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Association between low-density lipoprotein cholesterol with cholelithiasis among hospitalized people living with HIV: a retrospective case-control study

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Abstract

Objective

To investigate the association between low-density lipoprotein cholesterol (LDL-C) levels and cholelithiasis among hospitalized people living with HIV.

Methods

We conducted a single-center retrospective case-control study including 259 hospitalized people living with HIV admitted between January 2019 and January 2025. The case group comprised 98 patients with imaging-confirmed cholelithiasis, and the control group comprised 161 patients without imaging evidence of cholelithiasis during the same period. Demographic characteristics, co-infections, antiretroviral therapy-related variables, and laboratory parameters were collected. Logistic regression models were used to evaluate the association between LDL-C and cholelithiasis. Model I was adjusted for sex, age, and body mass index (BMI), and Model II was further adjusted for hepatitis B virus (HBV) co-infection, duration since confirmed HIV diagnosis, albuvirtide (ABT) treatment, and CD4 + T-cell count. Smooth-curve fitting and segmented regression were used to explore a potential nonlinear association. Stratified analyses and interaction tests were conducted as exploratory analyses.

Results

Compared with controls, patients with cholelithiasis were younger (50.22 ± 11.71 vs. 56.30 ± 16.00 years) and more likely to be female (40.82% vs. 6.21%). BMI was similar between groups. The case group had higher total cholesterol, high-density lipoprotein cholesterol, and LDL-C levels than the control group, with mean LDL-C levels of 3.08 ± 0.96 mmol/L and 2.42 ± 0.75 mmol/L, respectively. In univariable analysis, LDL-C was significantly associated with cholelithiasis (OR = 2.54, 95% CI: 1.80–3.58; P < 0.001). This association remained significant after multivariable adjustment (Model II: OR = 2.71, 95% CI: 1.79–4.11; P < 0.001). Smooth-curve fitting suggested a nonlinear association, with an exploratory inflection point at 2.28 mmol/L. Below this threshold, the association was not statistically significant; above it, the positive association was substantially stronger. No significant interaction was observed for HBV or ABT.

Conclusion

Among hospitalized people living with HIV, elevated LDL-C was independently associated with cholelithiasis. The data also suggest a possible nonlinear association, with a stronger effect above 2.28 mmol/L. These findings may help identify metabolic risk factors for cholelithiasis in this population, but confirmation in larger prospective studies is required.

Introduction

Human immunodeficiency virus (HIV) infection has evolved from a rapidly fatal disease into a chronic and increasingly manageable condition. With the widespread use of combination antiretroviral therapy

(cART), life expectancy among people living with HIV has increased substantially. At the same time, however, metabolic complications have become an increasingly important clinical concern [1–3]. Previous studies have shown that HIV infection itself, together with the accompanying chronic inflammatory state, can disrupt lipid metabolism and contribute to metabolic abnormalities such as metabolic syndrome and insulin resistance [4–6]. In addition, people living with HIV often exhibit elevated cholesterol and triglyceride levels, some of which are closely related to antiretroviral therapy [7]. These factors collectively pose greater challenges for metabolic health management in this population.

Dyslipidemia is a well-recognized contributor to cholelithiasis. Epidemiological and clinical studies have consistently shown that patients with cholelithiasis often present with abnormal lipid profiles, including elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, along with reduced high-density lipoprotein cholesterol (HDL-C) levels [8–10]. Among these lipid parameters, LDL-C has attracted particular attention. A Mendelian randomization study demonstrated that the effect of free thyroxine (FT4) on cholelithiasis risk was partially mediated by LDL-C and apolipoprotein B, accounting for 17.4% and 13.5% of the total mediating effect, respectively [11]. Another study reported that genetically proxied LDL-C reduction mediated by single-nucleotide polymorphisms near the *HMGCR* gene, mimicking the pharmacological effect of statins, was significantly associated with a lower risk of cholelithiasis [12]. Moreover, multivariable analyses of modifiable risk factors for cholelithiasis have suggested that the relationship between LDL-C and cholelithiasis risk may be more complex than previously appreciated [13]. Clinical evidence has further shown that patients with cholelithiasis have significantly higher preoperative LDL-C levels than healthy controls, and that lipid profiles tend to normalize after cholecystectomy [9], further supporting a potential link between LDL-C abnormalities and gallstone formation.

Despite these observations, evidence regarding the association between LDL-C and cholelithiasis in people living with HIV remains limited. Previous studies have suggested that HIV-infected individuals with cholelithiasis may exhibit higher LDL-C levels and enhanced bile acid synthetic activity, and that these features may be influenced by factors such as age and cART regimens [7]. However, the available evidence has largely been derived from small observational studies or has focused on other metabolic indicators. To date, systematic retrospective case-control analyses specifically examining the association between LDL-C levels and cholelithiasis among hospitalized people living with HIV are lacking. Furthermore, HIV-related chronic inflammation, immune reconstitution, and drug–metabolism interactions may lead to a distinct pattern in the relationship between lipid metabolism and cholelithiasis in this population [14]. Current risk models for cholelithiasis also rarely incorporate HIV infection status as a relevant clinical context [15–17].

Against this background, we conducted a single-center retrospective case-control study among hospitalized people living with HIV admitted between January 2019 and January 2025 to investigate the association between LDL-C levels and cholelithiasis. We further explored whether this association was potentially nonlinear and evaluated the robustness of the findings through stratified analyses and interaction tests. This study aimed to clarify the association between LDL-C levels and cholelithiasis in

hospitalized people living with HIV, to further explore the potential nonlinear nature of this relationship, and to provide a clinical basis for future prospective studies.

Patients and Methods

1. Study design and participants

This was a single-center retrospective case-control study. We included hospitalized people living with HIV who were admitted to the Public Health Clinical Center of Chengdu between January 2019 and January 2025. According to the results of abdominal imaging examinations performed during hospitalization, including ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), participants were classified into a case group and a control group. The case group comprised patients with HIV infection who had imaging-confirmed cholelithiasis, whereas the control group comprised hospitalized people living with HIV during the same period who had no imaging evidence of cholelithiasis. The detailed inclusion and exclusion criteria were as follows.

