ISSN: 2714-4674 (Online)
ISSN: 2714-4666 (Print)

Annals of Clinical and Experimental Medicine

(ACEMedicine)

This Journal Is A Publication of

ASSOCIATION OF SPECIALIST MEDICAL DOCTORS IN ACADEMICS SOKOTO STATE CHAPTER

Volume 3, No. 1, January - June 2025

In this issue

www.acemedicine.asmeda.org

Serum IL-6 and hs-CRP as Biomarkers of Metabolic Syndrome in HIV Patients on HAART: A Prospective Cohort Study in Sokoto, Northwestern Nigeria.

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DOI:10.47838/acem.202531.2

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Abstract

Background: The highly active antiretroviral therapy (HAART) significantly improves the life expectancy and quality of life of HIV-infected patients but leads to cardiovascular complications and metabolic disorders. Therefore, we aim to determine the utility of IL-6 and high-sensitivity C-reactive protein (hs-CRP) as biomarkers for the development of metabolic syndrome (MetS) among HIV-positive treatment-naïve and HAART-experienced patients.

Materials and Methods: We employed a prospective cohort design to evaluate metabolic syndrome development in HAART-naive HIV patients. We enrolled eighty-six participants and followed them up for 24 months, with standardized assessments every six months of parameters including fasting glucose, lipid profiles, and inflammatory markers. MetS was defined using NCEP-ATP III and IDF criteria. To analyze these data, we used Spearman correlation to assess MetS component relationships and logistic regression to evaluate IL-6/hs-CRP predictive capacity.

Results: Metabolic correlations differed significantly between treatment-naive and HAART-exposed patients. Among treatment-naive patients with HIV, MetS correlated positively and significantly with triglycerides (TG; $p < 0.001$) and high-density lipoprotein cholesterol (HDL-C; $p < 0.001$), as well as positively but insignificantly with high-sensitivity C-reactive protein (hs-CRP; $p = 0.078$). In contrast, fasting blood glucose (FBS) and IL-6 showed a significant inverse relationship ($p<0.001$ versus $p = 0.012$). In HAART-exposed HIV patients, hs-CRP was correlated with metS positively and significantly and IL-6 negatively but non-significantly. However, longitudinal analysis at twelve and twenty-four months post-HAART revealed that only TG and HDL-c show the power to independently and significantly predict MetS.

Conclusion: IL-6 and hs-CRP failed to demonstrate predictive accuracy as biomarkers of MetS in HIV patients on HAART.

Key words: Serum Biomarker, hs-CRP, IL-6, MetS, and HAART.

Introduction

HIV-infected individuals face elevated cardiovascular disease risk through incompletely understood inflammatory mechanisms, despite availability of effective antiretroviral therapy (1). Inflammatory biomarkers, particularly IL-6 and high-sensitivity C-reactive protein (hs-CRP), offer potential for predicting clinical outcomes. IL-6 directly stimulates hepatic hs-CRP production, resulting in predictable, correlated increases in the levels of both markers (2).
CDC and AHA classify cardiovascular risk as low (hs-CRP<1.0 mg/L), intermediate (1.0-3.0 mg/L), or high (>3.0 mg/L). Although elevation in hs-CRP levels has been documented to increase cardiovascular disease risk in general populations (3), hs-CRP has not been fully validated yet as a predictive marker in HIV patients. Similarly, the comparative predictive value of IL-6 and hs-CRP for specific clinical outcomes requires clarification (4,5).

HIV patients typically exhibit decreased LDL-C and HDL-C levels, accompanied by elevated triglyceride concentrations (6). HAART therapy contributes to dyslipidaemia and metabolic complications in patients. Combination antiretroviral therapy improves life expectancy, but it also introduces long-term metabolic morbidities (7). We hypothesise that since inflammation underlies metabolic syndrome processes, pro-inflammatory factors, including IL-6 and hs-CRP, may be helpful as biomarker predictors of metS in HAART-exposed HIV patients. The current study is aimed at testing this hypothesis.

Materials and Methods

This is a prospective multicentre study design conducted at Sokoto metropolis, North-Western Nigeria. The centres comprise the Institute for Human Virology (IHVN) of Usmanu Danfodiyo University Teaching Hospital (UDUTH) and the Specialist Hospital Sokoto (SHS). The study aims to investigate IL-6 and hs-CRP biomarkers for predicting metabolic syndrome components in HIV/AIDS patients receiving HAART. The participants comprise 86 HIV seropositive HAART-naïve patients and 86 HIV-negative controls.

