Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Low-Level Viremia as an Independent Risk Factor for Metabolic Syndrome in People Living with HIV Receiving Antiretroviral Therapy: A 6-Year Retrospective Cohort Study

Zixuan Wang[1], Yong Jin[2], Guoqing Qian[1]

[1]Department of Infectious Diseases, The First Affiliated Hospital of Ningbo University, Ningbo, Zhejiang, People's Republic of China; [2]Department of Infectious Diseases, Ningbo Yinzhou No.2 Hospital, Ningbo, Zhejiang, People's Republic of China

Correspondence: Guoqing Qian, Department of Infectious Diseases, The First Affiliated Hospital of Ningbo University, No. 1601 Airport South Road, Ningbo, Zhejiang, People's Republic of China, Email bill.qian@outlook.com; Yong Jin, Department of Infectious Diseases, Ningbo Yinzhou No.2 Hospital, No. 998 Qianhe North Road, Ningbo, Zhejiang, People's Republic of China, Email yongjin1993@163.com

Purpose: Metabolic syndrome (MetS) in people living with HIV (PLWH) is more complicated and multifactorial than in the general population. HIV infection is increasingly recognized as a direct contributor to metabolic dysfunction. This study aims to assess the long-term risk of MetS in PLWH with low-level viremia (LLV) receiving antiretroviral therapy (ART).

Patients and Methods: In this 6-year retrospective cohort study, we analysed 848 PLWH receiving ART. Participants were classified into three viremia categories: no LLV (all HIV viral loads <50 copies/mL or undetectable), LLV 51–200 (two consecutive viral loads between 51–200 copies/mL), and LLV 201–500 (two consecutive viral loads between 201–500 copies/mL). MetS incidence was assessed using time-dependent Cox regression analysis, while immune and metabolic trajectories were analyzed via linear mixed models. To further validate the robustness of our primary findings, sensitivity analyses stratified by ART regimens were performed.

Results: Over a median follow-up of 3.9 years, 31.3% of participants developed MetS. The incidence rates of MetS were 160.4, 136.6, and 83.0 cases per 1000 person-years in the LLV 201–500, LLV 51–200, and no LLV groups, respectively. Time-dependent Cox regression analysis demonstrated that LLV was an independent risk factor for MetS. Sensitivity analyses demonstrated that patients experiencing LLV, irrespective of ART regimen, had a persistently higher incidence of MetS. Additionally, LLV was associated with persistently elevated CD8 counts, reduced CD4 recovery, and worsening metabolic profiles.

Conclusion: LLV independently predicts MetS risk in PLWH on ART. LLV should be regarded not only as a virological concern but also as a metabolic risk factor that warrants closer clinical attention in the post-ART era.

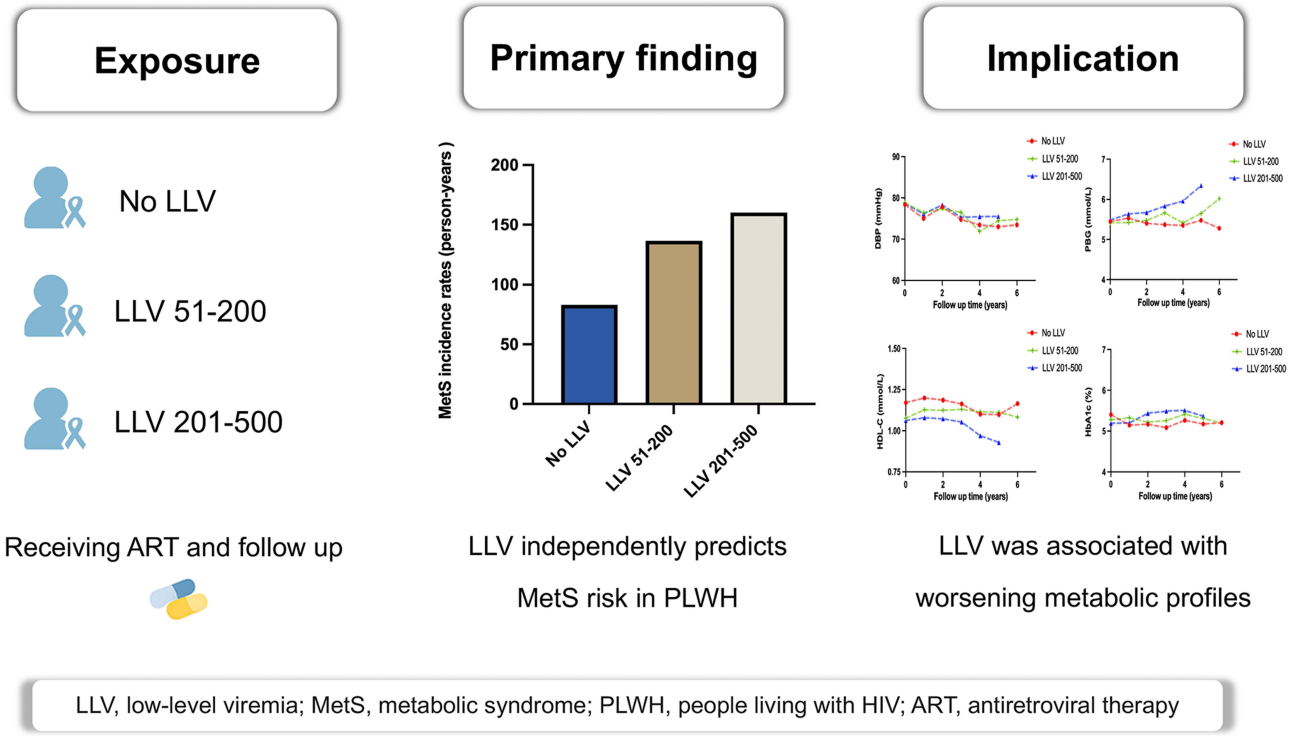
Keywords: low-level viremia, metabolic syndrome, HIV, risk factor, antiretroviral therapy

Introduction

In the post-antiretroviral therapy (ART) era, metabolic syndrome (MetS)—a cluster of abnormalities including glucose dysregulation, dyslipidemia, hypertension, and central obesity—has emerged as a critical comorbidity among people living with HIV (PLWH).[1] Studies have reported that the prevalence of MetS in this population exceeds that in the general population.[2] Traditionally, MetS in PLWH was primarily attributed to long-term ART use, especially older protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), which were associated with mitochondrial dysfunction and lipodystrophy.[3] However, HIV itself is now recognized as a direct contributor to metabolic dysfunction via chronic immune activation and systemic inflammation, even among individuals with viral suppression.[4] Therefore, elucidating the role of HIV infection in MetS is essential for optimizing management and preventing complications in this vulnerable population.

Received: 9 July 2025
Accepted: 16 October 2025
Published: 30 October 2025

Graphical Abstract



LLV, low-level viremia; MetS, metabolic syndrome; PLWH, people living with HIV; ART, antiretroviral therapy

Low-level viremia (LLV) is generally defined as the persistence of detectable HIV RNA levels above the assay's lower limit of detection but below the threshold for virologic failure. This condition is observed in approximately 5.3–38.7% of individuals receiving ART.[5–7] Reported prevalence varies due to differences in the thresholds used to define viral suppression across regions, resulting in no universally accepted definition of LLV. The absence of a globally harmonized LLV definition reflects differences in resource availability, diagnostic technologies, and public health priorities. Recently, Delphi consensus proposed an accepted definition of LLV as an HIV RNA range of 50 to 500 copies/mL,[8] which has been strongly associated with virological failure.[9] Previously considered benign "virologic blips", LLV is now increasingly recognized as a predictor of virologic failure, drug resistance, and systemic immune activation.[10,11] Emerging evidence suggests that LLV contributes to metabolic dysregulation. Persistent LLV has been associated with an increased risk of serious non-AIDS events in PLWH. A follow-up study of 2528 PLWH found that chronic kidney disease was the most common event (7.6%), followed by cardiovascular disease (5.2%) and non-AIDS-defining cancers (3.8%).[12] Furthermore, levels of growth differentiation factor-15 (a cytokine associated with metabolic disorders) and D-dimer were significantly elevated in individuals with LLV, suggesting a potential link between LLV and metabolic disease.[13]

In PLWH, the pathogenesis of MetS may involve distinct mechanisms compared to the general population. LLV may play a critical role in the onset and progression of MetS. These are two key and unavoidable issues among PLWH in the post-ART era. In this context, a retrospective cohort study was conducted to assess the long-term risk of developing MetS in individuals with LLV receiving ART.

Methods

Study Population and Design

This retrospective cohort study used data from the Ningbo Yinzhou No. 2 Hospital HIV Service Database and electronic medical records, representing one of the largest prospective HIV cohorts in Ningbo, China, with over 1300 PLWH enrolled since November 2018. The cohort included both newly diagnosed individuals and those transferred from other institutions due to changes in residency. Inclusion criteria were: (1) age ≥18 years; (2) ≥6 months of ART exposure; (3) at least one documented viral suppression (HIV RNA <50 copies/mL or undetectable); (4) ≥2 documented viral load measurements taken at least one month apart after ART initiation. Exclusion criteria included: (1) baseline MetS; (2) virologic failure (viral loads >1000 copies/mL) after 6 months of ART; (3) missing baseline data. A summary of the study design was presented in Figure 1.