1.1 Inclusion criteria

Participants were eligible if they met all of the following criteria: (1) age ≥ 18 years; (2) confirmed HIV infection based on an initial positive HIV antibody screening test and subsequent confirmation by the Chinese Center for Disease Control and Prevention, with the diagnosis of AIDS made in accordance with the *Chinese Guidelines for the Diagnosis and Treatment of HIV/AIDS*; (3) complete abdominal imaging data during hospitalization, including ultrasonography, CT, or MRI, sufficient to determine the presence or absence of gallstones; (4) availability of LDL-C results obtained within 24–48 hours after admission; (5) complete clinical data.

1.2 Exclusion criteria

Participants were excluded if they met any of the following criteria: (1) age < 18 years; (2) pregnancy or puerperium; (3) presence of biliary tract malignancy, congenital biliary malformations, primary sclerosing cholangitis, or other severe conditions that could interfere with assessment, such as severe cardiovascular or cerebrovascular disease, hematologic disorders, or other malignancies; (4) missing imaging data, LDL-C values, or other key clinical information; (5) LDL-C measured only after biliary intervention or after severe infection/shock; (6) previous cholecystectomy; (7) repeated hospitalizations for the same patient, in which case only the first admission was retained.

A total of 259 eligible patients were ultimately included in the analysis, comprising 98 cases and 161 controls (Fig. 1).

2. Data collection and variable definitions

Data were collected on demographic characteristics, medical history, co-infections, HIV-related variables, and laboratory findings. Demographic and clinical variables included age, sex, body mass index (BMI), ethnicity, marital status, smoking history, alcohol consumption, hypertension, diabetes mellitus, and coronary heart disease. Co-infections included hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and *Mycobacterium tuberculosis* infection. HIV-related variables included duration since confirmed HIV infection, whether the patient was newly diagnosed with HIV infection, combination antiretroviral therapy (cART) regimen, and albuvirtide (ABT) treatment.

Laboratory parameters included complete blood count variables, including white blood cell count (WBC), neutrophil count (Neu), hemoglobin (Hb), and platelet count (PLT); biochemical indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin (Alb), globulin (Glo), total bilirubin (TBIL), urea, creatinine (Cr), calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}), and chloride (Cl^{-}); lipid profile variables, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); coagulation function, represented by prothrombin time (PT); CD4 + T-cell count, CD8 + T-cell count, CD4+/CD8 + ratio, and plasma HIV-1 RNA.

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Duration since confirmed HIV infection was defined as the time from the first confirmed HIV diagnosis to the index hospitalization and was expressed in months. Plasma HIV-1 RNA was categorized as ≤ 20 copies/mL and > 20 copies/mL. Values reported as < 20 copies/mL were classified into the ≤ 20 copies/mL group, indicating that the HIV-1 RNA level was below the lower limit of quantification of the assay.

3. Statistical analysis

All statistical analyses were performed using R software (version 4.2.0; The R Foundation for Statistical Computing, Vienna, Austria) and EmpowerStats. Normally distributed continuous variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median and interquartile range (IQR). Categorical variables are presented as number (percentage). Between-group comparisons were performed using the independent-samples *t* test or Wilcoxon rank-sum test for continuous variables, as appropriate, and the chi-square test or Fisher's exact test for categorical variables.

Univariable logistic regression analyses were first conducted to evaluate the associations between clinical variables and cholelithiasis. Multivariable logistic regression models were then fitted to assess the association between LDL-C and cholelithiasis. Covariates were prespecified on the basis of clinical relevance, prior literature, and model parsimony. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided P value < 0.05 was considered statistically significant; values < 0.001 are reported as P < 0.001.

To explore a potential nonlinear association between LDL-C and cholelithiasis, smooth-curve fitting was performed after multivariable adjustment. When a nonlinear trend was suggested, segmented logistic regression was used to estimate the exploratory inflection point and the effect sizes on either side of the threshold. Stratified analyses were conducted according to age, sex, BMI, HBV co-infection status, duration since confirmed HIV diagnosis, receipt of ABT, and CD4 + T-cell count. Interaction terms were incorporated into the final model to explore potential effect modification. Both stratified and interaction analyses were interpreted as exploratory.

Results

1. Clinical characteristics

1.1 Demographic and clinical characteristics

A total of 259 hospitalized people living with HIV were included, of whom 98 had cholelithiasis and 161 did not. Compared with controls, patients with cholelithiasis were younger (50.22 ± 11.71 vs. 56.30 ± 16.00 years) and more likely to be female (40.82% vs. 6.21%). BMI was similar between the two groups (23.00 ± 2.91 vs. 22.71 ± 3.17 kg/m²). The case group also had a higher prevalence of HBV co-infection (8.16% vs. 2.50%) and a higher proportion of ABT treatment (83.67% vs. 57.76%). The median duration since confirmed HIV diagnosis was similar between groups. Detailed baseline characteristics are presented in Table 1.

Table 1
Baseline demographic and clinical characteristics of 259 hospitalized patients

Characteristics	Controls(n = 161)	Cases(n = 98)
Age, Mean ± SD, y	56.30 (16.00)	50.22 (11.71)
Sex, N(%)		
Women	10 (6.21%)	40 (40.82%)
Men	151 (93.79%)	58 (59.18%)
BMI, Mean ± SD	22.71 (3.17)	23.00 (2.91)
Ethnicity, N(%)		
Han	155 (96.27%)	86 (87.76%)
Tibetan	4 (2.48%)	4 (4.08%)
Yi	2 (1.24%)	7 (7.14%)
Miao	0 (0.00%)	1 (1.02%)
Marital Status, N(%)		
Single	30 (18.63%)	15 (15.31%)
Married	119 (73.91%)	76 (77.55%)
Divorced	9 (5.59%)	6 (6.12%)
Widowed	3 (1.86%)	1 (1.02%)
Smoking, N(%)		
NO	84 (52.17%)	69 (70.41%)
YES	77 (47.83%)	29 (29.59%)
Alcohol Consumptionn, N(%)		
NO	122 (75.78%)	85 (86.73%)
YES	39 (24.22%)	13 (13.27%)
Hypertension, N(%)		
NO	135 (83.85%)	86 (87.76%)
YES	26 (16.15%)	12 (12.24%)
Diabetes Mellitus, N(%)		

