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ORIGINAL RESEARCH

Risk Factors Associated with Virological Failure in HIV Patients with Low Level Viremia: A Retrospective Study

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Introduction: The objective of the current investigation was to develop a clinical predictive model for virological treatment failure in HIV patients with low level viremia.

Methods: The study included 786 patients with HIV-associated low-level viremia (LLV). Using Lasso and multivariable logistic regression, we developed a predictive model from clinical and laboratory variables to identify significant predictors. This predictive model was presented as a nomogram and subsequently transformed into a scoring system. Following model construction, internal validation was performed to evaluate the model's calibration capability and clinical utility.

Results: The final model incorporated five predictors (HLLV, NVP/3TC/AZT, WHO stage 1, ART delay, triglyceride) into a point-based scoring system. Using the Youden index, a threshold of 6 points was determined. The model demonstrated good performance, with training and internal validation AUCs of 0.762 and 0.759, respectively, and satisfactory calibration and diagnostic accuracy.

Conclusion: New scoring system predicts virological failure in low-level viremia, supporting early clinical intervention.

Keywords: HIV/AIDS, low-level viremia, virological failure, nomogram, predictive scoring system

Introduction

As a persistent global health threat, HIV/AIDS elimination is targeted in the UN 2030 Agenda.[1] Through targeted depletion of CD4+ T lymphocytes, HIV infection induces progressive cell-mediated immunodeficiency, consequently predisposing individuals to opportunistic infections and tumors. Antiretroviral therapy (ART) controls HIV infection by suppressing viral load to <50 copies/mL, halting disease progression and reducing long-term morbidity and mortality.[2] Evidence shows that persistent low level viremia (50–1000 copies/mL) in 10–30% of ART-treated individuals at 6 months, preventing complete virologic suppression.[3] Low-level viremia (LLV), as defined by the World Health Organization (WHO), designates this virologic state.[4]

The etiology of LLV remains controversial. Some investigators posit that the occurrence of LLV is closely linked to the persistent existence of HIV latent reservoirs. Following HIV infection, viral RNA is reverse transcribed into cDNA, which is integrated into the host CD4+ T-cell genome by viral integrase, establishing a HIV reservoir. These latently

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infected cells do not express viral proteins, thereby evading immune surveillance and clearance by ART.[5,6] When stimulated by mitogens, immune responses, and inflammatory factors, infected cells proliferate. This subsequently leads to the production of new virions with replicative capacity, which are released into the bloodstream. Consequently, viral RNA is persistently detected in peripheral blood.[5–8] Furthermore, the emergence and progression of antiretroviral drug resistance mutations represent another key etiology driving the progression of LLV. Newly developed resistance mutations can compromise the genetic barrier and clinical efficacy of the treatment regimen, leading to incomplete viral suppression and thereby sustaining persistent LLV. Studies have shown that participants with low-level viremia and drug resistance mutations appear to exhibit a higher risk of subsequent virological failure.[9–11]

Low-level viremia confers an elevated risk of subsequent virological failure, as evidenced by multinational studies.[12–18] Virological failure initiates a pathogenic cascade: heightened viral dissemination, progressive CD4+ depletion, and elevated transmission risk. This progression necessitates early detection of low-level viremia to deploy targeted interventions that re-establish virologic control.