Exposure

The primary exposure of interest was the viremia category during ART. LLV was defined as two consecutive HIV RNA measurements between 50 and 500 copies/mL.[14] To assess the impact of varying LLV levels on the timing of metabolic outcomes, LLV cases were divided into two mutually exclusive exposure groups. Participants were ultimately categorized into three viremia categories: No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART), LLV 51–200 (two consecutive viral loads between 51–200 copies/mL), and LLV 201–500 (two consecutive viral loads between 201–500 copies/mL). When PLWH who previously achieved stable viral suppression developed LLV, specialized healthcare professionals conducted a comprehensive clinical assessment. This assessment typically included

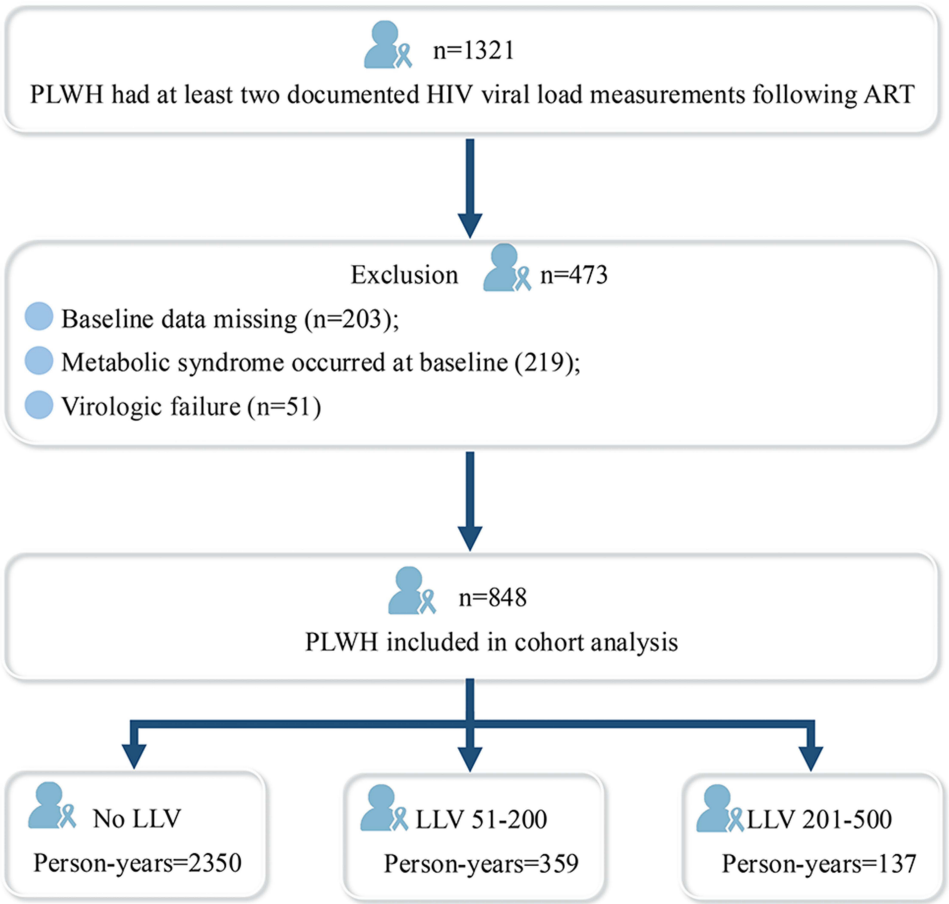


Figure 1 Flowchart of sample selection process. No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL).

https://doi.org/10.2147/IDR.S552365

a detailed review of the patient's medical history, including ART regimen, documented HIV drug resistance, and historical CD4 and HIV RNA data. Additionally, healthcare providers carefully assessed treatment adherence and considered pharmacological factors, such as potential drug-food interactions or issues affecting drug absorption. Concurrently, intensified monitoring of HIV RNA was recommended, typically at intervals of 1 to 3 months, to promptly detect emerging virological failure. A longer duration of LLV exposure was associated with poorer clinical outcomes. Consequently, viremia category was included as a time-varying covariate in subsequent analyses to accurately reflect evolving clinical risk.

Baseline Data Collection

Baseline was defined as the date of each patient's initial hospital visit. In addition to viremia category, baseline demographic, clinical, and laboratory data were collected as covariates to assess their associations with the incidence of MetS. Demographic variables included age, sex, and self-reported HIV transmission routes (heterosexual contact, men who have sex with men [MSM], or other/unknown). According to the management guidelines in China,[15] initial ART regimens were categorized as standardized therapy, defined as two NRTIs plus a third agent: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a PI. To further explore the effect of tenofovir disoproxil fumarate (TDF) on MetS, TDF use was also included as a covariate. During the treatment of PLWH, ART regimens often changed in response to evolving clinical guidelines, availability of newer medications, physician preferences, or patient side effects; therefore, ART regimen and TDF use were treated as time-varying covariates in subsequent analyses. Anthropometric measurements, including blood pressure and waist circumference (WC), were collected by trained nurses. Baseline laboratory data included fasting blood glucose (FBG), postprandial blood glucose (PBG), glycated hemoglobin (HbA1c), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and immune parameters including CD4 and CD8 counts, and HIV viral load. Baseline HIV viral load was log10-transformed for normalization and classified into three categories: viral suppression (viral loads <50 copies/mL or undetectable), low viral load (detectable but <3 $\log_{10}$ copies/mL), and high viral load (>3 $\log_{10}$ copies/mL).

Outcome Definitions

The primary outcome was the incidence of MetS during the follow-up period. Follow-up visits occurred every three months to assess metabolic parameters including SBP, DBP, WC, FBG, PBG, fasting TG, HDL-C, and HbA1c. Immune parameters (CD4 and CD8 counts, HIV viral load) were assessed every six months, in accordance with the management requirements of Chinese Center for Disease Control and Prevention (CDC). Diagnostic criteria adhered to national guidelines,[16] as all participants resided in mainland China. Participants presenting with three or more of the following five components were diagnosed with MetS: (1) Abdominal obesity, defined as a WC ≥90 cm for men and ≥ 85 cm for women; (2) Hyperglycemia, defined as FBG ≥ 6.1 mmol/L, 2-hour post-glucose load blood glucose ≥ 7.8 mmol/L, or a diagnosis of diabetes; (3) Hypertension, defined as blood pressure ≥ 130/85 mmHg or previously diagnosed and treated hypertension; (4) Elevated fasting TG ≥1.70 mmol/L; and (5) Low fasting HDL-C <1.04 mmol/L. The follow-up period began on the date of the participant's initial clinic visit and ended on January 9, 2025. Time to MetS was defined as the number of days from the baseline assessment to the assessment when the participant first met criteria for MetS. Participants who did not develop MetS during the follow-up period were censored at their last recorded visit.

Statistical Analyses

Data analyses were performed using R v4.4.2, SPSS v29.0, and GraphPad Prism v10. Normality was evaluated using Kolmogorov–Smirnov tests. Due to their non-parametric distribution, continuous variables were presented as medians with interquartile ranges (IQRs), and categorical variables as frequencies with percentages. Comparative analyses for categorical data were conducted using the χ^2-test or Fisher's exact test, depending on sample size and expected cell frequencies. Continuous variables across groups were compared using the Mann–Whitney *U*-test or Kruskal–Wallis H-test, depending on the number of groups. Person-years of observation were calculated for each viremia category, and incidence rates of MetS were obtained by dividing the number of MetS events by the corresponding total person-years of follow-up. Kaplan–Meier survival analysis was performed to compare time to MetS between groups using the Log rank

test. Notably, intersection points observed in Kaplan–Meier survival curves when comparing viremia categories and different ART regimens indicated violations of the proportional hazards assumption. Consequently, these covariates were treated as time-varying variables in Cox regression analyses, avoiding potential pitfalls due to immortal time bias. Schoenfeld residuals were examined to assess the proportional hazards assumption for other covariates, and no further violations were detected ($p > 0.05$). Before constructing multivariable Cox regression models, Spearman's rank correlation analyses were performed to evaluate relationships among variables. No significant correlations indicative of collinearity ($r > 0.4$) were identified. Multicollinearity was further assessed using variance inflation factors (VIFs), and all variables included in the multivariable analysis demonstrated acceptable VIF values (<5). Univariable and multivariable Cox proportional hazards models with time-varying covariates were used to assess the association between LLV and time to MetS. To further validate the robustness of our main findings, sensitivity analyses stratified by ART regimens and TDF used were performed.