Table 1
Continued

Characteristics	Controls(n = 161)	Cases(n = 98)
NO	151 (93.79%)	89 (90.82%)
YES	10 (6.21%)	9 (9.18%)
Coronary Heart Disease, N(%)		
NO	159 (98.76%)	97 (100.00%)
YES	2 (1.24%)	0 (0.00%)
HBV, N(%)		
NO	156 (97.50%)	90 (91.84%)
YES	4 (2.50%)	8 (8.16%)
HCV, N(%)		
NO	161 (100.00%)	97 (98.98%)
YES	0 (0.00%)	1 (1.02%)
Syphilis, N(%)		
NO	157 (97.52%)	93 (94.90%)
YES	4 (2.48%)	5 (5.10%)
Tuberculosis, N(%)		
NO	158 (98.14%)	94 (95.92%)
YES	3 (1.86%)	4 (4.08%)
Duration since confirmed HIV infection, M (IQR), Months	29.00 (6.00–60.00)	29.50 (5.00–60.00)
Patients with newly diagnosed HIV infection, N(%)		
NO	139 (86.34%)	86 (87.76%)
YES	22 (13.66%)	12 (12.24%)
cART Regimen, N(%)		
Not used	22 (13.66%)	16 (16.33%)
Potentially LDL-C friendly	3 (1.86%)	1 (1.02%)
Potentially LDL-C unfavorable	136(84.47%)	81 (82.65%)
Treated with ABT, N(%)		

Characteristics	Controls(n = 161)	Cases(n = 98)
NO	68 (42.24%)	16 (16.33%)
YES	93 (57.76%)	82 (83.67%)

1.2 Laboratory characteristics

Comparison of laboratory parameters showed that patients in the case group had higher levels of TC, HDL-C, and LDL-C than those in the control group [5.09 (1.13) mmol/L vs. 4.36 (0.74) mmol/L; 1.21 (0.32) mmol/L vs. 1.11 (0.35) mmol/L; and 3.08 ± 0.96 mmol/L vs. 2.42 ± 0.75 mmol/L, respectively]. CD4 + T-cell counts were slightly higher in the case group than in the control group [366.50 (245.50-484.50) cells/μL vs. 317.00 (192.00-445.00) cells/μL], whereas CD8 + T-cell counts were comparable between the two groups [494.00 (343.25–709.50) cells/μL vs. 482.00 (329.00-706.00) cells/μL]. In addition, PLT and GGT levels were higher in the case group, whereas urea levels and prothrombin time were lower than those in the control group. Detailed laboratory findings are shown in Table 2.

Table 2
The Laboratory characteristics of 259 hospitalized patients

Laboratory Tests	Controls(n = 161)	Cases(n = 98)
	Mean ± SD or M (IQR)	Mean ± SD or M (IQR)
WBC, 10^9/L	5.32 (4.35–7.46)	5.73 (2.16)
Neu, 10^9/L	3.26 (2.53–5.40)	3.35 (2.65–4.42)
Hb, g/L	136.20 (21.02)	136.63 (18.43)
PLT, 10^9/L	166.22 (59.15)	183.92 (56.03)
ALT, U/L	26.00 (19.00–40.00)	28.00 (21.00-54.25)
AST, U/L	24.00 (20.00–33.00)	26.00 (19.00–38.00)
ALP, U/L	95.09 (32.30)	95.50 (77.50-120.75)
GGT, U/L	35.00 (24.00–57.00)	53.00 (26.00-137.25)
Alb, g/L	40.63 (5.91)	41.18 (4.67)
Glo, g/L	29.25 (5.56)	30.09 (7.24)
TBIL, umol/L	8.40 (5.80–11.70)	8.00 (5.65–14.60)
Urea, mmol/L	5.66 (1.89)	4.75 (1.61)
Cr, umol/L	71.69 (18.20)	66.66 (29.13)
Ca^{2+}, mmol/L	2.21 (0.16)	2.21 (0.14)
$Na^{\pm}$, mmol/L	139.34 (11.04)	140.48 (2.87)
K^{+}, mmol/L	4.09 (0.35)	4.02 (0.41)
CL^{-}, mmol/L	105.21 (3.84)	105.40 (4.22)
TC, mmol/L	4.36 (0.74)	5.09 (1.13)
TG, mmol/L	1.34 (1.01–1.95)	1.50 (1.08–2.10)
HDL-C, mmol/L	1.11 (0.35)	1.21 (0.32)
LDL-C, mmol/L	2.42 (0.75)	3.08 (0.96)
PT, s	13.26 (1.21)	12.87 (1.49)
$CD4^{\pm}$T cell, cells/ul	317.00 (192.00-445.00)	366.50 (245.50-484.50)
$CD4^{\pm}$T cell, cells/ul, N(%)		
< 200	42 (26.09%)	19 (19.39%)

Laboratory Tests	Controls(n = 161)	Cases(n = 98)
	Mean ± SD or M (IQR)	Mean ± SD or M (IQR)
≥ 200, < 500	87 (54.04%)	56 (57.14%)
≥ 500	32 (19.88%)	23 (23.47%)
$CD8^{\pm}$T cell, cells/ul	482.00 (329.00-706.00)	494.00 (343.25–709.50)
$CD4^{\pm}$T cell/$CD8^{\pm}$T cell ratio	0.66 (0.35–1.09)	0.69 (0.41–1.06)
CD4 + T cell/CD8 + T cell ratio, N(%)		
< 1	113 (70.19%)	70 (71.43%)