The multifactorial pathophysiology underlying virological failure in low-level viremia constrains the prognostic utility of univariate predictors. Multivariable risk stratification models are thus necessitated to enhance predictive precision beyond conventional metrics. A nomogram is a graphical calculation tool that translates a complex multivariate regression model (such as logistic or Cox regression) into an intuitive, paper-based scoring system. It displays each predictor as a calibrated axis, allowing the user to assign points for an individual's specific values. The sum of these points is then mapped directly to a probability or risk axis, providing an immediate prediction without computational tools. In recent years, nomograms have emerged as a highly practical tool for clinicians, effectively transforming complex predictive models into intuitive probabilities of specific events. These tools have been extensively utilized in the assessment of the incidence and prognosis of various diseases, including HIV infection. Their application has significantly streamlined clinical workflows and enhanced the precision of medical decision-making.[19–22] as a means to further simplify predictive model, scoring systems derived from nomograms are now being used clinically.[23] A scoring model to predict subsequent virologic failure in patients with LLV is currently unreported. However, constructing a universally applicable model presents significant challenges. Firstly, despite the biological importance of viral reservoir characteristics, host immune factors, and drug resistance, precise assessment methods for these elements remain lacking in routine clinical practice, particularly within healthcare settings characterised by substantial disparities in medical resources. Precisely for this reason, developing simplified risk assessment tools utilising readily accessible clinical parameters from routine diagnostics holds urgent practical significance and broader application prospects. Based on key predictive factors, we derived a clinically applicable scoring system from a nomogram to identify LLV patients at high risk of virologic failure requiring early intervention.

Materials and Methods

Study Design and Population

This retrospective study utilized data from The Chinese Center for Disease Control and Prevention (CDC). We included people living with HIV (PLWH) receiving antiretroviral therapy at Wuhan Jinyintan Hospital between 2007 and 2023 for development and internal validation of the predictive model.

Inclusion criteria comprised: (1) documented HIV diagnosis with complete laboratory data; (2) receipt of first-line ART (2 NRTIs + 1 NNRTI) in China; (3) ≥24 months of follow-up. Exclusion criteria were: (1) prior ART exposure; (2) age <15 years.

According to the 2016 WHO guidelines, LLV was defined as a viral load of 50–1000 copies/mL following sustained virologic suppression (≥6 months of ART).[24] Combined with previous research, the study was divided into three groups: high-level LLV (HLLV) at 400–1000 copies/mL, medium-level LLV (MLLV) at 200–400 copies/mL, and low-level LLV (LLLV) at 50–200 copies/mL. (3) Virologic failure was defined as a confirmed viral load exceeding 1000 copies/mL after ≥6 months of continuous antiretroviral therapy. Sustained virological suppression in the manuscript was defined as maintaining a plasma HIV RNA level below 50 copies/mL during antiretroviral therapy.[25]

Data Collection

Demographic, clinical, and laboratory parameters were collected, including: age at ART initiation, sex, body mass index (BMI), marital status, transmission route, diagnosis-to-ART interval, WHO clinical stage, symptoms, opportunistic infections, malignancies, ART regimen, $CD4^+$ T-cell count, viral load (VL), white blood cells (WBC), platelets (Plt), hemoglobin (Hb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), serum creatinine (Scr), triglycerides, total cholesterol (TC), and fasting blood glucose (FBG). Continuous variables were dichotomized using optimal cutoffs derived from receiver operating characteristic (ROC) curve analysis. All parameters were recorded by trained clinicians at 3-month intervals.

Data Processing

Following Riley et al's methodology,[26] We calculated the sample size based on the sample size formula derived from it and concluded that a minimum sample size of 529 is required to develop this model, with a minimum of 53 positive events and at least 10.58 positive events for each candidate prediction parameter. Additionally, This satisfies the established 10 EPP (events per parameter) criterion for prediction models.[19]

Variables with <20% missing values were imputed using random forest; those with >20% missing values were excluded to ensure model stability, reliability, and predictive power. Additionally, missing values in the training set were assessed (sFigure 1).

We employed odds ratios (OR) to quantify the strength of the association between exposure factors and the outcome of virological failure in patients with low-level viremia. The OR quantifies the association strength: an OR > 1 indicates increased odds (a risk factor), an OR < 1 indicates decreased odds, and an OR = 1 suggests no association. In this study, a specific value (eg, OR=3.254) precisely measures both the direction and magnitude of the effect, offering a more powerful metric than simple rate comparisons. The forest plot visually compares subgroup ORs and their confidence intervals. It allows for immediate assessment of statistical significance (relative to OR=1) and heterogeneity based on the overlap of these intervals.

Statistical Analysis

Continuous variables in the training set were summarized as median (interquartile range [IQR]), and categorical variables as frequencies and percentages.