The sample size calculation was performed using the formula for a descriptive study with a finite population. n *f* = n/1+ (n/N) (7).
Where
n f = minimum required sample size adjusted for non-response and attrition.
n = minimum sample size required for population >10000, which is 76 (8).

N = population size required for the study. 960 (estimated from the monthly turnout of patients at the two centres)
n *f*= 76/1+ (76/960)
= 76/1+0.076
= 76/1.076 = 70.6 ~ 71
A 20% attrition factor was applied to account for patient loss during the 24-month follow-up period.
20x71/100= 14.2 ~ 15 subjects = 86.
71+15 = 86
Therefore, n = 86.
Baseline data were collected at recruitment, prior to the commencement of HAART. TLD HAART regimen (Lamivudine, Tenofovir, Dolutegravir) was administered, with a 24-month follow-up. Ethical approval for the research was secured from the institutional review boards of UDUTH (Ref. UDUTH/HREC/2019/No. 827) and SHS (Ref. SHS/SUB/33/Vol. 1) ethics committees. A written informed consent was obtained from each of the participants prior to enrollment. HAART-naïve HIV seropositive patients constituted the eligible study population. Consenting HIV-positive patients receiving care at IHVN UDUTH and SHS comprised the inclusion criteria. The exclusion criteria include current HAART therapy, external care provision, smoking, alcohol consumption, urinary tract infections, chronic liver disease history, tuberculosis, herpes zoster infection, and pediatric patients. Inflammatory biomarker analysis was performed, including hs-CRP via Accubind ELISA and IL-6 via PARS Biochem ELISA kits. hs-CRP quantification was performed using a Rayto 2100 microplate reader C (11). Serum IL-6 levels were estimated using a semi-automated sandwich ELISA methodology (11). Metabolic parameter analysis of glucose and lipids was conducted via Mindary BA88a semi-automated analyser with Randox reagents. Glucose concentration was quantified using the glucose oxidase method (Trinder) (12), and triglyceride concentration was determined via the Trinder methodology (13). HDL-cholesterol was quantified via the method of Burstein (14).

Statistical Analysis

Data was entered into an Excel spreadsheet and statistically analysed via SPSS IBM version 23. The NCEP ATP III and IDF classification criteria were employed for the classification of metabolic syndrome components. Associations between the inflammatory markers (IL-6 and hs-CRP) and MetS were examined using Spearman correlation, while the predictive power of the markers was assessed using linear regression modelling. Inflammatory marker predictive power assessment through linear regression and logistic regression modelling. The statistical significance threshold was set at $p<0.05$.

Results

One hundred and seventy-two (172) subjects (97 females (56.4%) and 75 males (43.6%)), comprising 86 HIV-positive HAART-naïve patients and 86 HIV-negative controls, participated in the study. HIV-positive subjects began HAART following baseline data collection, with a 24-month follow-up. Repeated measurements included clinical anthropometry, blood pressure, fasting serum glucose, lipid profile, inflammatory markers (IL-6, hs-CRP), and urine creatinine and microalbumin.

Socio-demographic characteristics of the study subjects revealed a female predominance in the patient group (47 females vs 39 males) but a male predominance in the control group (59 males vs 27 females) (Table 1). The participants are predominantly married (44.8%), followed by those who are single (40.7%), with the divorced (10.5%) and the widowed (4.1%) comprising the remainder. Hausa represents the predominant ethnicity, with 141 subjects (82%), followed by Yoruba (11, 6.4%) and Igbo (8, 4.7%) as secondary groups. Only 12 subjects (14%) represent the other tribes. Islam is the predominant religious affiliation for the participants. Educationally, tertiary education was the most common among the participants, with 81 subjects (47.1%), followed by non-formal education with 49 subjects (28.5%), secondary education with 27 subjects (31.4%), and primary education with 15 subjects (17.4%). Trading is the primary occupation, followed by business and unemployment.