Table 2
Continued

Laboratory Tests	Controls(n = 161)	Cases(n = 98)
	Mean ± SD or M (IQR)	Mean ± SD or M (IQR)
≥ 1	48 (29.81%)	28 (28.57%)
Plasma HIV-1 RNA, copies/mL, N(%)		
≤ 20	111 (68.94%)	67 (68.37%)
> 20	50 (31.06%)	31 (31.63%)

2. Association between LDL-C and cholelithiasis in patients with HIV infection

2.1 Univariable logistic regression analysis for cholelithiasis

In univariable logistic regression analysis, LDL-C was significantly and positively associated with cholelithiasis (OR = 2.54, 95% CI: 1.80–3.58, $P < 0.001$). TC and HDL-C were also positively associated with cholelithiasis, with ORs (95% CIs) of 2.47 (1.77–3.44) and 2.37 (1.12–5.02), respectively (both $P < 0.05$). HBV co-infection showed a borderline significant positive association with cholelithiasis (OR = 3.47, 95% CI: 1.02–11.84, $P = 0.050$), and ABT treatment was associated with a higher likelihood of cholelithiasis (OR = 3.75, 95% CI: 2.02–6.97, $P < 0.001$). Detailed univariable results are provided in Table 3.

Table 3
Univariate analysis for cholelithiasis

Covariate	Statistics	OR (95%CI)	p-value
Age	54.00 ± 14.80	0.97(0.96, 0.99)	< 0.001
Sex			
Women	50 (19.31%)	Reference	
Men	209 (80.69%)	0.10 (0.05, 0.21)	< 0.001
BMI	22.82 ± 3.07	1.03 (0.95, 1.12)	0.46
Ethnicity			
Han	241 (93.05%)	Reference	
Tibetan	8 (3.09%)	1.80 (0.44, 7.39)	0.41
Yi	9 (3.47%)	6.31 (1.28, 31.04)	0.02
Miao	1 (0.39%)	3817649.96 (0.00, Inf)	0.99
Marital Status			
Single	45 (17.38%)	Reference	
Married	195 (75.29%)	1.28 (0.65, 2.53)	0.48
Divorced	15 (5.79%)	1.33 (0.40, 4.45)	0.64
Widowed	4 (1.54%)	0.67 (0.06, 6.97)	0.73
Smoking			
NO	153 (59.07%)	Reference	
YES	106 (40.93%)	0.46 (0.27, 0.78)	0.001
Alcohol Consumptionn			
NO	207 (79.92%)	Reference	

Table 3
Continued

Covariate	Statistics	OR (95%CI)	p-value
YES	52 (20.08%)	0.48 (0.24, 0.95)	0.04
Hypertension			
NO	221 (85.33%)	Reference	
YES	38 (14.67%)	0.73 (0.35, 1.51)	0.39
Diabetes Mellitus			
NO	240 (92.66%)	Reference	
YES	19 (7.34%)	1.53 (0.60, 3.90)	0.38
Coronary Heart Disease			
NO	256 (99.22%)	Reference	
YES	2 (0.78%)	0.00 (0.00, Inf)	0.98
HBV			
NO	246 (95.35%)	Reference	
YES	12 (4.65%)	3.47 (1.02, 11.84)	0.05
HCV			
NO	258 (99.61%)	Reference	
YES	1 (0.39%)	3515742.02 (0.00, Inf)	0.99
Syphilis			
NO	250 (96.53%)	Reference	
YES	9 (3.47%)	2.11 (0.55, 8.06)	0.27
Tuberculosis			
NO	252 (97.30%)	Reference	
YES	7 (2.70%)	2.24 (0.49, 10.23)	0.30
Duration since confirmed HIV infection	29.00 (0.00-168.00)	1.00 (0.99, 1.00)	0.47
Patients with newly diagnosed HIV infection			
YES	34 (13.13%)	Reference	
NO	225 (86.87%)	1.13 (0.53, 2.41)	0.74
cART Regimen			

Covariate	Statistics	OR (95%CI)	p-value
Not used	38 (14.67%)	Reference	
Potentially LDL-C friendly	4 (1.54%)	0.46 (0.04, 4.82)	0.52
Potentially LDL-C unfavorable	217 (83.79%)	0.82 (0.41, 1.65)	0.58
Treated with ABT			
NO	84 (32.43%)	Reference	
YES	175 (67.57%)	3.75 (2.02, 6.97)	0.001
WBC	5.32 (2.28–22.45)	0.90 (0.83, 0.98)	0.02
Neu	3.26 (1.12–57.70)	0.97 (0.91, 1.04)	0.35
Hb	136.37 ± 20.05	1.00 (0.99, 1.01)	0.87

Table 3. **Continued**

Covariate	Statistics	OR (95%CI)	p-value
PLT	172.92 ± 58.51	1.01 (1.00, 1.00)	0.02
ALT	27.00 (6.00-562.00)	1.01 (1.00, 1.01)	0.01
AST	25.00 (6.00-718.00)	1.01 (1.00, 1.01)	0.04
ALP	92.00 (27.00-1079.00)	1.01 (1.00, 1.01)	0.001
GGT	39.00 (7.00-1182.00)	1.01 (1.00, 1.01)	0.001
Alb	40.84 ± 5.48	1.02 (0.97, 1.07)	0.43
Glo	29.57 ± 6.25	1.02 (0.98, 1.06)	0.30
TBIL	8.20 (2.00-143.40)	1.04 (1.01, 1.06)	0.01
Urea	5.31 ± 1.84	0.73 (0.62, 0.86)	0.001
Cr	69.79 ± 23.03	0.99 (0.97, 1.00)	0.09
Ca^{2+}	2.21 ± 0.15	1.20 (0.23, 6.35)	0.83
Na^{+}	139.77 ± 8.89	1.04 (0.95, 1.14)	0.36
K^{+}	4.07 ± 0.38	0.58 (0.30, 1.15)	0.12
CL^{-}	105.29 ± 3.98	1.01 (0.95, 1.08)	0.71
TC	4.64 ± 0.97	2.47 (1.77, 3.44)	< 0.001
TG	1.38 (0.51–9.58)	1.23 (0.95, 1.59)	0.11
HDL-C	1.15 ± 0.34	2.37 (1.12, 5.02)	0.02
LDL-C	2.67 ± 0.89	2.54 (1.80, 3.58)	<0.001
PT	13.11 ± 1.33	0.79 (0.63, 0.98)	0.03
CD4 + T cell	332.00 (5.00-1369.00)	1.00 (0.99, 1.00)	0.20
CD4 + T cell			
<200	61 (23.55%)	Reference	
≥200, < 500	143 (55.21%)	1.42 (0.75, 2.69)	0.28
≥500	55 (21.24%)	1.57 (0.74, 3.40)	0.23
CD8 + T cell	492.00 (112.00-1651.00)	1.00 (0.99, 1.00)	0.30
CD4 + T cell/CD8 + T cell ratio	0.67 (0.01–3.55)	0.91(0.61, 1.35)	0.63
CD4 + T cell/CD8 + T cell ratio			