Additionally, linear mixed models (LMMs) were employed to evaluate longitudinal changes in number of censoring events, immune and metabolic parameters across viremia categories. Given the inevitable presence of missing data during follow-up, all missing values were filled with a median value of all patients. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Baseline Characteristics

Of the 1321 PLWH screened, 848 met the inclusion criteria, while 473 were excluded due to missing baseline data (n = 203), baseline MetS (n = 219), or virologic failure (n = 51) (Figure 1). The cohort had a median age of 36 years (IQR 29–46), comprising 86.7% male and 13.3% female participants (Table 1). Most participants initiated ART with NNRTI +NRTIs regimens (77.0%), followed by INSTI+NRTIs (16.9%) and PI+NRTIs (6.1%) regimens. No significant differences were observed in sex distribution, age, HIV transmission risk, hyperglycemia, elevated TG, or baseline CD8 counts among the three viremia categories. However, significant differences were found in abdominal obesity, hypertension, reduced HDL, baseline CD4 counts, baseline HIV viral load, ART regimen, and TDF use among the groups ($p < 0.05$).

To further explore potential inherent differences between the MetS and non-MetS groups, comprehensive subgroup comparisons were conducted (Table S1). During a median follow-up of 3.9 years (IQR 1.9–4.7), 31.3% of participants developed MetS. 21.3% of PLWH exhibited LLV, including 14.7% in the LLV 51–200 group and 6.6% in the LLV 201–500 group. The incidence rates of MetS were 160.4, 136.6, and 83.0 cases per 1000 person-years in the LLV 201–500, LLV 51–200, and no LLV groups, respectively. Compared to the non-MetS group, the MetS group was significantly older, had a higher proportion of hypertension and higher baseline CD8 counts, and experienced a longer follow-up duration. Sex distribution, HIV transmission routes, and viremia categories also significantly differed between the groups ($p < 0.05$). No significant baseline differences were observed in proportion of abdominal obesity, hyperglycemia, elevated TG, reduced HDL, CD4 count, HIV viral load, ART regimen and TDF use ($p > 0.05$).

Number of HIV Viral Load Tests

Figure 2A illustrated the average number of HIV viral load tests conducted across different viremia categories throughout the follow-up period. Longitudinal analyses indicated that PLWH in the LLV 201–500 group underwent the highest average frequency of viral load monitoring, followed by those in the LLV 51–200 group, whereas the no-LLV group had the lowest testing frequency. This finding suggested that patients who experienced episodes of LLV required more frequent monitoring to promptly detect potential adverse clinical outcomes. Figure 2B further illustrated the relationship between the total number of tests and HIV viral load levels within each viremia category throughout the entire follow-up period. The total numbers of tests conducted were 3277, 656, and 303 for the no-LLV, LLV 51–200, and LLV 201–500 groups, respectively. As anticipated, the chi-square trend test revealed a significant linear increase in the proportion of high viral load measurements across the three viremia categories ($\chi^2 = 331.797$, $p < 0.001$). This trend underscored that PLWH experiencing LLV tended to exhibit elevated viral loads over time, further supporting the necessity of intensified viral load monitoring in this population.

Table 1 Baseline Clinical Characteristics of PLWH Across Different Viremia Categories

	Overall (n=848)	No LLV (n=667)	LLV 51–200 (n=125)	LLV 201–500 (n=56)	P Value
Sex (n, %)					0.508
Male	735 (86.7)	573 (85.9)	112 (89.6)	50 (89.3)	
Female	113 (13.3)	94 (14.1)	13 (10.4)	6 (10.7)	
Age (years)	36 (29,46)	35 (29,45)	37 (27.5,49.5)	39 (31,45)	0.224
HIV Transmission Risk (n, %)					0.211
MSM	426 (50.2)	344 (51.6)	57 (45.6)	25 (44.6)	
Heterosexual	359 (42.3)	269 (40.3)	61 (48.8)	29 (51.8)	
Other/unknown	63 (7.4)	54 (8.1)	7 (5.6)	2 (3.6)	
Abdominal obesity (n, %)					0.011
Yes	10 (1.2)	4 (0.6)	4 (3.2)	2 (3.6)	
No	838 (98.8)	663 (99.4)	121 (96.8)	54 (96.4)	
Hyperglycemia (n, %)					0.894
Yes	17 (2.0)	13 (1.9)	3 (2.4)	1 (1.8)	
No	831 (98.0)	654 (98.1)	122 (97.6)	55 (98.2)	
Hypertension (n, %)					0.016
Yes	41 (4.8)	25 (3.7)	11 (8.8)	5 (8.9)	
No	807 (95.2)	642 (96.3)	114 (91.2)	51 (91.1)	
Elevated TG (n, %)					0.679
Yes	25 (2.9)	22 (3.3)	2 (1.6)	1 (1.8)	
No	823 (97.1)	645 (96.7)	123 (98.4)	55 (98.2)	
Reduced HDL (n, %)					0.015
Yes	121 (14.3)	83 (12.4)	27 (21.6)	11 (19.6)	
No	727 (85.7)	584 (87.6)	98 (78.4)	45 (80.4)	
Baseline CD4 count (cells/μL)	407.0 (279.0,531.8)	414.0 (299.0,537.0)	393.0 (258.0,518.0)	360.0 (229.8,518.0)	0.037
Baseline CD8 count (cells/μL)	647.5 (480.3,921.0)	650.0 (481.0,911.0)	640.0 (478.5,960.0)	641.5 (470.0,982.8)	0.877
Baseline HIV viral load (n, %)					<0.001
Viral suppression	688 (81.1)	587 (88.0)	79 (63.2)	22 (39.3)	
Low HIV viral load	115 (13.6)	54 (8.1)	34 (27.2)	27 (48.2)	
High HIV viral load	45 (5.3)	26 (3.9)	12 (9.6)	7 (12.5)	
ART regimen (n, %)					<0.001
NNRTIs+NRTIs	653 (77.0)	543 (81.4)	80 (64.0)	30 (53.6)	
PIs+NRTIs	52 (6.1)	46 (6.9)	6 (4.8)	0 (0.0)	
INSTIs+NRTIs	143 (16.9)	78 (11.7)	39 (31.2)	26 (46.4)	
TDF use (n, %)					0.009
Non-TDF-based	574 (67.7)	469 (70.3)	72 (57.6)	33 (58.9)	
TDF-based	274 (32.3)	198 (29.7)	53 (42.4)	23 (41.1)	

Notes: Viral suppression (baseline viral loads <50 copies/mL or undetectable), low viral load (detectable but baseline viral loads <3 $\log_{10}$ copies/mL), and high viral load (baseline viral loads >3 $\log_{10}$ copies/mL). No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL).

Abbreviations: PLWH, people living with HIV; MetS, metabolic syndrome; MSM, men who have sex with men; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; ART, antiretroviral therapy; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors; TDF, tenofovir disoproxil fumarate; LLV, Low-level viremia.

Kaplan–Meier Analysis

In Figure 3A, Kaplan–Meier curves stratified by viremia category demonstrated a graded association between LLV magnitude and MetS incidence (Log rank test, $p < 0.001$). The maximum follow-up duration was 5 years for the LLV 201–500 group and 6 years for the other groups. Cumulative MetS incidence was highest in the LLV 201–500 group (39.3% at 5 years), intermediate in LLV 51–200 group (39.2% at 6 years), and lowest in no LLV group (29.2% at 6 years). This dose–response relationship highlighted the clinical significance of LLV severity in the development of MetS. Additionally, the incidence of MetS across different ART regimens was further explored in Figure 3B. As shown in Figure 3B, the INSTI +NRTI regimen exhibited the poorest metabolic outcomes compared with other regimens (Log rank test, $p < 0.001$).