To identify potential predictive features, we employed least absolute shrinkage and selection operator (LASSO) regression.[27] Based on the clinical significance of each variable, we ultimately selected five predictive factors for inclusion in the subsequent study and applied multivariate logistic regression to construct a nomogram. To enhance clinical utility, we converted the nomogram into a points-based scoring system by assigning integer weights derived from the β-coefficients of the multivariate logistic regression model. These β-coefficients, obtained via maximum likelihood estimation, objectively reflect the direction and strength of each variable's association with the outcome: the sign indicates whether a variable is a risk or protective factor, while the magnitude represents its contribution. A unified scoring system was then created by proportionally converting these β-coefficients into standardized points. Optimal cut-off values for individual predictors and the total score were determined using the Youden index.[28]

Based on five significant variables, we developed a clinical model with good predictive ability. Through the receiver operating characteristics (ROC) curve, we quantified the discrimination of the model and conducted internal validation using the bootstrap method (resampling times =1000).[29] Calibration was assessed using the Hosmer-Lemeshow test, Spiegelhalter's Z statistic, and calibration curves. Clinical utility was evaluated via decision curve analysis (DCA) across threshold probabilities.[30]

Statistical analysis was performed using R-studio (version 4.4.1) and SPSS 26.0 (IBM Inc., Chicago, IL, USA). P value < 0.05 was considered statistically significant.

Results

Based on the inclusion and exclusion criteria, 773 participants from Wuhan Jinyintan hospital were enrolled and all assigned to the training set. The study flowchart is presented in sFigure 2, characteristics of the training set are shown in Table 1.

Table 1 Comparison of the Baseline Characteristic Between the Two Groups

	Total (n = 773)	No VF (n = 696)	VF (n = 77)
LLV, n (%)			
LLLV	560 (72)	517 (74)	43 (56)
MLLV	120 (16)	110 (16)	10 (13)
HLLV	93 (12)	69 (10)	24 (31)
Sex, n (%)			
Female	64 (8)	58 (8)	6 (8)
Male	709 (92)	638 (92)	71 (92)
Marital status, n (%)			
Married	398 (51)	358 (51)	40 (52)
Unmarried	230 (30)	214 (31)	16 (21)
Divorced or widowed	145 (19)	124 (18)	21 (27)
Route of HIV exposure, n (%)			
MSM	494 (64)	443 (64)	51 (66)
Heterosexual transmission	272 (35)	249 (36)	23 (30)
Injection	7 (1)	4 (1)	3 (4)
ART initiation regimen, n (%)			
EFV 3TC TDF	427 (55)	391 (56)	36 (47)
EFV 3TC AZT	111 (14)	96 (14)	15 (19)
NVP 3TC AZT	93 (12)	72 (10)	21 (27)
Others	142 (19)	137 (20)	5 (6)
WHO stage, n (%)			
WHO stage 1	155 (20)	151 (22)	4 (5)
WHO stage 2	362 (47)	316 (45)	46 (60)
WHO stage 3	156 (20)	135 (19)	21 (27)
WHO stage 4	100 (13)	94 (14)	6 (8)
Skin damage, n (%)			
No	716 (93)	645 (93)	71 (92)
Yes	57 (7)	51 (7)	6 (8)
Fever ≥1 month, n (%)			
No	710 (92)	641 (92)	69 (90)
Yes	63 (8)	55 (8)	8 (10)
Diarrhea ≥ 1 month, n (%)			
No	742 (96)	668 (96)	74 (96)
Yes	31 (4)	28 (4)	3 (4)
Night_sweats, n (%)			
No	733 (95)	658 (95)	75 (97)
Yes	40 (5)	38 (5)	2 (3)
Diarrhea, n (%)			
No	734 (95)	658 (95)	76 (99)
Yes	39 (5)	38 (5)	1 (1)
Rash, n (%)			
No	729 (94)	657 (94)	72 (94)
Yes	44 (6)	39 (6)	5 (6)
Lymphadenectasis, n (%)			
No	728 (94)	656 (94)	72 (94)
Yes	45 (6)	40 (6)	5 (6)
BMI, kg/m^2	23 (20.3, 23)	23 (20.3, 23)	23 (20.3, 23)
ART age, year	35 (26, 52)	35 (26, 52)	38 (28, 53)
ART delay, month	1.2 (0.7, 3)	1.1 (0.6, 2.6)	2.3 (1.3, 8.6)
CD4+ T-cell counts, cells/μL	350 (214, 519)	348.5 (206.5, 517.25)	371 (266, 541)
WBC, $10^9/L$	5.45 (4.5, 6.67)	5.44 (4.49, 6.69)	5.5 (4.85, 6.35)