Covariate	Statistics	OR (95%CI)	p-value
<1	183 (70.66%)	Reference	
≥1	76 (29.34%)	0.94 (0.54, 1.64)	0.83
Plasma HIV-1 RNA			
≤20	178 (68.73%)	Reference	
>20	81 (31.27%)	1.03 (0.6.0, 1.76)	0.92

2.2 Multivariable logistic regression analysis of the association between LDL-C and cholelithiasis

In the unadjusted model, LDL-C was significantly associated with cholelithiasis (OR = 2.54, 95% CI: 1.80–3.58, *P* < 0.001). In Model I, after adjustment for sex, age, and BMI, the association remained significant (OR = 2.54, 95% CI: 1.73–3.71, *P* < 0.001). In Model II, after further adjustment for HBV co-infection, ABT treatment, duration since confirmed HIV infection, and CD4 + T-cell count, the association remained stable and the effect estimate was slightly strengthened (OR = 2.71, 95% CI: 1.79–4.11, *P* < 0.001). These findings support an independent association between elevated LDL-C and cholelithiasis in this inpatient HIV population (Table 4).

Table 4
Relationship between LDL-C and cholelithiasis

Outcome	Crude Model		Model □		Model □	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
LDL-C	2.54 (1.80, 3.58)	< 0.001	2.54 (1.73, 3.71)	<0.001	2.71 (1.79, 4.11)	< 0.001

2.3 Nonlinear relationship and threshold effect analysis of LDL-C and cholelithiasis

Smooth-curve fitting suggested a possible nonlinear association between LDL-C and cholelithiasis. Segmented logistic regression identified an exploratory inflection point at 2.28 mmol/L. Below this threshold, LDL-C was not significantly associated with cholelithiasis (effect estimate = 0.66, 95% CI: 0.194–2.23; P = 0.50). At or above 2.28 mmol/L, LDL-C was strongly and positively associated with cholelithiasis (effect estimate = 4.31, 95% CI: 2.324–7.994; P < 0.001). These findings suggest that the association may become more pronounced above a certain LDL-C level (Fig. 2 and Table 5).

A threshold, nonlinear association between LDL-C and cholelithiasis was found in a generalized additive model (GAM). Solid rad line represents the smooth curve fit between variables. Blue bands represent the

95% of confidence interval from the fit. All adjusted for sex, age, and BMI, HBV co-infection, ABT treatment, duration since confirmed HIV infection, and CD4 + T-cell count.

Table 5
Threshold effect analysis of LDL-C and cholelithiasis using piecewise linear regression.

Inflection point of LDL-C	Effect size(β)	95%CI	P value
< 2.28	0.66	0.194 to 2.23	0.50
≥ 2.28	4.31	2.324 to 7.994	< 0.001

2.4 Stratified and interaction analyses

In exploratory stratified analyses, the positive association between LDL-C and cholelithiasis was directionally consistent across most subgroups. The association was statistically significant across all age strata and among men, patients with BMI > = 18 kg/m², those with longer duration since confirmed HIV diagnosis, and those with CD4 + T-cell counts across all prespecified categories ($P < 0.05$). In the HBV co-infection and ABT treatment stratified analyses, the association was more pronounced in the non-HBV-infected subgroup and the ABT-treated subgroup. Although the direction of association remained consistent in the HBV-infected subgroup and the non-ABT-treated subgroup, statistical significance was not reached (Table 6).

Interaction analyses did not show significant effect modification by HBV or ABT. In the fully adjusted model, the association between LDL-C and cholelithiasis remained significant in the non-HBV-infected subgroup and in the ABT-treated subgroup; however, the P values for interaction were 0.862 and 0.212, respectively (Table 7).

Table 6
Stratified Analysis of the Association Between LDL-C and Cholelithiasis

Characteristic	Number of cases	OR (95%CI)	p-value
Age, y			
21–48	85	2.29 (1.27, 4.13)	0.006
49–62	86	4.33 (2.02, 9.28)	0.000
63–85	88	2.12 (1.12, 3.98)	0.020
Sex			
Women	50	2.11 (0.83, 5.35)	0.116
Men	209	2.57 (1.72, 3.85)	< 0.0001
BMI, kg/m^2			
<18	13	3.03 (0.58, 15.70)	0.187
>=18, < 24	163	2.53 (1.59, 4.02)	< 0.0001
>=24	83	2.37 (1.38, 4.07)	0.002
HBV			
NO	246	2.65 (1.84, 3.80)	<0.0001
YES	12	1.65 (0.52, 5.29)	0.396
Duration since confirmed HIV infection, Months			

Table 6
Continued

Characteristic	Number of cases	OR (95%CI)	p-value
0–11	81	1.82 (1.11, 3.00)	0.017
12–46	82	2.91 (1.50, 5.66)	0.002
48–168	96	3.63 (1.85, 7.12)	0.000
Treated with ABT			
NO	84	1.76 (0.92, 3.39)	0.089
YES	175	2.97 (1.91, 4.60)	<0.0001
$CD4^+$ T cell, cells/ul			
<200	61	2.12 (1.13, 3.97)	0.019
≥200, < 500	143	2.68 (1.64, 4.39)	< 0.0001
≥500	55	2.85 (1.38, 5.86)	0.005