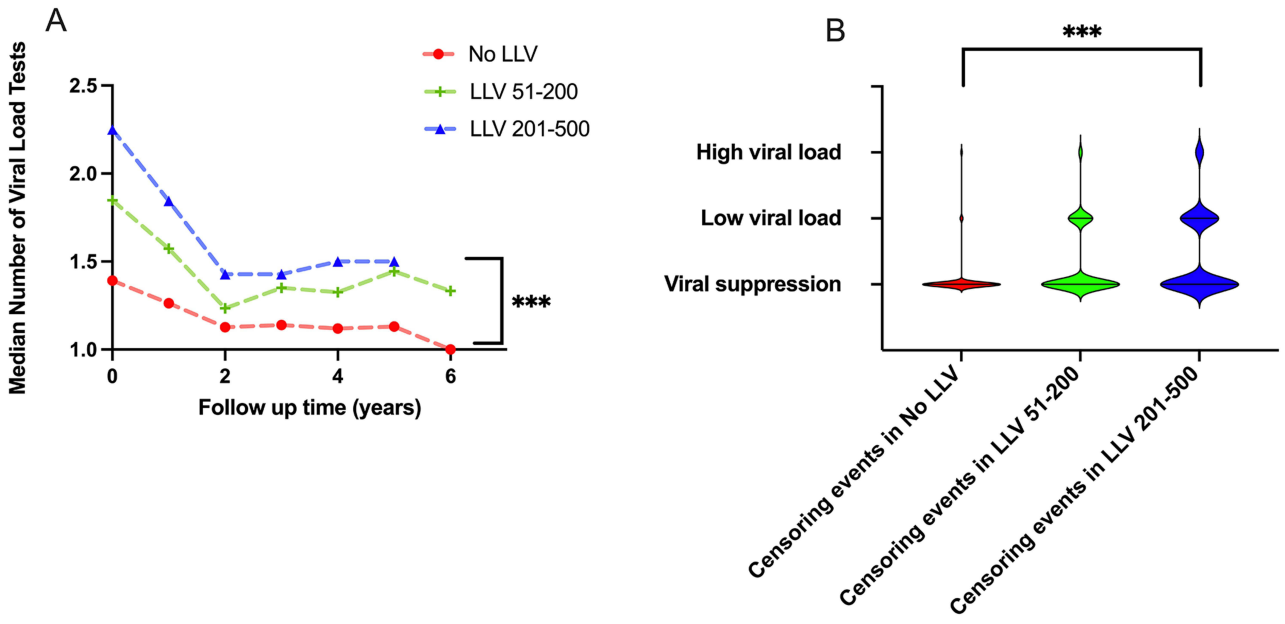


Figure 2 Average number of viral load assessments per viremia category over the entire follow-up period (**A**). Total number of viral load assessments by viremia category during the entire follow-up period (**B**). Viral suppression (baseline viral loads <50 copies/mL or undetectable), low viral load (detectable but baseline viral loads <3 $\log_{10}$ copies/mL), and high viral load (baseline viral loads >3 $\log_{10}$ copies/mL). No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL). ***: $p < 0.001$.

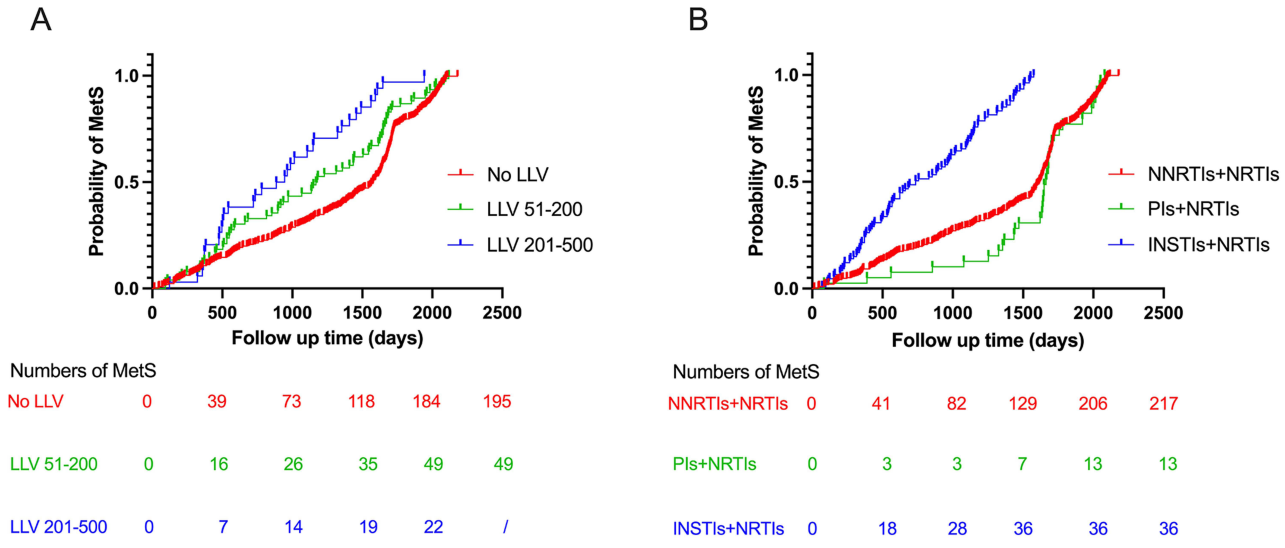


Figure 3 Cumulative incidence of MetS across viremia categories (**A**) and ART regimens (**B**). No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL). Tick marks (|) indicate censored data.

Risk Factors Analysis of MetS

To identify factors associated with the incidence of MetS, univariable and multivariable time-dependent Cox regression analyses were performed, with ART regimen and viremia category treated as time-dependent covariates. The forest plot of the univariate analysis (Figure 4) showed that male sex, older age, abdominal obesity, hypertension, reduced HDL, higher baseline CD8 counts, high baseline HIV viral load, and an INSTI+NRTI regimen were significantly associated with an increased risk of MetS. Compared with the No LLV group, both the LLV 51–200 group (HR = 1.082, 95% CI = 1.030–1.135, p = 0.002) and the LLV 201–500 group (HR = 1.170, 95% CI = 1.093–1.253, p < 0.001) exhibited

https://doi.org/10.2147/IDR.S552365

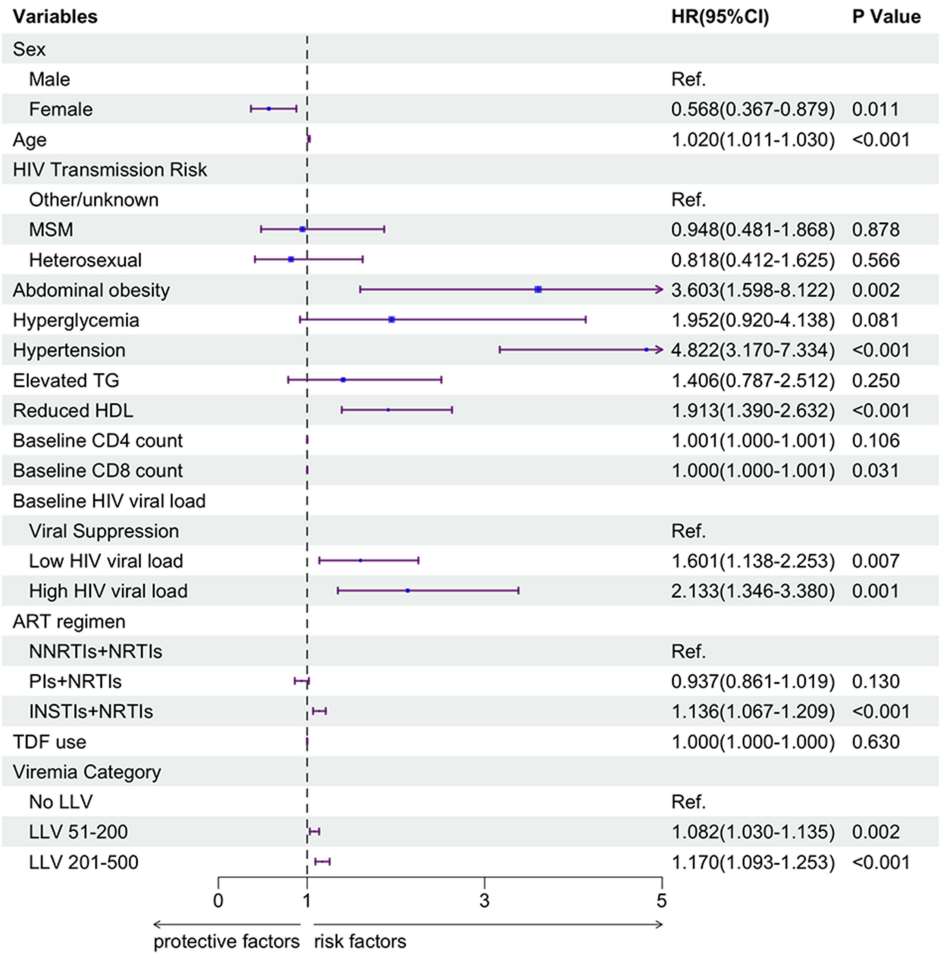


Figure 4 Forest plot of univariate time-dependent cox regression analysis of MetS in PLWH. Viral suppression (baseline viral loads <50 copies/mL or undetectable), low viral load (detectable but baseline viral loads <3 $\log_{10}$ copies/mL), and high viral load (baseline viral loads >3 $\log_{10}$ copies/mL). No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL).

a significantly higher risk of developing MetS. These variables were subsequently included in the multivariate time-dependent Cox regression model. The forest plot (Figure 5) confirmed that LLV 201–500 remained an independent risk factor for MetS compared to the no LLV group (HR = 1.108, 95% CI = 1.028–1.195, p = 0.008), along with male sex, older age, abdominal obesity, hypertension, reduced HDL, higher baseline CD8 counts, high baseline HIV viral load, and use of an INSTI+NRTI regimen.

Sensitivity Analysis

To comprehensively address potential confounding by ART regimen, additional time-dependent Cox regression was conducted to evaluate the robustness of the association between LLV and MetS (Table 2). In analysis A, involving patients treated with NNRTIs+NRTIs, a significantly elevated risk of MetS was observed in the LLV 201–500 group compared with the no LLV group (HR = 1.097, 95% CI: 1.004–1.198, p = 0.040). In analysis B, which involved patients treated with PIs+NRTIs, the LLV 201–500 group was not represented due to sample size limitations; nonetheless, the LLV 51–200 group still exhibited a significantly increased risk of MetS (HR = 1.383, 95% CI: 1.093–1.749, p = 0.007). Furthermore, analysis C, which included patients treated with INSTIs+NRTIs, similarly confirmed that viremia categories remained a significantly risk factor of MetS (HR = 1.235, 95% CI = 1.066–1.431, P = 0.005 for LLV 51–200 vs No LLV, and HR = 1.208, 95% CI =1.007–1.450, P = 0.042 for LLV 201–500 vs No LLV). To further explore the potential confounding of TDF use on MetS, PLWH were stratified into subgroups based on TDF use (Table S2).