Table 1: Socio-demographic characteristics of the study subjects

Categories	Cases (%)	Controls (%)
N	86	86
Sex		
Males	39(45.4%)	59(68.6%)
Females	47(54.7%)	27(31.4%)
Marital Status		
Single	20(23.3%)	50(58.1%)
Married	43(50%)	34(39.5%)
Widow	7(8.1%)	0(0%)
Divorce	16(18.6%)	2(2.3%)
Tribes		
Hausa	71(82.6%)	70(81.4%)
Yoruba	6(7.0%)	5(5.8%)
Igbo	5(5.8%)	3(3.5%)
Others	4(4.7%)	8(9.3%)
Religion		
Islam	68(79.1%)	66(76.7%)
Christianity	18(20.9%)	20(23.3%)
Educational level		
NF	43(50%)	6(7.0%)
Primary	13(15.1%)	2(2.3%)
Secondary	17(19.8%)	10(11.6%)
Tertiary	13(15.1%)	68(79.1%)
Occupation		
Trader	22(25.6%)	2(2.3%)
Business	15(17.4%)	4(4.7%)
Un employed	9(10.5)	0(0%)
Carpenter	1(1.2%)	0(0%)
Mechanics	2(2.3%)	0(0%)
Tailors	3(3.5%)	0(0%)
Food vendors	2(2.3%)	0(0%)
Drivers	1(1.2%)	0(0%)
Civil servant	78.1%)	37(43.0%)
Butchers	1(1.2%)	0(0%)
Farmers	7(8.1%)	0(0%)
House wives	11(12.8)	1(1.2%)
Students	4(4.7%)	40(46.5%)
Okada	1(1.2%)	0(0%)
Retire	0(0%)	1(1.2%)
Copper	0(0%)	1(1.2%)

Data are frequencies (%)

The prevalence of metabolic syndrome (MetS) shows a rapid increase during the initial six months of treatment (Table 2). MetS components showed a progressive increase with treatment duration, despite effective viral suppression being achieved by the treatment regimens. Reduced HDL cholesterol is the most prevalent component across diagnostic criteria, with elevated triglycerides being the second most common, and its prevalence declines over extended treatment periods. Elevated fasting blood glucose and blood pressure levels showed a higher frequency during the initial twelve months, subsequently declining.

Table 2: Prevalence of components of metabolic syndrome over 24 months periods

Parameters	Controls	Baseline	6 months	12 months	18 months	24 months
	Overall	MetS by	Gender			
MetS (%)	16 (18.6%)	15(17.4%)	55(65.5%)	38(45.3%)	39(46.4%)	51(60.7%)
Male	5 (5.8%)	23(26.7%)	23(27.4%)	15(17.9%)	15(17.9%)	22(26.2%)
Female	11 (12.8%)	32(37.2%)	32(38.1%)	34(40.5%)	24(28.6%)	29(34.5%)
		NCEP-ATP	III	Criteria		
MetS	9(10.5%)	14(16.3%)	44(52.4%)	49(58.3%)	27(32.1%)	38(45.2%)
↑WC	9(10.5%)	7(8.1%)	9(10.7%)	7(8.3%)	9(10.7%)	9(10.7%)
↓HDL	41(47.7%)	62(72.1%)	54(62.3%)	36(42.9%)	27(32.1%)	41(48.8%)
↑TG	73(84.9%)	86(100%)	41(48.8%)	75(89.3%)	79(94.1%)	82(97.6%)
↑FBG	8(9.3%)	5(5.8%)	52(61.9%)	51(60.7%)	32(38.1%)	44(52.4%)
↑SBP	12(14%)	16(18.6%)	49(58.3%)	49(58.3%)	47(56.0%)	12(14.3%)
↑DBP	14(16.3%)	18(20.9%)	36(42.9%)	36(42.9%)	38(45.2%)	14(16.7%)
		IDF	Criteria			
MetS	12(13.9%)	11(12.8%)	18(21.4%)	20(23.8%)	17(20.2%)	23(27.4%)
↑WC	18(20.9%)	11(12.8%)	23(27.4%)	20(23.8%)	22(26.2%)	18((21.4%)
↓HDL	41(47.7%)	62(72, 1%)	54(64.3%)	36(42.9%)	27(32.1%)	41(48.1%)
↑TG	73(84.9%)	86(100%)	41(48.8%)	75(89.3%)	79(94.1%)	82(97.6%)
↑FBG	11(12.8%)	5(5.8%)	53(63.1%)	51(60.7%)	32(38.1%)	44(52.4%)
↑SBP	121(3.9%)	16(18.6%)	49(58.3%)	49(58.3%)	47(55.9%)	12(13.1%)
↑DBP	14(16.3%)	18(20.9%)	36(42.9%)	36(42.9%)	38(45.2%)	14(16.7%)

MetS metabolic syndrome, WC waist circumference, HDL high density lipoprotein, TG triglycerides, FBG fasting blood glucose, SBP systolic blood pressure, DBP diastolic blood pressure. ↑increased value is diagnostic, ↓ decreased value is diagnostic.