(*Continued*)

Table 1 (Continued).

	Total (n = 773)	No VF (n = 696)	VF (n = 77)
PLT, 10^9/L	212 (177, 252)	214 (177.75, 254)	197 (170, 227)
HB, g/L	146 (135, 156)	146 (135, 157)	143 (130, 152)
Scr, μmol/L	71.2 (63, 83)	71.6 (63, 83)	69 (61.1, 77)
Triglyceride, mmol/L	1.54 (1.06, 2.33)	1.51 (1.06, 2.28)	1.89 (1.24, 2.71)
TC, mmol/L	4.23 (3.72, 4.81)	4.24 (3.73, 4.83)	4.22 (3.51, 4.75)
FBG, mmol/L	5.5 (5.03, 6.18)	5.5 (5.04, 6.17)	5.54 (4.98, 6.28)
ALT, U/L	22 (15, 34)	22 (15, 34)	23 (16, 32)
AST, U/L	24 (20, 31)	24.55 (20, 31)	23 (19, 28)
TBIL, mol/L	9.4 (7.1, 12.2)	9.4 (7.2, 12.29)	8.7 (6.5, 11.1)

Abbreviations: MSM, men who have sex with men; EFV, Efavirenz; 3TC, Lamivudine; TDF, Tenofovir Disoproxil Fumarate; AZT, Azidothymidine; NVP, Nevirapine; WHO, World Health Organization; BMI, body mass index; ART, Antiretroviral Therapy; WBC, white blood cell; PLT, platelet; HB, hemoglobin; Scr, serum creatinine; TC, total cholesterol; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

In the training set, the incidence of virologic failure among patients with LLV was 10% (77/773). Among the 27 variables collected, multilevel categorical variables were converted into dummy variables, and continuous variables were dichotomized using optimal cut-off values determined by ROC curve analysis for the outcome of interest (sTable 1). To select the most predictive features for model development, the preprocessed variables were included in LASSO regression analysis (Figure 1). Five independent risk factors significantly associated with virologic failure in Figure 2

