	0.357		
Others	0.86 (0.48–1.55)	0.622		
Employment status				
Unemployed	1.00			
Employed	0.72 (0.41–1.27)	0.260		
BMI				
<25 kg/m^2	1.00		1.00	
25–29 kg/m^2	**1.72 (1.05–2.84)**	**0.033**	1.07 (0.59–1.93)	0.830
≥30 kg/m^2	**4.52 (2.01–10.16)**	**<0.001**	1.51 (0.49–4.66)	0.470
Smoking				
Nonsmoker	1.00		1.00	
Ever smoked	**1.90 (1.02–3.57)**	**0.044**	**2.85 (1.35–6.02)**	**0.006**
Alcohol status				
Never consumed	1.00		1.00	
Ever consumed	0.69 (0.45–1.07)	0.094	0.66 (0.40–1.08)	0.100
MUAC (cm)	**1.17 (1.09–1.25)**	**<0.001**	1.09 (0.99–1.20)	0.078
Vegetable and fruit intake				
<5 servings per day	1.00			
≥5 servings per day	0.45 (0.09–2.15)	0.318		
Number of days per week of vegetable and fruit intake				
≤4	1.00			
>4	2.16 (0.79–5.93)	0.134		
Poor sleep quality (global PSQI score)				
Good quality (≤5)	1.00		1.00	
Poor quality (>5)	1.19 (0.74–1.91)	0.465	0.68 (0.36–1.27)	0.227

(continued)

Table 3. Continued.

Variable	Bivariate analysis		Multivariate analysis	
	cOR (95% CI)	p value	aOR (95% CI)	p value
OSA				
Low risk of OSA	1.00		1.00	
High risk of OSA	**2.24 (1.34–3.74)**	**0.002**	1.70 (0.78–3.74)	0.184
Sleep duration (h)				
>7	1.00		1.00	
6–7	0.86 (0.50–1.48)	0.594		
5–6	0.49 (0.20–1.18)	0.112		
<5	1.22 (0.41–3.66)	0.720		
Family history of hypertension				
No	1.00		1.00	
Yes	**2.18 (1.26–3.76)**	**0.005**	1.61 (0.77–3.38)	0.205
Family history of diabetes mellitus				
No	1.00		1.00	
Yes	1.32 (0.82–2.15)	0.255	0.82 (0.44–1.51)	0.519
Family history of cardiovascular diseases				
No	1.00			
Yes	3.80 (0.93–15.43)	0.062		
Family history of dyslipidemia				
No	1.00			
Yes	1.11 (0.39–3.11)	0.849		
Family history of kidney disease				
No	1.00			
Yes	1.01 (0.57–1.79)	0.970		
DTG-based ART duration				
≤2 years	1.00		1.00	
>2 years	**2.24 (1.36–3.70)**	**0.002**	1.30 (0.69–2.44)	0.412
Na^+ (mmol/L)	0.97 (0.94–1.01)	0.132	0.98 (0.94–1.02)	0.395
K^+ (mmol/L)	0.78 (0.54–1.13)	0.187	0.85 (0.55–1.31)	0.461
CL^- (mmol/L)	0.97 (0.93–1.00)	0.048	0.96 (0.92–1.01)	0.087
AST	**0.97 (0.95–0.99)**	**0.013**	0.97 (0.95–1.00)	0.070
ALT	1.00 (0.98–1.02)	0.920	1.01 (0.98–1.04)	0.435
ALP	1.00 (1.00–1.01)	0.521	1.00 (1.00–1.01)	0.385
GGT	1.00 (0.98–1.02)	0.873	1.00 (0.98–1.02)	0.719

Hosmer–Lemeshow test: $p = 0.6617$.
This table examines the association between a high TC/HDL-C ratio and MetS using bivariate and multivariate logistic regression analyses. Results are expressed as crude odds ratios (cOR) and adjusted odds ratios (aOR) with 95% confidence intervals (CIs). Key variables include demographic factors, clinical indicators, metabolic markers, and sleep quality. Statistical significance (indicated by bold values) is determined at $p < 0.05$.
aOR: adjusted odds ratio; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BMI: body mass index; CI: confidence interval; cOR: crude odds ratio; DTG: dolutegravir; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; MUAC: mid-upper arm circumference; N: number of participants; OSA: obstructive sleep apnea; PSQI: Pittsburgh sleep quality index; TC: total cholesterol; TG: triglyceride.