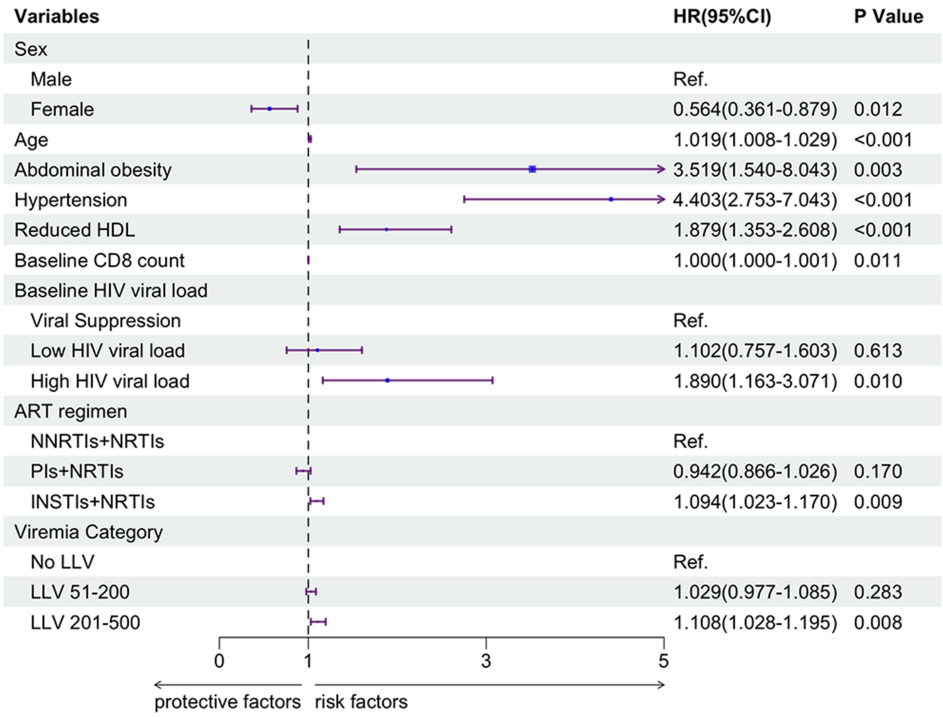


Figure 5 Forest plot of multivariate time-dependent cox regression analysis of MetS in PLWH. No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL).

Consistent with the above results, LLV remained a risk factor for MetS across subgroups. Despite inherent variations in ART regimens and differences in sample sizes, the consistent findings across multiple sensitivity analyses robustly demonstrated that patients experiencing LLV, irrespective of ART regimen, had a persistently higher incidence of MetS compared with patients without LLV, underscoring the clinical relevance and reliability of these observations.

Trajectories of Immune and Metabolic Parameters Over Time

LMMs revealed divergent trajectories in immune parameters (Figure 6A and B) and metabolic parameters (Figure 6C–I) across viremia categories over seven follow-up intervals (T0–T6). Longitudinal analyses revealed significant differences in CD4 and CD8 counts, diastolic blood pressure (DBP), PBG, HDL-C, and HbA1c (Figure S1) across viremia categories ($p < 0.05$). No significant longitudinal differences were observed in systolic blood pressure (SBP), WC, or TG ($p > 0.05$). These findings suggested that LLV may affect the long-term trajectories of immune and specific metabolic parameters.

Table 2 Sensitivity Analysis of LLV as an Independent Risk Factor for MetS Across ART Regimens

	Sensitivity Analysis A	Sensitivity Analysis B	Sensitivity Analysis C
No LLV	Ref.	Ref.	Ref.
LLV 51–200	0.980 (0.918–1.046)	1.383 (1.093–1.749) **	1.235 (1.066–1.431) **
LLV 201–500	1.097 (1.004–1.198) *	/	1.208 (1.007–1.450) *

Notes: Covariate-adjusted analyses included sex, age, abdominal obesity, hypertension, reduced HDL, baseline CD8 counts, and baseline HIV viral load. Sensitivity analysis A: PLWH receiving NNRTI + NRTI regimens. Sensitivity analysis B: PLWH receiving PI + NRTI regimens. Sensitivity analysis C: PLWH receiving INSTI + NRTI regimens. No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL). *: $p < 0.05$; **: $p < 0.01$.

https://doi.org/10.2147/IDR.S552365

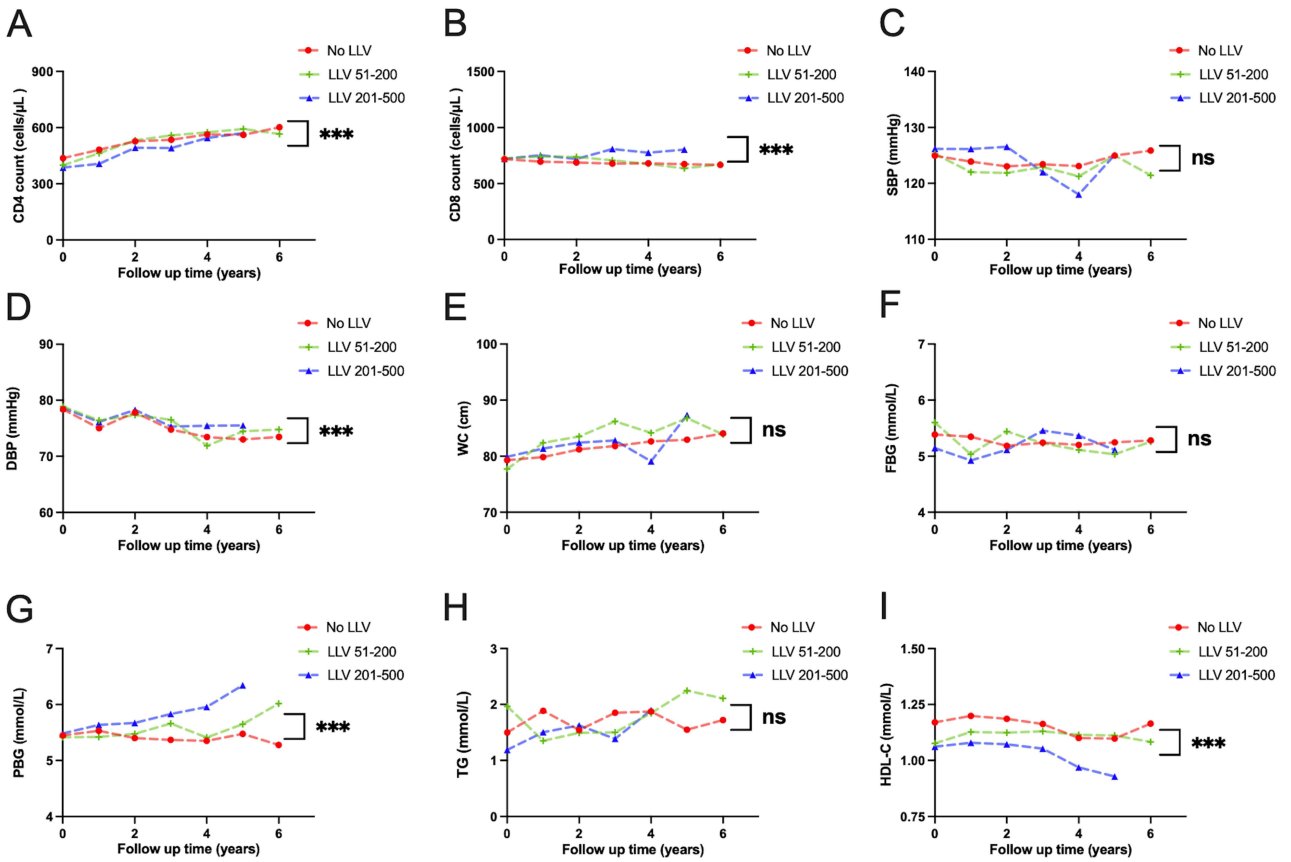


Figure 6 Longitudinal comparisons of immune and metabolic parameters across viremia categories over seven time points. (**A**) CD4 count; (**B**) CD8 count; (**C**) systolic blood pressure (SBP); (**D**) diastolic blood pressure (DBP); (**E**) waist circumference (WC); (**F**) fasting blood glucose (FBG); (**G**) postprandial blood glucose (PBG); (**H**) triglycerides (TG); (**I**) high-density lipoprotein cholesterol (HDL-C). No LLV (all viral loads <50 copies/mL or undetectable after 6 months of ART); LLV 51–200 (two consecutive viral loads between 51–200 copies/mL); LLV 201–500 (two consecutive viral loads between 201–500 copies/mL). Non-significant (ns): $p > 0.05$; ***: $p < 0.001$.