Correlation analysis between MetS development and cardiovascular risk factors revealed distinct patterns across biomarker categories (Table 3). Significant positive correlations with MetS emerged for triglycerides (p=0.0001), HDL-C (p=0.0001), and inflammatory marker hs-CRP (p=0.010). Conversely, negative correlations characterized anthropometric and clinical parameters: BMI, WHR, SBP, DBP, disease duration (DOD), and drug duration (DODR). IL-6 and while urine microalbumin (UMALB) showed a marginally non-significant negative correlation (p = 0.055) with MetS development and non-significant positive correlation, respectively.

Table 3: The correlation of IL-6, hs-CRP, gender, BMI, and other risk factors of cardiovascular disease with the development of MetS among HIV-positive HAART-exposed patients

Parameters	R	p value
hs-CRP (µg/ml)	0.125	0.010*
IL-6 (ng/ml)	-0.093	0.055
TG (mmol/l)	0.189	0.0001**
HDL-c (mmol/l)	0.236	0.0001**
FBG (mmol/l)	-0.291	0.0001**
UMALB (µg/min)	0.059	0.226
BMI (kg/m^2)	-0.289	0.0001**
WHR (cm)	-0.179	0.0001**
SBP (mmHg)	-0.425	0.0001**
DBP (mmHg)	-0.468	0.0001**
DOD (years)	-0.108	0.026*
DODR (years)	-0.119	0.014*

hs-CRP, High sensitivity CRP; IL-6, Interleukin-6; TG, Triglycerides; HDL-C, High density lipoproteins; FBG, Fasting blood glucose; UMALB, Urine micro-albumin; BMI, body mass index; WHR, Waist to hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CLIN. SYN, Clinical symptoms; R.F MetS, Risk factors of metabolic syndrome; DOD, Duration of disease; DODR, Duration of drugs(** p < 0.0001, * p<0.05) statistics by spearman's correlation.

Association analysis, presented in Table 4, examined MetS relationships with inflammatory markers (IL-6, hs-CRP) and lipid profile parameters to inform MetS prediction modeling. hs-CRP, triglycerides, and HDL-C demonstrated Significant positive correlations with MetS development. Conversely, IL-6 and FBG showed Significant negative associations with MetS and total cholesterol, LDL-C, urine microalbumin, and albumin-creatinine ratio exhibited non-significant correlation.

Table 4: Pearson correlation coefficient showing the association of MetS with IL-6, hs-CRP, and lipid parameters among HAART Naïve patients.

Parameter	R	p value
hs-CRP (µg/ml)	0.117	0.008*
IL-6 (ng/ml)	-0.085	0.042*
TC (mmol/l)	0.007	0.442
TG (mmol/l)	0.148	0.001*
HDL-C (mmol/l)	0.218	0.0001**
LDL-C (mmol/l)	-0.078	0.055
FBG (mmol/l)	-0.272	0.0001**
UMALB (µg/min)	0.074	0.064
ACR (mg %)	0.076	0.061

hs-CRP, High sensitivity CRP, IL-6, Interleukin-6, TC, Total cholesterol, TG, Triglyceride, HDL-C, High density lipoprotein cholesterol, LDL-C, Low density lipoprotein cholesterol, FBG, Fasting blood glucose, UMALB, Urine micro albumin, ACR, Albumin creatinine ratio.(** p<0.001; * p<0.05). Statistic by linear Regression model enter method.