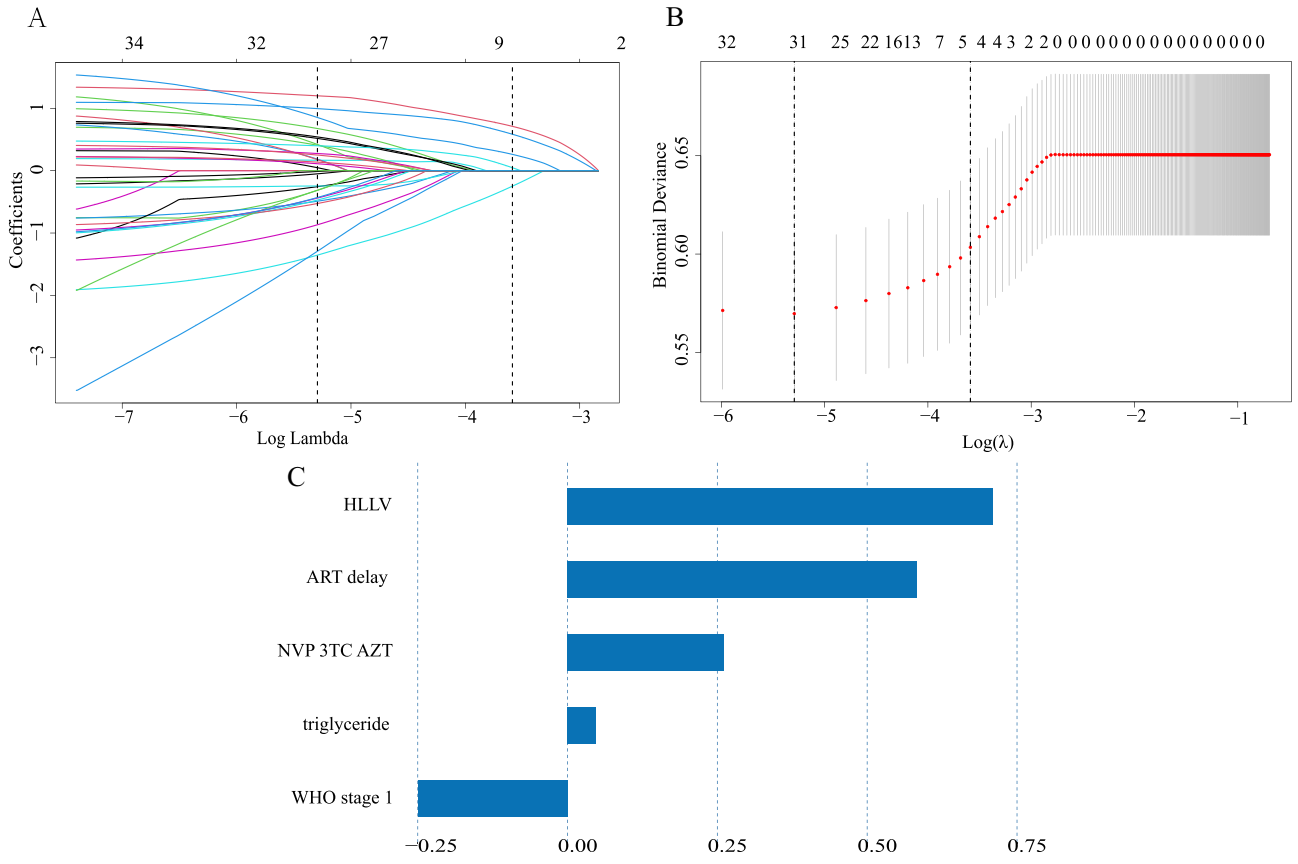

Figure 1 Variable Selection in LASSO Regression. (**A**) LASSO Coefficient Paths. Each colored line represents the coefficient value of a variable. (**B**) Deviance-based λ selection in LASSO regression: minimum criterion (left dotted) and 1-SE criterion (right dotted). (**C**) Final model coefficients at optimal λ. Clinically significant predictors include HLLV, ART delay, NVP/3TC/AZT, triglyceride, and WHO stage 1.

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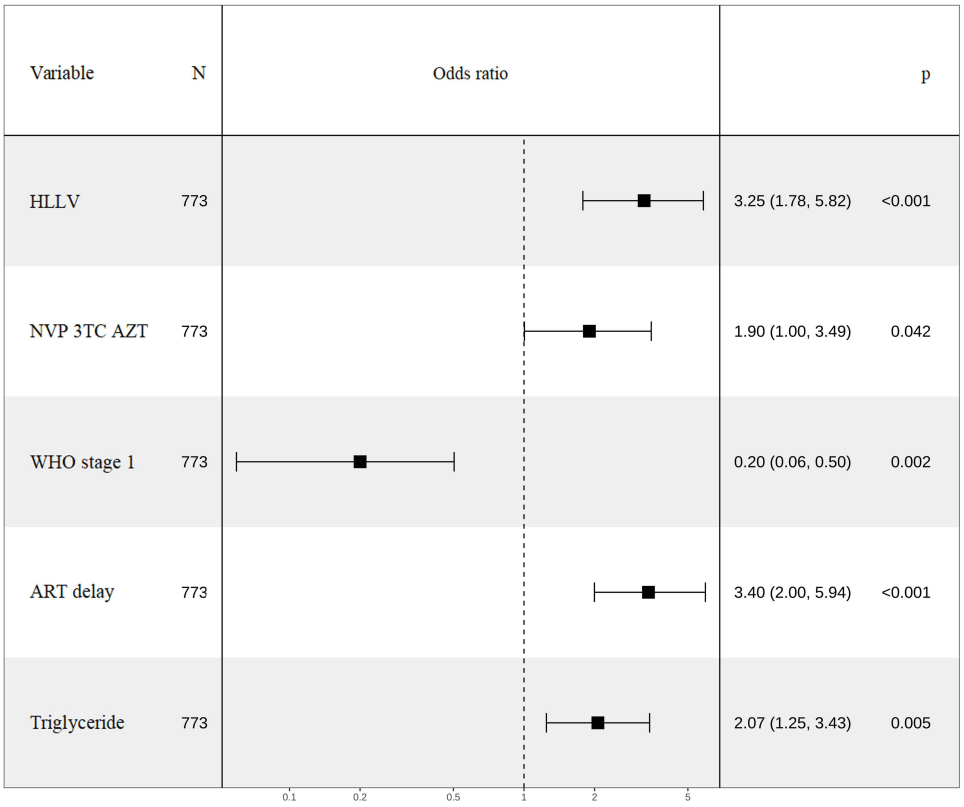