Discussion

In this retrospective cohort study of 848 PLWH, we identified a significant association between LLV and the subsequent development of MetS. These findings are consistent with emerging global evidence linking persistent viral activity to metabolic dysregulation and provide new insights into the dose-dependent relationship between LLV severity and MetS risk within a Chinese cohort. We found that persistent LLV—especially within the range of 201–500 copies/mL—was an independent risk factor for MetS, even in individuals who intermittently achieved viral suppression.

During a median follow-up of 3.9 years, 31.3% of PLWH developed MetS. This finding is consistent with global reports of MetS prevalence among PLWH, ranging from 16.7% to 31.3%.[17,18] MetS in PLWH is recognized as a multifactorial condition, involving a more complex interplay of contributing factors than in the general population. The prevalence of MetS among PLWH vary significantly across regions. Our cohort exhibited a relatively high incidence of MetS, attributable to several key factors. First, diagnostic criteria for MetS play a pivotal role in determining its reported prevalence; even within Chinese populations, different definitions result in a wide variation in prevalence rates, ranging from 21.25% to 38.63%.[19] Second, shorter follow-up periods in cohort studies may lead to underestimation of MetS incidence among HIV populations, as evidenced by a reported rate of 16.9% in certain cohorts.[20] In contrast, the six-year follow-up period in our study allowed for a more comprehensive assessment and increased the likelihood of detecting new cases of metabolic syndrome. Third, long-term use of ART, while essential for effective viral suppression, is closely associated with the development of metabolic complications. In our study, Figures 4 and 5 specifically highlighted the promoting effect of INSTI-based ART regimens on the incidence of metabolic syndrome, a finding further corroborated by Papaioannu et al,[21] who reported an increase in overall MetS prevalence during the COVID-19

pandemic from 29.4% to 33.8%, with INSTI use identified as a significant contributing factor. Fourth, variations in inclusion and exclusion criteria among cohort studies can significantly affect observed prevalence rates. For example, Han et al[22] excluded individuals with abnormal baseline levels of MetS components and reported a comparatively lower prevalence of 8.4% among PLWH. In contrast, our study Included patients with less than three baseline MetS diagnostic components, allowing for a clearer demonstration of how factors such as abdominal obesity, hyperglycemia, hypertension, elevated triglycerides, and reduced HDL contribute to MetS development. Finally, regional differences in lifestyle habits and healthcare accessibility further contribute to the heterogeneity observed in both the prevalence and outcomes of MetS among PLWH.[18] Notably, our cohort demonstrated a graded increase in MetS risk across viremia categories: compared with the no-LLV group (83.0 cases per 1000 person-years), the LLV 51–200 and LLV 201–500 groups exhibited significantly higher incidence rates (136.6 and 160.4 cases per 1000 person-years, respectively). The minimal difference between LLV subgroups suggests that even low-grade viremia (50–500 copies/mL) may exceed a threshold for triggering metabolic dysregulation, regardless of viral load magnitude. This phenomenon underscores the need to redefine current LLV management paradigms. Existing guidelines lack consensus on LLV thresholds, resulting in inconsistencies in clinical monitoring and treatment decisions. Our findings support defining LLV as 50–500 copies/mL, given the comparable metabolic burden observed between the LLV 51–200 and LLV 201–500 groups. Integrating both LLV subgroups into unified monitoring protocols may optimize resource allocation and facilitate timely intervention.

In our cohort, PLWH with LLV underwent significantly more average number of HIV viral load assessments than those without LLV (Figure 2A). This observation accurately reflects real-world HIV management. In practice, PLWH with LLV are scheduled for more frequent viral load measurements to assist clinicians in identifying early signs of virologic breakthrough or treatment failure and to intervene before adverse outcomes occur. While standard ART protocols generally call for viral load testing every six months, individuals with LLV often transition to monthly or quarterly assessments until sustained suppression is achieved.[23] Our findings highlight the importance of more frequent monitoring, which is critical for promptly detecting potential adverse clinical outcomes. Moreover, we observed a pronounced linear trend in the proportion of high viral load readings across the three viremia categories in Figure 2B, further supporting the notion that PLWH with LLV exhibit higher HIV viral load over time. The elevated viral load levels observed in LLV groups are most likely attributable to underlying biological factors—such as intermittent viral replication or adherence challenges—rather than solely to increased diagnostic scrutiny.

Abdominal obesity, hypertension, and reduced HDL are key diagnostic components of MetS. Numerous studies have confirmed their value as independent predictors of the onset of MetS in the general population.[24–26] In this study, after adjusting for these covariates in multivariable Cox regression and sensitivity analyses, LLV remained an independent risk factor for metabolic syndrome. Increasing evidence identifies LLV as a significant risk factor for metabolic disease in PLWH. Recent cohort studies have supported this association. A prediction model for LLV divided PLWH into two groups based on the median risk score; the high-risk LLV group was more likely to exhibit adverse metabolic profiles, including elevated triglyceride and blood glucose levels, compared with the low-risk group.[27] Additionally, a Chinese longitudinal study linked LLV to an increased risk of type 2 diabetes mellitus, reinforcing the notion that LLV contributes to metabolic deterioration.[28] However, these findings should be interpreted with caution. Although the dataset derived from the Chinese CDC had the advantage of a large sample size, it did not consistently distinguish between fasting and non-fasting laboratory measurements. This may have led to an overestimation of metabolic impact due to postprandial fluctuations in glucose and lipid levels. This methodological limitation highlights the importance of fasting detection in metabolic research, as adopted in our study, to ensure result accuracy. A study by Esber et al,[29] using data from the African Cohort Study, reported that PLWH with persistent LLV had a significantly higher incidence of non-communicable diseases (aHR:1.22; 95% CI:1.02–1.47), including elevated blood pressure, hypercholesterolemia, and hyperglycemia, compared to individuals with fully suppressed viral loads. The study also implicated immune activation pathways—particularly tumor necrosis factor-α and the chemokine CCL2/MCP-1—as potential mediators of LLV-associated metabolic dysfunction. However, the study adopted a broader LLV definition (HIV RNA <1000 copies/mL) and reliance on dichotomous outcomes for metabolic parameters. These methodological choices may obscure more nuanced, dose-dependent relationships between virological status and continuous metabolic changes. In contrast, our

study addressed several of these limitations and provided further evidence supporting the association between LLV and MetS. Both univariate and multivariate time-dependent cox regression analyses confirmed that LLV is an independent risk factor for MetS, independent of baseline HIV viral load or ART regimen. Notably, LLV was stratified into two distinct categories, and both subgroups showed similarly high MetS incidence. This stratification revealed that even lower levels of viremia may confer comparable metabolic risk. Furthermore, longitudinal analysis of metabolic parameters revealed significant differences in DBP, PBG, HDL-C, and HbA1c across viremia categories over seven follow-up intervals. These findings suggest a persistent and progressive metabolic vulnerability among PLWH with LLV. Therefore, incorporating quarterly metabolic panels into routine care may offer an effective strategy for the early detection of metabolic abnormalities. This approach would enable clinicians to identify emerging risks at a stage when lifestyle modification or pharmacological intervention is most effective, thereby helping to mitigate long-term cardiovascular and metabolic complications. Importantly, this strategy complements rather than replaces virological monitoring, providing a more comprehensive framework for addressing the dual challenges of viral control and metabolic health in individuals receiving antiretroviral therapy.

In the Kaplan–Meier analysis (Figure 3B), PLWH receiving INSTI+NRTI regimens exhibited a significantly greater likelihood of developing MetS over time compared with those on PI+NRTI or NNRTI+NRTI combinations (log-rank $p < 0.001$). This observation aligns with our previous research.[30] INSTI-based regimens' propensity to induce rapid adipose accumulation and impair insulin sensitivity may accelerate central obesity[31] and insulin resistance[32]—both cardinal features of MetS. Metabolic risk in patients receiving INSTI-based regimens should be monitored at an early stage. Although studies have confirmed that switching from non–INSTI-based regimens to INSTI-based regimens is associated with weight gain,[33,34] the metabolic benefits of switching back from INSTI to non-INSTI regimens remain uncertain. A key clinical question is whether the weight gained after INSTI initiation is reversible upon discontinuation. Recent evidence addressing this issue, which included PLWH who had experienced ≥7% weight gain within 24 months after the first switch to TAF and/or INSTI while remaining viral suppression, showed that switching to a non-INSTI regimen led to only modest weight reduction after 12 months. This suggests that INSTI-associated weight gain may not be fully reversible.[35] At the same time, INSTI-based therapy has been shown to reduce the risk of LLV and to provide more effective virological control.[36] Therefore, for patients with LLV who concurrently develop MetS, discontinuation of INSTIs may not be a straightforward solution. Clinical management in such cases should instead integrate metabolic risk profiling with routine virological monitoring, and treatment decisions must carefully balance the benefits of sustained viral suppression against the increased risk of MetS. Beyond regimen-specific effects, we conducted time-dependent Cox regression–based sensitivity analyses stratified by ART category to determine whether LLV remained an independent predictor of MetS. In all three ART strata, LLV was consistently associated with a higher hazard of developing MetS compared with no LLV, despite inherent differences in abdominal obesity, hypertension, reduced HDL, baseline CD4 count, HIV viral load, and ART selection. Specifically, among participants on NNRTI+NRTI regimens, the LLV 201–500 group exhibited a 9.7% increased risk of MetS (HR = 1.097, 95% CI: 1.004–1.198, p = 0.040). Within the PI+NRTI cohort, although no individuals fell into the LLV 201–500 category (likely due to smaller sample size), the LLV 51–200 subgroup still exhibited a 38.3% higher risk of MetS (HR = 1.383, 95% CI: 1.093–1.749, p = 0.007). Crucially, in the INSTI+NRTI stratum—where MetS incidence was highest—patients with LLV 51–200 category had a 23.5% increased risk of MetS (HR = 1.235, 95% CI = 1.066–1.431, P = 0.005) and patients with LLV 201–500 category had a 20.8% increased risk of MetS (HR = 1.208, 95% CI =1.007–1.450, P = 0.042). The persistence of LLV's impact on MetS across all ART backbones underscores its robustness as an independent risk factor.