Comparative regression analysis (Table 5) examined lipid parameters compared to inflammatory markers (hs-CRP, IL-6) as predictors of MetS within the HIV-positive HAART-naïve population. Lipid parameters demonstrated superior predictive performance for MetS (p = 0.0001) compared to IL-6 (p = 0.012) and hs-CRP (p = 0.078) in this population. Fasting blood glucose similarly showed superior predictive power (p = 0.0001, 95% CI: -0.101 to -0.041) compared to IL-6 (p = 0.012, 95% CI: -0.004 to 0.001) and hs-CRP (p = 0.078, 95% CI: 0.000 to 0.008). Conversely, urine microalbumin (p = 0.337) and albumin creatinine ratio (p = 0.613) demonstrated no significant predictive value.

Table 5: The coefficient of regression model and 95% CI with co-linearity statistics in the prediction of MetS among HIV HAART-naïve patients.

Model	B	SE	Beta	t	p value	95% CI for B
MetS	1.837	0.131		14.265	0.0001**	1.615- 2.131
hs-CRP (µg/ml)	0.004	0.002	0.081	1.768	0.078	0.000- 0.008
IL-6 (ng/ml)	-0.002	0.001	-0.129	-2.532	0.012*	-0.004- -0.001
TC (mmol/l)	-0.315	0.067	-0.787	-4.695	0.0001**	-0.447- -0.183
TG (mmol/l)	0.125	0.032	0.212	3.855	0.0001**	0.061- 0.189
HDL-c (mmol/l)	0.525	0.078	0.600	6.754	0.0001**	0.373- 0.679
LDL-c (mmol/l)	0.291	0.068	0.633	4.302	0.0001**	0.158- 0.424
FBG (mmol/l)	-0.071	0.015	-0.220	-4.685	0.0001**	-0.101- -0.041
UMALB (µg/min)	0.001	0.001	0.045	0.961	0.337	-0.001- -0.004
ACR (mg %)	-0.045	0.089	-0.032	-0.506	0.613	-0.221- 0.130

B, Regression coefficient; SE, standard error; hs-CRP, High sensitivity CRP, IL-6, Interleukin-6, TC, Total cholesterol, TG, Triglyceride, HDL-C, High density lipoprotein cholesterol, LDL-C, Low density lipoprotein cholesterol, FBG, Fasting blood glucose, UMALB, Urine micro albumin, ACR, Albumin creatinine ratio.(* p<0.05, ** p<0.01) Statistic by linear Regression model enter method.

Table 6 presents the logistic regression model for MetS prediction among HAART-naïve patients, demonstrating overall statistical significance ($p < 0.0001$) for predicting MetS components at baseline. Among all clinical parameters, BMI emerged as the sole significant predictor (OR = 37.909, 95% CI: 1.874-767.060, $p = 0.018$), while all other clinical parameters lacked statistically significant predictive power. Specifically, inflammatory markers hs-CRP ($p = 0.996$, 95% CI: 0.152-6.655) and IL-6 ($p = 0.170$, 95% CI: 0.679-8.954) demonstrated weak predictive power. Similarly, traditional metabolic parameters (triglycerides, HDL, and fasting glucose) showed no significant predictive power.

Table 6: The odds and adjusted odds ratio for clinical and laboratory components and some risk factors' power in prediction of MetS among HAART-naïve patients.

Parameters	Odds Ratio	Adj. Odds ratio Exp. (B)	p value	95% CI for Exp(B)
Model	1.555	4.733	0.000	
Age (years)	-0.181	0.834	0.890	0.064- 10.939
BMI (kg/m^2)	3.635	37.909	0.018*	1.874- 767.060
WC (cm)	22.592	64769	0.999	0.000-
WHR (cm)	1.492	4.446	0.239	0.371- 53.227
SBP (mmHg)	1.870	6.489	0.136	0.556- 75.698
DBP (mmHg)	0.167	1.182	0.897	0.094- 14.826
hs-CRP (µg/ml)	0.005	1.005	0.996	0.152- 6.6547
IL-69 (ng/ml)	0.903	2.466	0.170	0.679- 8.954
TG (mmol/l)	-0.254	0.776	0.676	0.236- 2.555
HDL-c (mmol/l)	-1.566	0.209	0.154	0.024- 1.801
FBG (mmol/l)	1.251	3.372	0.217	0.491- 23.177

BMI, Body mass index, WC, Waist circumference, WHR, Waist to hip ratio, SBP, Systolic blood pressure, DBP, Diastolic blood Pressure, hs-CRP, High sensitivity CRP, IL-6, Interleukin-6, TG, Triglycerides, HDL-C, High density lipoprotein cholesterol, FBG, Fasting blood glucose. Statistics by Logistic regression model.