Figure 2 Forest plot from multivariable logistic regression.

(HLLV, NVP/3TC/AZT, WHO stage 1, ART delay, triglyceride) were entered into a multivariable logistic regression model (Table 2). Using the regression coefficients from this model, a predictive nomogram was developed (Figure 3).

To enhance clinical utility, the nomogram was converted into a scoring system (Table 3), with points assigned as follows: HLLV (7 points), NVP/3TC/AZT (4 points), WHO stage 1 (10 points), ART delay (8 points), and triglyceride (5 points). In the training set, the optimal threshold for this scoring system, determined using Youden's index, was 6 points. Patients with LLV scoring ≥6 points had an increased likelihood of virologic failure, while those scoring <6 points had a decreased likelihood.

In the training set, we used the ROC curve to show that the prediction model had good discriminant power, with an AUC of 0.762 (95% CI 0.704–0.82) (Figure 4A). To maximize statistical power using all available data, we performed internal validation with bootstrap (resamples = 1000),[24] achieving an AUC of 0.759 (95% CI: 0.699–0.759). Calibration curve demonstrated good calibration, with statistical confirmation from a Hosmer-Lemeshow test (P = 0.937) and Spiegelhalter's Z-test (z = −0.15) (Figure 4B). We assessed the clinical applicability of the predictive model using the

Table 2 Multivariate Regression Analysis for Constructing Nomogram in Training Set

Variables	Beta	S.E	OR	95% CI	P
HLLV	1.18	0.301	3.254	1.804–5.87	<0.001
NVP 3TC AZT	0.642	0.317	1.901	1.021–3.539	0.042
WHO stage 1	−1.609	0.531	0.2	0.071–0.567	0.002
ARTdelay	1.222	0.277	3.395	1.973–5.843	<0.001
Triglyceride	0.726	0.258	2.066	1.246–3.426	0.005

Abbreviations: HLLV, High Low-Level Viremia; NVP, Nevirapine; 3TC, Lamivudine; AZT, Azidothymidine; WHO, World Health Organization; ART, Antiretroviral Therapy.