LLV may contribute to the pathogenesis of MetS in PLWH through multifactorial mechanisms, most notably chronic inflammation and immune activation. An HIV viral load of 50 copies/mL is generally recognized as the threshold for viral suppression; however, incomplete suppression above this level permits continuous production of viral proteins and residual viremia. This persistent viral activity sustains chronic, low-grade systemic inflammation,[37] a well-established driver of metabolic disorders.[38] Our study demonstrated that an HIV viral load exceeding 50 copies/mL was associated with a higher risk of MetS. These findings suggest a potential "threshold effect" of MetS in PLWH. In this context, minimal residual viremia just above 50 copies/mL may be sufficient to trigger inflammatory cascades that promote metabolic disturbances. Interestingly, the risk of MetS remained relatively stable across the viral load ranges of 51–200

and 201–500 copies/mL, suggesting that once the inflammatory pathway is activated beyond this threshold, further increases in viral load within the low-level range may not proportionally amplify metabolic risk. In addition, PLWH with LLV had lower CD4 counts compared to No LLV group (Figure 6). This suggests a link between ongoing viral activity and reservoir-driven immune exhaustion. CD4 cells are primary targets of HIV, and their depletion further indicates that viral replication remains ongoing in the context of LLV. Concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), correlate positively with HIV RNA levels in PLWH. Although ART significantly reduces circulating levels of IL-6 and TNF-α, these markers remain elevated compared with healthy controls,[39] indicating chronic inflammation despite virological suppression. TNF-α and IL-6 are secreted by inflammatory cells within dysfunctional adipose tissue and have been implicated in multiple components of MetS, including obesity, insulin resistance, dysregulated lipid metabolism, and hypertension.[40] In addition, C-reactive protein, a nonspecific biomarker regulated by IL-6 and other inflammatory mediators, has been consistently linked to an increased risk of MetS in PLWH.[41,42] Collectively, these findings suggest that HIV-driven chronic inflammation persists even under long-term ART and exerts systemic metabolic effects that contribute to the onset and progression of MetS in PLWH. In addition to persistent viral activity, LLV-related MetS has been associated with sustained immune activation, particularly involving CD8 cells.[43–45] CD8 cell activation is a recognized immunological hallmark of HIV infection and has been increasingly implicated in the pathophysiology of MetS in PLWH.[46] Overactivated CD8 cells secrete proinflammatory cytokines, including IFN-γ, thereby promoting adipose tissue inflammation and contributing to metabolic disorders.[47] This is consistent with our findings that baseline CD8 counts independently predict MetS risk, and longitudinal MLMs demonstrate elevated CD8 counts trajectories in LLV subgroups. The persistent elevation of CD8 counts supports the hypothesis that LLV promotes MetS development through chronic immune activation.

This study has several limitations that warrant consideration. First, MetS is a multifactorial condition influenced by behavioral, environmental, and biological factors. The duration of LLV exposure, key lifestyle variables (eg, diet, exercise), and comorbidities such as hepatitis C were not adjusted for in our analyses. Future studies should incorporate them to provide a more comprehensive assessment of risk. Second, the study was conducted using data from a single-center cohort, which may limit the generalizability of the findings to broader or more diverse populations. Multicenter validation is needed, particularly in regions with different ART access, healthcare systems, or genetic backgrounds, to confirm the applicability of our results. Third, at baseline, individuals with LLV had greater abdominal obesity, a higher prevalence of hypertension, and lower HDL levels, all of which could predispose them to MetS. Although these factors were adjusted for in multivariable and sensitivity analyses, residual confounding is likely to remain. Furthermore, although this analysis supports an association between LLV and MetS, the underlying biological mechanisms remain incompletely understood. Future studies should validate these findings in ethnically diverse populations through large-sample, multicenter, and prospective cohort designs, and should also integrate multi-omics approaches—such as metabolomics (eg, insulin resistance) and inflammatory cytokine profiling (eg, TNF-α, IL-6, CRP) —to comprehensively elucidate the pathophysiological mechanisms linking LLV to metabolic disturbances.

Conclusion

Our study demonstrated that LLV is an independent risk factor for MetS and highlighted the need for more frequent metabolic monitoring in PLWH with LLV. These findings provide novel clinical insights into the pathogenesis of MetS in PLWH. LLV should be regarded not only as a virological concern but also as a metabolic risk factor that warrants closer clinical attention in the post- ART era.

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author, Dr. Yong Jin.

Ethical Statement

The Institutional Review Board of Ningbo Yinzhou No.2 Hospital approved this study (Approval No. 2023-050), and written informed consent was obtained from all the participants. Data confidentiality was strictly maintained by removing all personal identifiers. This study was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

We thank all the participants of the study for their participation.

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.

Funding

The study was supported by the Medical Health Science and Technology Project of Zhejiang Province (grant no. 2024KY1608).

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Chang HH. Weight gain and metabolic syndrome in human immunodeficiency virus patients. *Infect Chemother*. 2022;54(2):220–235. doi:10.3947/ic.2022.0061
2. Rogalska-Płońska M, Grzeszczuk A, Rogalski P, Łucejko M, Flisiak R. Metabolic syndrome in HIV infected adults in Poland. *Kardiol Pol*. 2018;76(3):548–553. doi:10.5603/KP.a2017.0249
3. Lagathu C, Béréziat V, Gorwood J, et al. Metabolic complications affecting adipose tissue, lipid and glucose metabolism associated with HIV antiretroviral treatment. *Expert Opin Drug Saf*. 2019;18(9):829–840. doi:10.1080/14740338.2019.1644317
4. Zicari S, Sessa L, Cotugno N, et al. Immune activation, inflammation, and non-AIDS co-morbidities in HIV-infected patients under long-term ART. *Viruses*. 2019;11(3):200. doi:10.3390/v11030200
5. Zhang T, Ding H, An M, et al. Factors associated with high-risk low-level viremia leading to virologic failure: 16-year retrospective study of a Chinese antiretroviral therapy cohort. *BMC Infect Dis*. 2020;20(1):147. doi:10.1186/s12879-020-4837-y
6. Bai R, Lv S, Hua W, et al. Factors associated with human immunodeficiency virus-1 low-level viremia and its impact on virological and immunological outcomes: a retrospective cohort study in Beijing, China. *HIV Med*. 2022;23(Suppl 1):72–83. doi:10.1111/hiv.13251
7. Li Q, Chen M, Zhao H, et al. Persistent low-level viremia is an independent risk factor for virologic failure: a retrospective cohort study in China. *Infect Drug Resist*. 2021;14:4529–4537. doi:10.2147/idr.S332924
8. Rindi LV, Zaçe D, Compagno M, et al. Management of low-level HIV viremia during antiretroviral therapy: delphi consensus statement and appraisal of the evidence. *Sex Transm Infect*. 2024;100(7):442–449. doi:10.1136/sextrans-2024-056199
9. Vandenhende MA, Ingle S, May M, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *Aids*. 2015;29(3):373–383. doi:10.1097/qad.0000000000000544
10. Fleming J, Mathews WC, Rutstein RM, et al. Low-level viremia and virologic failure in persons with HIV infection treated with antiretroviral therapy. *Aids*. 2019;33(13):2005–2012. doi:10.1097/qad.0000000000002306
11. Liu P, You Y, Liao L, et al. Impact of low-level viremia with drug resistance on CD4 cell counts among people living with HIV on antiretroviral treatment in China. *BMC Infect Dis*. 2022;22(1):426. doi:10.1186/s12879-022-07417-z
12. Ganesan A, Hsieh HC, Chu X, et al. Low level viremia is associated with serious non-AIDS events in people with HIV. *Open Forum Infect Dis*. 2024;11(4):ofae147. doi:10.1093/ofid/ofae147
13. Elvstam O, Medstrand P, Jansson M, Isberg PE, Gisslén M, Björkman P. Is low-level HIV-1 viraemia associated with elevated levels of markers of immune activation, coagulation and cardiovascular disease? *HIV Med*. 2019;20(9):571–580. doi:10.1111/hiv.12756
14. Ryscavage P, Kelly S, Li JZ, Harrigan PR, Taiwo B. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. *Antimicrob Agents Chemother*. 2014;58(7):3585–3598. doi:10.1128/aac.00076-14
15. Acquired Immunodeficiency Syndrome Professional Group SoID, Chinese Medical Association. Chinese guidelines for the diagnosis and treatment of human immunodeficiency virus infection/acquired immunodeficiency syndrome (2024 edition). *Chin Med J*. 2024;137(22):2654–2680. doi:10.1097/cm9.0000000000003383
16. Chinese Society of Health Management CJoHMEC, National Research Center for Clinical Medicine of Geriatric Diseases (Xiangya Hospital). Expert consensus on health education for prevention and control of metabolic syndrome in adults. *Chin J Health Manage*. 2024;18(2):81–92. doi:10.3760/cma.j.cn115624-20231201-00314
17. Trachunthong D, Tipayamongkholgul M, Chumseng S, Darasawang W, Bundhamcharoen K. Burden of metabolic syndrome in the global adult HIV-infected population: a systematic review and meta-analysis. *BMC Public Health*. 2024;24(1):2657. doi:10.1186/s12889-024-20118-3
18. Nguyen KA, Peer N, Mills EJ, Kengne AP. A meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population. *PLoS One*. 2016;11(3):e0150970. doi:10.1371/journal.pone.0150970
19. Ma K, Liu H, Guo L, et al. Comparison of metabolic syndrome prevalence and characteristics using five different definitions in China: a population-based retrospective study. *Front Public Health*. 2024;12:1333910. doi:10.3389/fpubh.2024.1333910
20. Tang J, Chen L, Pan W, et al. Prevalence of metabolic syndrome in people living with HIV and its multi-organ damage: a prospective cohort study. *BMC Infect Dis*. 2025;25(1):351. doi:10.1186/s12879-025-10735-7