Table 7 presents odds ratios and 95% confidence intervals for MetS components at twelve months. Clinical parameters synergistically predicted MetS within 12 months post-HAART (odds ratio 0.596, Exp (B) 1.767, $p < 0.013$). However, no individual clinical parameter independently predicted the presence of MetS. Among specific biomarkers, triglycerides and high-density lipoproteins showed strong predictive power for MetS ($p = 0.018$ and 0.002; adjusted odds ratios 0.065 and 0.138; 95% CI: 0.007-0.630 and 0.040-0.474, respectively). In contrast, inflammatory markers (hs-CRP and IL-6) demonstrated weak predictive power.

Table 7: The odds and adjusted odds ratio for clinical and laboratory components and some risk factors power in prediction of MetS at twelve months post-HAART.

Parameters	Odds Ratio	Adj. Odds ratio Exp. (B)	P value	95% CI for Exp.(B)
Model	0.569	1.767	0.013*	
Age (years)	0.623	1.864	0.586	0.199- 17.493
BMI (kg/m^2)	1.600	4.955	0.097	0.750- 32.726
WC (cm)	1.169	3.217	0.152	0.650- 15.932
WHR (cm)	0.351	1.420	0.562	0.434- 4.643
SBP (mmHg)	1.626	5.083	0.057	0.951- 27.164
DBP (mmHg)	0.998	2.712	0.158	0.680- 10.818
Model	0.474	1.607	0.049*	
hs-CRP (µg/ml)	-0.543	0.581	0.387	0.170- 1.988
IL-6 (ng/ml)	-0.332	0.717	0.699	0.133- 3.859
TG (mmol/l)	-2.736	0.065	0.018*	0.007- 0.630
HDL-c (mmol/l)	-1.981	0.138	0.002*	0.040- 0.474
FBG (mmol/l)	1.245	3.472	0.144	0.653- 18.461

BMI, Body mass index, WC, Waist circumference, WHR, Waist to hip ratio, SBP, Systolic blood pressure, DBP, Diastolic blood Pressure, hs-CRP, High sensitivity CRP, IL-6, Interleukin-6, TG, Triglycerides, HDL-C, High density lipoprotein cholesterol, FBG, Fasting blood glucose(*p< 0.05) Statistic by Logistic regression model.

Predictive analysis of MetS components at twenty-four months post-HAART (Table 8) examined odds ratios and 95% confidence intervals across multiple predictive models. The overall predictive model showed weak power for MetS (OR 0.425, 95% CI not

significant, p = 0.054). Combined clinical and anthropometric parameters, FBG and the inflammatory markers hs-CRP and IL-6 similarly lacked statistically significant predictive power. In contrast, triglycerides (p = 0.014, 95% CI 1.385-17.713) and HDL (p = 0.001, 95% CI 0.034-0.432) clinical parameters excluding waist circumference (OR 4.764, p = 0.017, 95% CI 1.322-17.166) independently predicted MetS with statistical significance.

Table 8: The odds and adjusted odds ratio for clinical and laboratory components and some risk factors power in prediction of MetS at twenty-four months post-HAART.

Parameters	Odds Ratio	Adj. Odds Exp. (B)	p value	95% CI for Exp. (B)
Model	0.425	1.529	0.054	
Age (years)	0.582	1.790	0.507	0.321-9.991
BMI (kg/m^2)	0.735	2.086	0.390	0.390-11.165
WC (cm)	1.561	4.764	0.017*	1.322-17.166
WHR (cm)	0.446	1.561	0.465	0.473-5.158
SBP (mmHg)	1.179	3.251	0.069	0.911-11.605
DBP (mmHg)	1.109	3.030	0.088	0.865-10.620
Model	0.449	1.567	0.055	
hs-CRP (µg/ml)	0.098	0.906	0.872	0.273-3.011
IL-6 (ng/ml)	0.044	1.045	0.399	0.944-1.156
TG (mmol/l)	1.600	4.953	0.014*	1.385-17.713
HDL-c(mmol/l)	-2.114	0.121	0.001*	0.034-0.432
FBG (mmol/l)	1.011	2.750	0.194	0.598-12.638

BMI, Body mass index, WC, Waist circumference, WHR, Waist to hip ratio, SBP, Systolic blood pressure, DBP, Diastolic blood Pressure, hs-CRP, High sensitivity CRP, IL-6, Interleukin-6, TG, Triglycerides, HDL-C, High density lipoprotein cholesterol, FBG, Fasting blood glucose. (* p value <0.05) Statistic by Logistic regression model.