of 2.06 (95% CI: 1.08–3.91, $p = 0.028$) (Table 3). The TC/HDL-C ratio at an optimal cutoff of 3.30 demonstrated a significant predictive ability (AUC = 0.696, 95% CI: 0.642–0.750) to differentiate participants with MetS from those without MetS, with a sensitivity of 73% and specificity of 60% (Figure 1). Other important variables in the multivariate analysis that were associated with MetS included female sex (aOR: 3.18, 95% CI: 1.83–5.55, $p < 0.001$) and a history of smoking (aOR: 2.85, 95% CI: 1.35–6.02, $p = 0.006$).

Discussion

In this Ugandan cohort of PLWH, a higher TC/HDL-C ratio strongly indicated MetS. Patients with MetS had a significantly higher median TC/HDL-C ratio (3.92 vs. 2.96; $p < 0.001$), and over half (52.5%) of those with a "high" ratio (≥5) had MetS versus 32.1% with a low ratio. After adjusting for confounders, a high TC/HDL-C ratio was associated with a two-fold increase in MetS risk (aOR = 2.06, $p = 0.028$). These findings are clinically meaningful—a raised TC/HDL-C ratio is a known atherogenic indicator. In the context of HIV, it may identify patients with multiple metabolic derangements. For example, van Rooyen et al.[33] found that among PLWH in Africa, a TC/HDL-C ratio ≥5.4 identified individuals at greater cardiovascular risk. Our results suggest that even at modest elevations (optimal cutoff = 3.30, AUC = 0.696), the ratio significantly distinguishes patients with MetS (sensitivity: 73%, specificity: 60%). In practice, routinely calculating TC/HDL-C

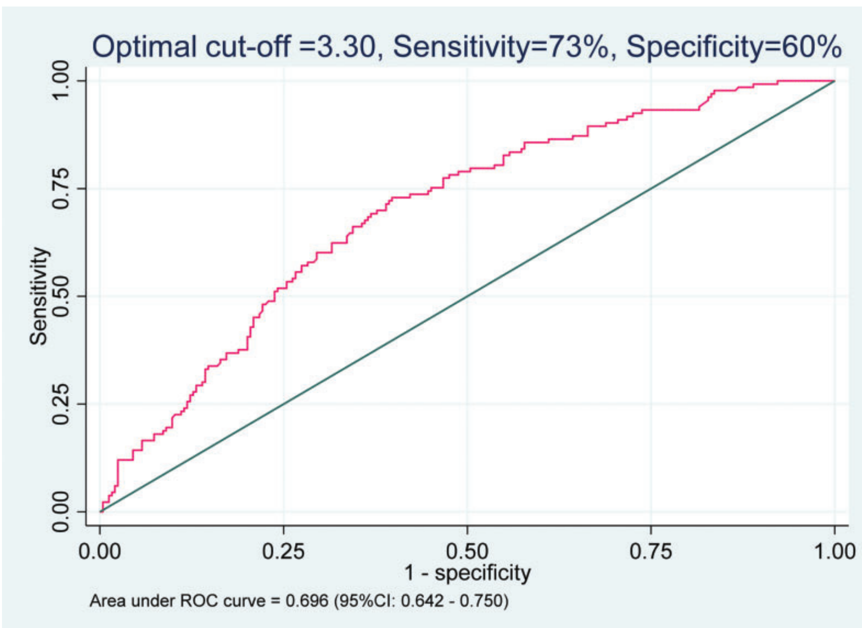


Figure 1. ROC curve showing the predictive performance of the TC/HDL-C ratio for MetS.
At an optimal cutoff point of 3.30, the TC/HDL-C ratio has a significant ability to discriminate PLWH on DTG-based ART with MetS from those without MetS with a sensitivity of 73% and specificity of 60%.
TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; MetS: metabolic syndrome; DTG: dolutegravir; ART: antiretroviral therapy.

ratios during HIV care could help identify patients who require early lifestyle or pharmacologic interventions to forestall diabetes, hypertension, and CVD.