Table 7
Interaction analyses of LDL-C with HBV and ABT in relation to cholelithiasis

Effect Modifier	Category	Adjusted OR (95% CI)	P value	P for interaction
HBV	NO	2.82 (1.81–4.38)	< 0.001	0.862
	YES	3.40 (0.41–27.99)	0.26	
ABT	NO	1.79 (0.87–3.65)	0.11	0.212
	YES	3.18 (1.86–5.42)	< 0.001	

Discussion

In this single-center retrospective case-control study of hospitalized people living with HIV, We systematically evaluated the association between LDL-C and cholelithiasis in hospitalized people living with HIV and further explored its potential nonlinear pattern, threshold effect, and consistency across subgroups. The results showed that patients in the case group were younger, more likely to be female, and had higher proportions of HBV co-infection and albuvirtide (ABT) treatment than those in the control group. Previous studies have shown that cholelithiasis is more common in women and in individuals with metabolic abnormalities, which may be related to disturbances in cholesterol metabolism, hormonal factors, and impaired gallbladder motility [18–22]. In addition, age and co-infection status may indirectly affect cholesterol homeostasis and bile composition through metabolic pathways [7, 23, 24]. In the present study, LDL-C levels were significantly higher in the case group than in the control group, a finding generally consistent with previous observations of elevated LDL-C levels and enhanced bile acid

synthesis in women with HIV infection and cholelithiasis [7]. Taken together, these factors may partly explain the lower risk of cholelithiasis observed in the control group.

In the association analyses, we found that LDL-C was significantly positively associated with cholelithiasis (OR = 2.54, 95% CI: 1.80–3.58, $P < 0.001$). This positive association remained statistically significant and robust after adjustment for potential confounders, including sex, age, BMI, HBV co-infection, ABT treatment, duration since HIV diagnosis, and CD4 + T-cell count. It should be noted that LDL-C, TC, HDL-C, and triglycerides are all lipid-related parameters and are physiologically highly correlated [25]. Simultaneous inclusion of these variables in the same multivariable model could therefore introduce multicollinearity [26, 27]. For this reason, LDL-C was treated as the primary exposure of interest, whereas TC, HDL-C, and TG were not included simultaneously in the final multivariable model. Similarly, although univariable analyses suggested that some liver function indicators, including ALT, AST, ALP, GGT, and TBIL, might be associated with cholelithiasis in patients with HIV infection, these markers may also lie downstream of the LDL-C–cholelithiasis relationship or may be affected by cholelithiasis itself [28–30]. To avoid overadjustment or collider bias, these liver function parameters were not included in the primary multivariable model [31, 32].

From a biological perspective, cholesterol is a major constituent of bile, and its homeostasis is regulated through multiple pathways, including endogenous synthesis, exogenous uptake, and biliary secretion [33–35]. Previous studies have shown that people living with HIV are prone to developing hypercholesterolemia after receiving combination antiretroviral therapy (cART) [6, 36, 37]. Meanwhile, patients with cholelithiasis often exhibit upregulated expression of key molecules involved in bile acid synthesis, such as *CYP7A1*, *HNF1α*, and *LXRβ*, suggesting that disordered cholesterol metabolism and abnormal bile acid synthesis may jointly contribute to gallstone formation [7, 38, 39]. When circulating LDL-C levels increase, more cholesterol may be delivered to the liver and enter biliary metabolic pathways, thereby increasing the risk of biliary cholesterol supersaturation and cholesterol crystal precipitation, which is one of the key pathological bases of cholesterol gallstone formation [40–42]. Previous studies have also supported a positive association between elevated LDL-C levels and an increased risk of cholelithiasis [43]. Nevertheless, the existing evidence is not entirely consistent. Some Mendelian randomization studies have suggested that genetically predicted elevations in LDL-C do not necessarily directly increase the risk of cholelithiasis [12], indicating that the relationship may not represent a simple linear causal pathway. Rather, it may be influenced by multiple factors, including population heterogeneity [44], gallstone subtype [45], and differences in LDL-C regulatory pathways [46]. For example, *HMGCR* variants that mimic the effects of statins have been associated with a reduced risk of cholelithiasis, whereas ezetimibe, which targets *NPC1L1*, and PCSK9 inhibitors do not appear to confer the same effect despite achieving comparable reductions in LDL-C. This suggests that the molecular target of lipid-lowering therapy, rather than a change in LDL-C level alone, may have a greater influence on gallstone formation [43]. Accordingly, the association observed in the present study is more likely to reflect a complex metabolic phenotype in people living with HIV, shaped by the combined effects of cART exposure, changes in immune status, and metabolic disturbances, rather than a direct causal effect of LDL-C alone.

To further characterize the relationship between LDL-C and cholelithiasis in patients with HIV infection, we performed smooth curve fitting and threshold effect analyses, which suggested a potential nonlinear association between the two. Specifically, in this special population of people living with HIV, the risk of cholelithiasis appeared to increase markedly when LDL-C reached or exceeded approximately 2.28 mmol/L, whereas no significant association was observed below this threshold. This threshold effect suggests that the contribution of LDL-C to cholelithiasis risk may not accumulate in a simple linear manner, but may instead follow a pattern of threshold-dependent or accelerated risk. It should be emphasized that this inflection point was derived from an exploratory analysis within the present sample and therefore primarily reflects a statistically identified pattern rather than a clinically generalizable diagnostic cutoff. Nevertheless, previous studies examining LDL-C in relation to other disease outcomes have also reported evidence of increased risk once LDL-C exceeds specific thresholds. For example, in a study of young adults in the United States, LDL-C ≥ 190 mg/dL was identified as a high-risk subgroup and was associated with a significantly increased risk of atherosclerotic cardiovascular disease (ASCVD) [47]. Similarly, in the acute phase of ischemic stroke, LDL-C ≥ 5.0 mmol/L (approximately 193 mg/dL) was associated with an increased risk of all-cause mortality (adjusted OR = 1.22, 95% CI: 0.98–1.50); although the confidence interval was close to the null, the overall trend analysis still suggested increased risk at higher LDL-C levels [48]. To our knowledge, the present study is the first to identify such a threshold pattern in people living with HIV. This finding provides a useful direction for future research, although larger studies are needed to determine whether this threshold is reproducible and broadly applicable.