21. Papaioannu Borjesson R, Galli L, Muccini C, et al. Increasing incidence and prevalence of metabolic syndrome in people living with HIV during the COVID-19 pandemic. *Front Med*. 2023;10:1220631. doi:10.3389/fmed.2023.1220631
22. Han WM, Law MG, Choi JY, et al. Weight changes, metabolic syndrome and all-cause mortality among Asian adults living with HIV. *HIV Med*. 2022;23(3):274–286. doi:10.1111/hiv.13211
23. AIDS Committee of Chinese Society of Tropical Disease and Parasitology IDPCoZSfMM, Committee of AIDS Diagnosis and Treatment Quality Control Management of Zhejiang Provincial STD/AIDS Prevention Association. Expert consensus on the management of low-level viremia in people living with HIV (2025 version). *Chin J Clin Infect Dis*. 2025;18(01):6–18. doi:10.3760/cma.j.issn.1674-2397.2025.01.002
24. Gui J, Li Y, Liu H, et al. Obesity- and lipid-related indices as a predictor of obesity metabolic syndrome in a national cohort study. *Front Public Health*. 2023;11:1073824. doi:10.3389/fpubh.2023.1073824
25. Martin-Iguacel R, Negredo E, Peck R, Friis-Møller N. Hypertension Is a key feature of the metabolic syndrome in subjects aging with HIV. *Curr Hypertens Rep*. 2016;18(6):46. doi:10.1007/s11906-016-0656-3
26. Liu X, Tao L, Cao K, et al. Association of high-density lipoprotein with development of metabolic syndrome components: a five-year follow-up in adults. *BMC Public Health*. 2015;15:412. doi:10.1186/s12889-015-1747-9
27. Zhang W, Shi J, Wang Y, et al. Risk factors and clinical prediction models for low-level viremia in people living with HIV receiving antiretroviral therapy: an 11-year retrospective study. *Front Microbiol*. 2024;15:1451201. doi:10.3389/fmicb.2024.1451201
28. Tao C, Wei L, Aung MT, et al. Low-level viremia increases the risk of diabetes mellitus in people with HIV in China: a 7-year retrospective longitudinal cohort study [Preprint]. *BMC Medicine*. 2024. doi:10.21203/rs.3.rs-5380470/v1
29. Esber AL, Colt S, Jian N, et al. Persistent low-level viraemia is associated with non-infectious comorbidities in an observational cohort in four African countries. *J Int AIDS Soc*. 2024;27(8):e26316. doi:10.1002/jia2.26316
30. Jin Y, Zhu J, Chen Q, et al. Development and validation of a nomogram for predicting the outcome of metabolic syndrome among people living with HIV after antiretroviral therapy in China. Original Research. *Front Cell Infect Microbiol*. 2025;15:1514823. doi:10.3389/fcimb.2025.1514823
31. Jemal M. A review of dolutegravir-associated weight gain and secondary metabolic comorbidities. *SAGE Open Med*. 2024;12:20503121241260613. doi:10.1177/20503121241260613
32. Ngono Ayissi K, Gorwood J, Le Pelletier L, et al. Inhibition of adipose tissue beiging by HIV integrase inhibitors, dolutegravir and bictegravir, is associated with adipocyte hypertrophy, hypoxia, elevated fibrosis, and insulin resistance in simian adipose tissue and human adipocytes. *Cells*. 2022;11(11):1841. doi:10.3390/cells11111841
33. Thivalapill N, Simelane T, Mthethwa N, et al. Transition to dolutegravir is associated with an increase in the rate of body mass index change in a cohort of virally suppressed adolescents. *Clin Infect Dis*. 2021;73(3):e580–e586. doi:10.1093/cid/ciaa1652
34. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr*. 2017;76(5):527–531. doi:10.1097/qai.0000000000001525
35. Verburgh ML, Wit F, Boyd A, Reiss P, Van der Valk M. No evidence of rapid reversibility of tenofovir alafenamide and/or integrase strand transfer inhibitor-associated weight gain. *Aids*. 2023;37(12):1843–1850. doi:10.1097/qad.0000000000003654
36. Shi J, Ying G, Zheng R, Zhang Z. Clinical significance and management of low-level HIV viremia in the era of integrase strand transfer inhibitors. *HIV Med*. 2024;25(3):361–369. doi:10.1111/hiv.13585
37. Eastburn A, Scherzer R, Zolopa AR, et al. Association of low level viremia with inflammation and mortality in HIV-infected adults. *PLoS One*. 2011;6(11):e26320. doi:10.1371/journal.pone.0026320
38. Weiss TW, Arnesen H, Seljeflot I. Components of the interleukin-6 transsignalling system are associated with the metabolic syndrome, endothelial dysfunction and arterial stiffness. *Metabolism*. 2013;62(7):1008–1013. doi:10.1016/j.metabol.2013.01.019
39. Okay G, Koc MM, Guler EM, Yabaci A, Kocyigit A, Akkoyunlu Y. The effect of antiretroviral therapy on IL-6, IL-1β, TNF-α, IFN-γ levels and their relationship with HIV-RNA and CD4+ T cells in HIV patients. *Curr HIV Res*. 2020;18(5):354–361. doi:10.2174/1570162x18666200712174642
40. Valado A, Cunha M, Pereira L. Biomarkers and seaweed-based nutritional interventions in metabolic syndrome: a comprehensive review. *Mar Drugs*. 2024;22(12):550. doi:10.3390/md22120550
41. Jeong H, Baek SY, Kim SW, et al. C reactive protein level as a marker for dyslipidaemia, diabetes and metabolic syndrome: results from the Korea national health and nutrition examination survey. *BMJ Open*. 2019;9(8):e029861. doi:10.1136/bmjopen-2019-029861
42. Arbune M, Plesea-Condratovici A, Arbune AA, Andronache G, Plesea-Condratovici C, Gutu C. Cardiovascular risk in people living with HIV: a preliminary case study from Romania. *Medicina*. 2025;61(8):1468. doi:10.3390/medicina61081468
43. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *Aids*. 2004;18(7):981–989. doi:10.1097/00002030-200404300-00005
44. Han J, Mu W, Zhao H, et al. HIV-1 low-level viremia affects T cell activation rather than T cell development in school-age children, adolescents, and young adults during antiretroviral therapy. *Int J Infect Dis*. 2020;91:210–217. doi:10.1016/j.ijid.2019.12.001
45. Zheng L, Taiwo B, Gandhi RT, et al. Factors associated with CD8+ T-cell activation in HIV-1-infected patients on long-term antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2014;67(2):153–160. doi:10.1097/qai.0000000000000286
46. Psomas C, Younas M, Reynes C, et al. One of the immune activation profiles observed in HIV-1-infected adults with suppressed viremia is linked to metabolic syndrome: the ACTIVIH study. *EBioMedicine*. 2016;8:265–276. doi:10.1016/j.ebiom.2016.05.008
47. Wang Q, Wang Y, Xu D. The roles of T cells in obese adipose tissue inflammation. *Adipocyte*. 2021;10(1):435–445. doi:10.1080/21623945.2021.1965314