Discussion

Baseline MetS prevalence among HAART-naïve HIV patients in this study was 17.4% compared to 18.6% in healthy controls, reflecting the expected body thinness and wasting characteristic of newly diagnosed HIV patients presenting with HIV wasting syndrome. These baseline rates align with Awosan et al.'s (14) 17.8% prevalence among civil servants. However, they remain substantially lower than Sabir et al.'s (15) 34.1% prevalence, as well as additional studies (9) that similarly report elevated MetS prevalence in treatment-naïve populations. Following HAART initiation, the prevalence of MetS increased markedly across 6-, 12-, 18-, and 24-month intervals, with an overall prevalence among HAART-treated patients reaching 37.5%. These increases may have resulted from improvements in anthropometric parameters (BMI, waist circumference) alongside HAART-induced vascular changes that increased lipid dysregulation and blood pressure. Specifically, dolutegravir (an integrase strand transfer inhibitor) is known to contribute to MetS development through increased insulin resistance, explaining the elevated fasting blood glucose observed. These treatment-associated prevalence rates align with Naidu et al. (16) and Calza et al. (17), who reported 30.5% and 20.9% respectively. Collectively, these findings suggest MetS prevalence among HIV patients may approach general population levels with continued treatment.

The current study observed a significant positive correlation between hs-CRP and MetS in HAART-exposed HIV patients, compared to the weak and nonsignificant association in treatment-naive patients, a finding which may reflect the impact of treatment-induced immunological changes. However, longitudinal analysis revealed that hs-CRP failed to demonstrate any significant power in predicting the development MetS at 12 and 24 months post-treatment.

HIV treatment has been documented to cause exaggerated inflammatory responses to opportunistic infections in the context of immune reconstitution (18). This alteration in inflammatory state could potentially interact with or exacerbate underlying MetS-related inflammation. Also, since MetS is more prevalent and better characterised in the post-treatment phase, detection of meaningful correlations may be facilitated. By contrast, in treatment-naive HIV patients, suppression of the immune system or disease heterogeneity may blunt hs-CRP responses, masking potential associations.

Previous studies on the relationship between hs-CRP and MetS have reported marginally significant associations, significant correlations in specific subgroups, and nonsignificant findings in others (3, 19, 20), strongly suggesting that confounding factors and population heterogeneity substantially affect the consistency of this relationship. The association between hs-CRP and MetS appears to be complex and influenced by multiple factors, including obesity, comorbidities, ethnicity, and possibly other unidentified biological or environmental variables. The findings in the current study, in the context of the mixed data from previous research, suggest that the role of hs-CRP may be context-dependent, influenced by treatment status and immune system dynamics rather than serving as a reliable predictive biomarker. It may be more useful for monitoring current MetS activity than for forecasting its future development. These findings underscore the need for further stratified analyses and mechanistic studies to clarify the conditional relevance of hs-CRP in different patient populations.

As for IL-6, its blood level was not elevated in treatment-naive patients with HIV in the current study, compared to healthy controls, suggesting no general upregulation in early disease. However, among all patients, those with MetS exhibited marginally higher levels of IL-6 than those without MetS, though this difference narrowly missed statistical significance. Another key finding is the statistically significant negative correlation between IL-6 levels and MetS among treatment-naive patients. This finding indicates that elevation of IL-6 levels is associated with a reduced likelihood of the development of MetS. This negative correlation persisted but failed to attain statistical significance among treatment-exposed patients. Furthermore, longitudinal analyses at 12 and 24 months post-treatment showed that IL-6 had no significant predictive power for MetS development over time.