In addition to the above considerations, the development of cholelithiasis involves the interaction of multiple factors. Previous studies have shown that metabolic syndrome (MetS) is a well-established risk factor for cholelithiasis, and that low HDL-C may be the MetS component most strongly associated with gallstone risk [19, 41]. Higher BMI may also indirectly increase the risk of cholelithiasis through lowering HDL-C and increasing triglyceride (TG) levels [41, 49]. Although the present study focused on LDL-C, our stratified analyses showed that the positive association between LDL-C and cholelithiasis was directionally consistent across most subgroups, including those defined by age, sex, BMI, HBV co-infection status, and immune status, as reflected by CD4 + T-cell count. This finding suggests that the risk associated with LDL-C is not confined to a single subgroup, but may be relatively broadly present among patients with HIV infection. Notably, the association between LDL-C and cholelithiasis appeared to be stronger among patients with a longer duration of HIV infection and among those receiving ABT treatment, indirectly suggesting that long-term infection, treatment exposure, and metabolic remodeling may jointly contribute to gallstone development [7]. However, the interaction tests for HBV and ABT were not statistically significant (both *P* for interaction > 0.05), indicating that the current sample does not provide sufficient evidence to support a clear effect-modifying role for either factor in the association between LDL-C and cholelithiasis. Given the limited sample size in some subgroups, statistical power may have been insufficient, and these subgroup findings should therefore be interpreted with caution. Further validation in larger studies is warranted.

This study still has several limitations. First, because of its retrospective design, causal inference is inherently limited, and we cannot definitively establish whether elevated LDL-C is a direct cause of gallstone formation. Second, this was a single-center analysis, which may limit the generalizability of the findings to other populations or geographic settings. In addition, several potential confounding factors, including dietary patterns, genetic background, gallbladder motility, and the gut microbiota, could not be fully accounted for, all of which may influence cholesterol metabolism and the risk of cholelithiasis [50, 51]. Finally, some subgroups, such as patients with HBV co-infection, had relatively small sample sizes, which may have reduced statistical power and limited our ability to detect potential effect modification. Therefore, the subgroup analyses, interaction analyses, and the identified inflection point of 2.28 mmol/L should all be interpreted as exploratory findings rather than definitive evidence. Future studies should employ prospective cohort designs or large multicenter investigations to further examine the causal relationship between LDL-C and cholelithiasis and to clarify the underlying biological mechanisms. In particular, a more comprehensive risk prediction framework could be developed by integrating multiple dimensions, including bile composition, hepatic cholesterol transport pathways, metabolic syndrome-related indicators, and immune-inflammatory status. In addition, evaluating whether LDL-C-targeted interventions can reduce the risk of cholelithiasis would help clarify the practical clinical value of LDL-C in gallstone prevention.

In summary, the present study suggests that elevated LDL-C levels are significantly associated with cholelithiasis among hospitalized people living with HIV, and that this association persists even after adjustment for multiple covariates. We further observed a possible nonlinear relationship in this dataset, with a stronger association above the exploratory inflection point of 2.28 mmol/L. These findings provide additional evidence regarding metabolic factors associated with cholelithiasis in people living with HIV. Nevertheless, future multicenter prospective studies, together with more comprehensive covariate adjustment, external validation, and mechanistic investigation, are still needed to determine whether LDL-C can offer incremental value in gallstone risk assessment in this special population.

Conclusion

Elevated LDL-C was independently associated with cholelithiasis among hospitalized people living with HIV, even after adjustment for multiple potential confounders. A possible nonlinear relationship was also observed, with a stronger association above an exploratory inflection point of 2.28 mmol/L. The association was directionally consistent across most subgroups, and no significant interaction was detected for HBV or ABT. Further large-scale prospective studies are warranted to validate these findings and to determine the potential clinical utility of LDL-C in gallstone risk stratification among people living with HIV.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of the Public Health Clinical Center of Chengdu (approval number: YJ-K2024-94-01). Given the retrospective design and the use of anonymized data extracted from existing medical records, the requirement for informed consent was waived by the ethics committee.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Authors’ contributions

Cheng Xingzhen and Chen Tingyu conceived and designed the study. Liu Dongxu, Gui Fuqiang, Yang Lei and Chen Jidong collected the data. Cheng Xingzhen and Yang Jing performed the statistical analysis. Tan Juan and Feng Shifeng interpreted the data. Chen Tingyu drafted the manuscript. Wei Guo, Zhao Yong and Wang Hua revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Authors' information (optional)