Biologically, the TC/HDL-C ratio captures the dyslipidemia underlying MetS. A high ratio reflects both excess TC (often from high LDL or TG-rich lipoproteins) and low HDL-C levels. Reduced HDL-C level is a core feature of MetS and insulin resistance, impairing reverse cholesterol transport and promoting endothelial dysfunction. Insulin resistance itself drives an atherogenic lipid profile (elevated very-low-density lipoprotein (VLDL)-TG and small dense LDL levels and suppressed HDL level).[16] Indeed, population studies show that the TC/HDL-C ratio is independently associated with insulin resistance and multiple MetS components.[16] In a large Japanese community sample, both TG/HDL-C and TC/HDL-C ratios were closely associated with the number of MetS features and homeostatic model assessment of insulin resistance (HOMA-IR).[16] Thus, the TC/HDL-C ratio likely serves as an integrated marker of the underlying pathophysiology, combining excess atherogenic lipoproteins with deficient protective HDL that promotes MetS.

Our findings not only align in part with prior literature but also highlight differences. Fernández-Aparicio et al.[34] performed a cross-sectional study of 981 Spanish adolescents and showed that the TC/HDL ratio robustly discriminated MetS (ROC AUC $>$ 0.83) in both sexes. Similarly, Zhang et al.[35] conducted a population-based study of 1669 Chinese adults and reported a significant association between the TC/HDL-C ratio and insulin resistance, a core MetS component. More recently, Babaahmadi-Rezaei et al.[36] analyzed 9809 Iranian adults and found significantly higher TC/HDL ratios among MetS cases; their ROC analysis yielded AUCs of 0.676 (95% CI: 0.661–0.690) in men and 0.743 (95% CI: 0.732–0.754) in women. Additional Iranian studies have consistently identified the TC/HDL-C ratio as a key diagnostic marker for MetS.[37,38] In Korea, the TC/HDL-C ratio showed a strong predictive value for MetS,[39] whereas the U.S. data associated an elevated TC/HDL-C ratio with peripheral artery disease,[40] further highlighting its cardiometabolic relevance. However, Rezapour et al.[38] reported that although the TC/HDL-C ratio had a high AUC (0.79), the TG/HDL-C ratio (AUC = 0.85) was a stronger predictor of MetS, a finding echoed by Saeedi et al.,[14] who showed that the TG/HDL-C ratio outperformed the TC/HDL-C ratio in an elderly Iranian cohort. These studies concluded that the TG/HDL-C ratio was superior to the TC/HDL-C ratio, in contrast to our emphasis on TC/HDL-C. Possible reasons include insufficient sample size and population differences; our PLWH on ART may exhibit greater perturbation of TC relative to TG or differences in age and comorbidities. Although our AUC estimate of 0.696 (95% CI: 0.642–0.750) did not reach the conventional threshold for strong discrimination, the CI excludes the null value of 0.5, indicating statistically significant discriminatory ability of the TC/HDL-C ratio for MetS beyond chance. This suboptimal predictive estimate with lower sensitivity may have been limited by the relatively small sample size and nonrepresentative sample in our study. van Rooyen et al,[33] who analyzed 140 black South Africans with HIV infection, identified a TC/HDL-C ratio $\geq$5.4 as a marker of cardiovascular risk, a threshold higher than ours, suggesting differing lipid norms due to ART or diet. Although Muyanja et al.[41] reported a high MetS prevalence in Ugandans on ART, the TC/HDL-C ratio was not specifically assessed. Overall, our findings support the TC/HDL-C ratio as a relevant MetS marker in HIV-infected populations, whereas discrepancies with non-HIV cohorts emphasizing the TG/HDL-C ratio may be attributed to variations in demographic characteristics, comorbid conditions, and lipid metabolism.