Taken together, these findings—alongside previously reported mixed results in the literature—highlight the complexity of IL-6's role. Reports of prior studies suggest that the relationship between IL-6 and MetS is likely influenced by a range of factors—including genetic background (21), presence of comorbidities (22), characteristics of the study population (22), and the specific methodologies used to measure IL-6 and to define MetS (23). The implication of these findings is that although IL-6 may not serve as a reliable predictive biomarker across heterogeneous populations or over time, it may still have some context-specific relevance. This emphasises the need for stratified analyses and more advanced modelling to uncover any clinically meaningful associations that may otherwise be hidden in aggregate-level analyses.

Our study revealed that TG levels negatively and significantly predicted MetS at 12 months post-treatment, but shifted to a positive and significant predictor at 24 months. In contrast, HDL-C levels consistently and significantly predicted a lower risk of MetS at both time points. These results suggest that TG and HDL-C may exert interdependent and not independent effects, with their predictive value becoming more pronounced when considered in

combination or as a ratio. These findings are consistent with emerging evidence from the literature indicating that TG is an independent risk factor for MetS (24) and that biomarker ratios, including TG/HDL-C ratio, often outperform single markers in the prediction of the development of MetS (25, 26). TG and HDL-C may reflect opposing or compensatory immune-metabolic pathways, and their balance may better capture the immunological state that predisposes individuals to MetS.

While previous research has highlighted correlations, few studies have investigated potential causal pathways using regression analysis, as done in the current study. Further mechanistic and longitudinal research is needed to clarify how these biomarkers interact over time and how they might be integrated into risk prediction models for MetS.

Conclusion

TG and HDL-c were demonstrated to be independent predictors of MetS. However, although hs-CRP and IL-6 failed to predict MetS in HIV patients on HAART across time points, their significant association with MetS in treatment-exposed and treatment-naive patients, respectively, suggest a potential context-dependent role for the two biomarkers. Specifically, the role of hs-CRP appears to reflect immune activation occurring in MetS, making it potentially useful for monitoring current MetS activity, rather than forecasting its future development.

Limitations

Several limitations exist in using IL-6 and hs-CRP as predictive markers for metabolic syndrome in this population. These include variability as both IL-6 and hs-CRP levels fluctuate due to multiple factors unrelated to MetS, such as infection, stress, ethnicity, individual variability, and other inflammatory processes common in HIV patients. Interleukin-6 and hs-CRP are also nonspecific markers of inflammation; generally, elevated levels may be associated with several conditions beyond MetS. Likewise, HAART may confound the relationship between inflammatory markers and MetS, especially those classes that are associated with immune activation. Furthermore, higher viral load and low CD4 count are associated with elevated IL-6 levels, which could affect its utility as a marker of MetS in patients with varying levels of viral suppression. Therefore, while IL-6 and hs-CRP can provide insight into inflammatory processes in HIV patients on HAART, their limitations as standalone predictive markers of MetS mean they are often used in combination with other markers for a more comprehensive assessment.

The current study is limited to a subcellular assessment of metabolic syndrome using inflammatory markers (hs-CRP and IL-6); therefore, there is a need to investigate their effect at the gene level for any association with the syndrome.

There is limited time for follow-up of patients to allow for comprehensive documentation of changes that may occur over time, which may facilitate a more accurate inference and conclusion of the main findings.

The number of study subjects may also limit the outcome of many parameters and their association with components of MetS. Hence, there is a need for a larger cohort study with sufficient time for follow-up of patients, allowing for surveillance of changes that may occur over time in the components of metabolic syndrome and enabling better statistical inference.

Recommendations

Future studies should account for genetic, clinical, and methodological variability to clarify the biomarker potential of IL6 and hs-CRP.

Further work at the molecular level to investigate interleukin 6 receptor gene (IL-6R) polymorphism, IL-6 gene PCR matching, and sequencing among patients with MetS in our environment is highly recommended.

Future studies should include a wide range of inflammatory markers to facilitate good segregation and selection for inclusion in the study, following a robust assessment of markers that may affect the components of MetS.

Acknowledgement

We wish to acknowledge the staff of the Chemical Pathology Laboratory at Usmanu Danfodiyo University Teaching Hospital, particularly Bashar Sani and Bashar B.B., for their assistance in sample management and analysis.

Conflict of Interest: The authors declare no conflict of interest.

Authors' contributions

AB, POA, RY, and MBA partake in the conception and design of the research, and AB wrote the first draft. AAF conducted data collection and management, while BAI performed the data analysis. However, all authors had read and approved the final version of the draft.

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