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Figures

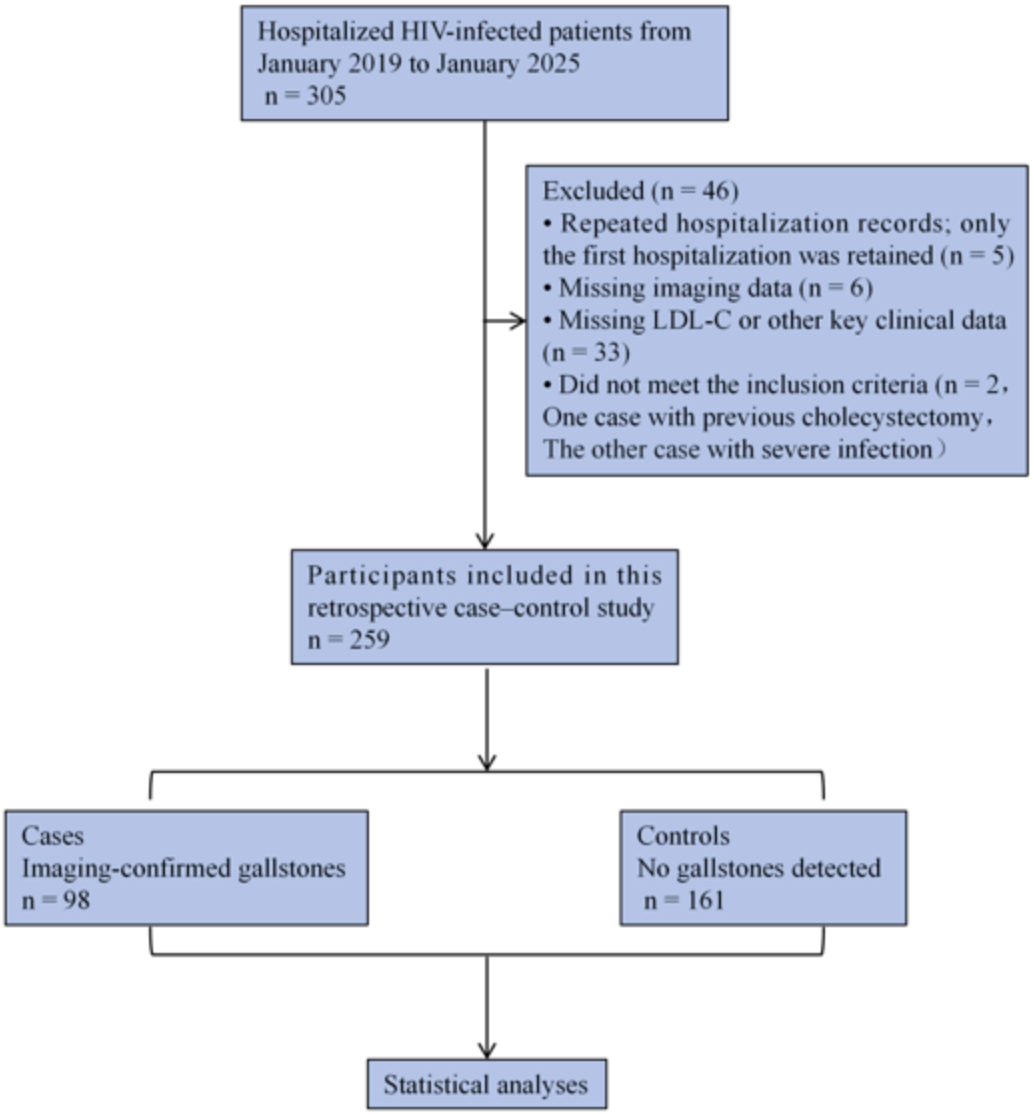


Figure 1

The flow diagram.

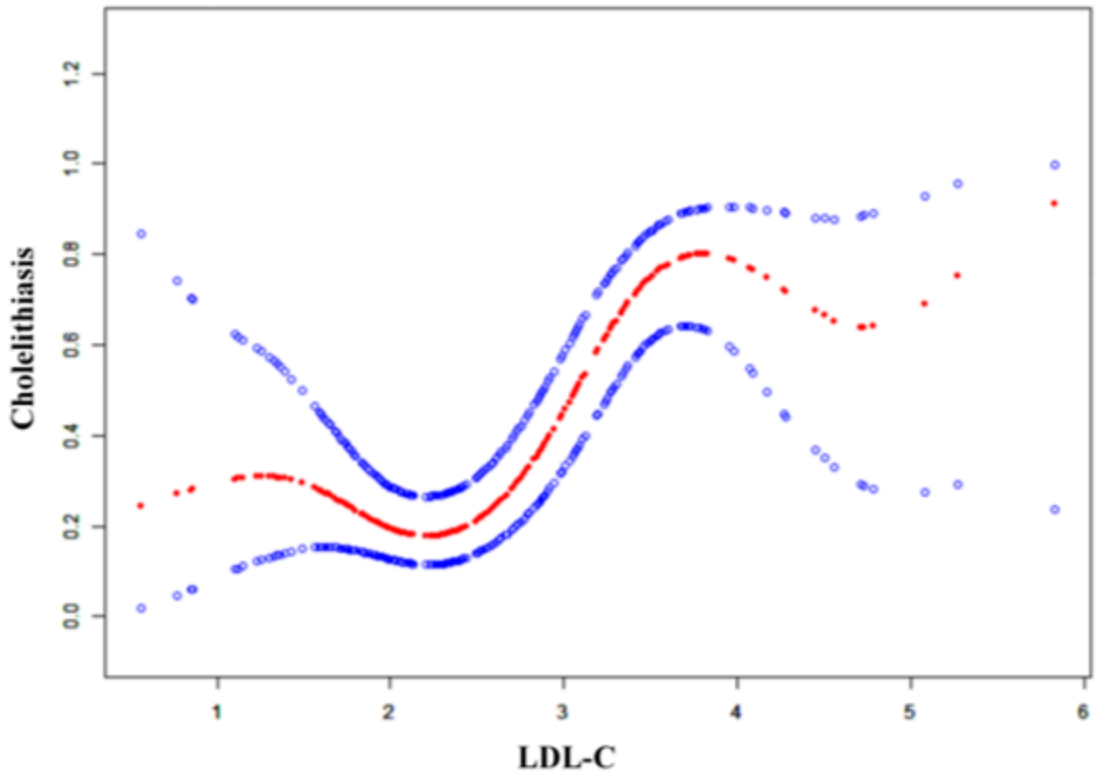


Figure 2

Association between LDL-C and cholelithiasis

A threshold, nonlinear association between LDL-C and cholelithiasis was found in a generalized additive model (GAM) . Solid rad line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. All adjusted for sex, age, and BMI, HBV co-infection, ABT treatment, duration since confirmed HIV infection, and CD4+ T-cell count.