Importantly, our study provides new insights into cardiometabolic risk in sub-Saharan Africa. It is among the first studies to identify the TC/HDL-C ratio as a predictor of MetS in an HIV-infected Ugandan cohort, filling a research gap. Most African HIV-infected cohorts focus on individual lipids or classic MetS criteria, rarely assessing composite lipid indices. By demonstrating that even a moderately elevated TC/HDL-C ratio (cutoff = 3.30) doubles the risk of MetS, we provide evidence that this simple measure could improve early risk detection in HIV care. In our resource-limited setting, the TC/HDL-C ratio readily computed from standard lipid panels could serve as an affordable screening tool for MetS, prompting targeted counseling or lipid-lowering interventions. Thus, our findings contribute to global knowledge by extending it to a high-HIV-burden, resource-constrained environment and underscore the need to employ cardiometabolic screening strategies, such as using the TC/HDL-C ratio, in the local patient population.

Recommendations

We recommend integrating routine TC/HDL-C ratio screening into HIV care protocols for individuals on DTG-based ART in Uganda. For healthcare providers, this can enhance the detection of MetS and associated cardiovascular risk early, enabling early intervention and individualized lifestyle modifications to foster improved health outcomes among this vulnerable group. Policymakers should consider updating national HIV treatment guidelines to include lipoprotein ratio monitoring and support capacity-building for lipid profiling within HIV clinics, ensuring sustainable implementation and improved long-term health outcomes for this high-risk population.

Limitations

There are some limitations in our study that must be kept in mind when interpreting the results. First, as a secondary analysis of a cross-sectional study, it provides only a snapshot of associations between the TC/HDL-C ratio and MetS, and we cannot establish causal directions or temporality of events easily. Additionally, some of the variables, including family history of hypertension, CVD, kidney disease, and diabetes mellitus, were reported by the participants themselves; therefore, there is a likelihood of incorrect information being provided. We also recognize the influence of unmeasured confounding factors, including lifestyle, other comorbid conditions, and medication use, which were not controlled for during analysis and can influence the observed associations. Even after controlling for established confounders, residual confounding could still exist. Finally, the generalizability of our results is restricted to PLWH on DTG-based ART, and the findings might not be relevant to other populations or to individuals on other ART regimens.

In light of the limitations identified in our study, we recommend several directions for future research to strengthen the understanding of the relationship of the TC/HDL-C ratio and other lipoprotein ratios with MetS among PLWH on DTG-based ART. First, longitudinal studies are essential to establish the temporal and causal relationships between an elevated TC/HDL-C ratio and the development of MetS, which helps address the inherent limitations of the cross-sectional design. Additionally, future research should incorporate objective clinical and biochemical assessments rather than self-reports for variables such as family history of chronic diseases to reduce the possibility of incorrect information. It is also critical to account for a broader range of potential confounding factors, including detailed information on lifestyle behaviors, concurrent comorbidities, and use of other medications, through comprehensive data collection and multivariable adjustment. Interventional studies may further explore whether targeted lipid-lowering or lifestyle interventions in patients with an elevated TC/HDL-C ratio can mitigate MetS risk. Finally, to enhance generalizability, future studies should include diverse HIV-positive populations across various ART regimens and geographic settings.

Conclusion

Our study demonstrates that a high TC/HDL-C ratio is strongly associated with MetS among PLWH on DTG-based ART in southwestern Uganda. This study highlights the potential utility of lipoprotein ratio profiling for the early identification of metabolic risk, enabling timely interventions to prevent cardiovascular complications in this vulnerable population.

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Author contributions

CNB, CN, and ES participated in conceptualization of the study. CNB performed data analysis and result interpretation. CNB, CN, ES, MJM, SO, FS, DN, RK, FS, BM, WA, DT, LOO, and SPR contributed to writing the first draft of the manuscript with CNB, ES, MJM, DT, and SPR providing critical revisions. All authors have read and approved the first draft of the manuscript.

Availability of data and materials

The datasets for this study have been submitted to the journal.

Consent for publication

All authors have consented to the publication of this work.

Declaration of conflicting interests

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