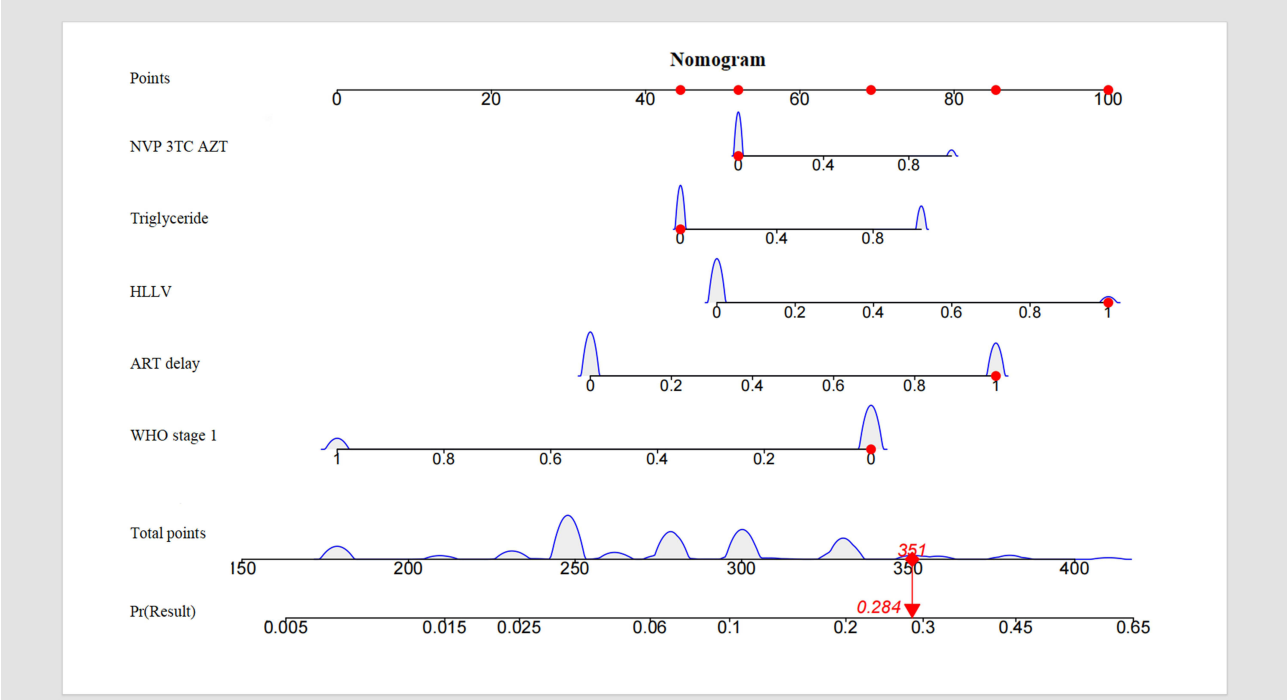

Figure 3 Nomogram model for predicting virologic failure in LLV.

DCA curve, and the DCA curve indicated that, with probability thresholds ranging from 4% to 62%, the nomogram we developed demonstrated good clinical effectiveness (Figure 4C). The model demonstrated consistent performance across the dataset, with a sensitivity of 64.9%, accuracy of 66.0%, specificity of 75.3%, an F1-score of 0.775, and a PRAUC of 0.635. These results indicate a robust trade-off between identifying true positives and false positives, with overall performance surpassing random chance.

Discussion

Global efforts aim to reduce HIV incidence by 90% by 2030, in line with UNAIDS' 90–90–90 targets. This will be done through population-wide testing, providing antiretroviral therapy, and suppressing viral load in people living with HIV.[1] While ART programs have expanded significantly, a group of people with LLV still does not respond to viral suppression. These individuals are more likely to experience virologic failure.

To facilitate early identification and timely therapeutic intervention for this patient population, this study successfully developed and validated a nomogram model for predicting the risk of virological failure in patients with low-level viremia, which was subsequently transformed into a user-friendly scoring system. This nomogram integrated five predictors: HLLV, NVP/3TC/AZT, WHO stage 1, ART delay and triglyceride. These factors collectively estimated

Table 3 A Scoring System Developed from a Nomogram in the Train Set

Variables	β (Absolute Values)	Score Generated from Nomogram (points)	Score Modified from Nomogram (points)
HLLV(Yes)	1.18	7.3	7
NVP 3TC AZT(Yes)	0.642	4	4
WHO stage 1(Yes)	1.609	10	10
ART delay (≥1.6 months)	1.222	7.6	8
Triglyceride (≥1.96 mmol/L)	0.726	4.5	5

Abbreviations: HLLV, High Low-Level Viremia; NVP, Nevirapine; 3TC, Lamivudine; AZT, Azidothymidine; WHO, World Health Organization; ART, Antiretroviral Therapy.

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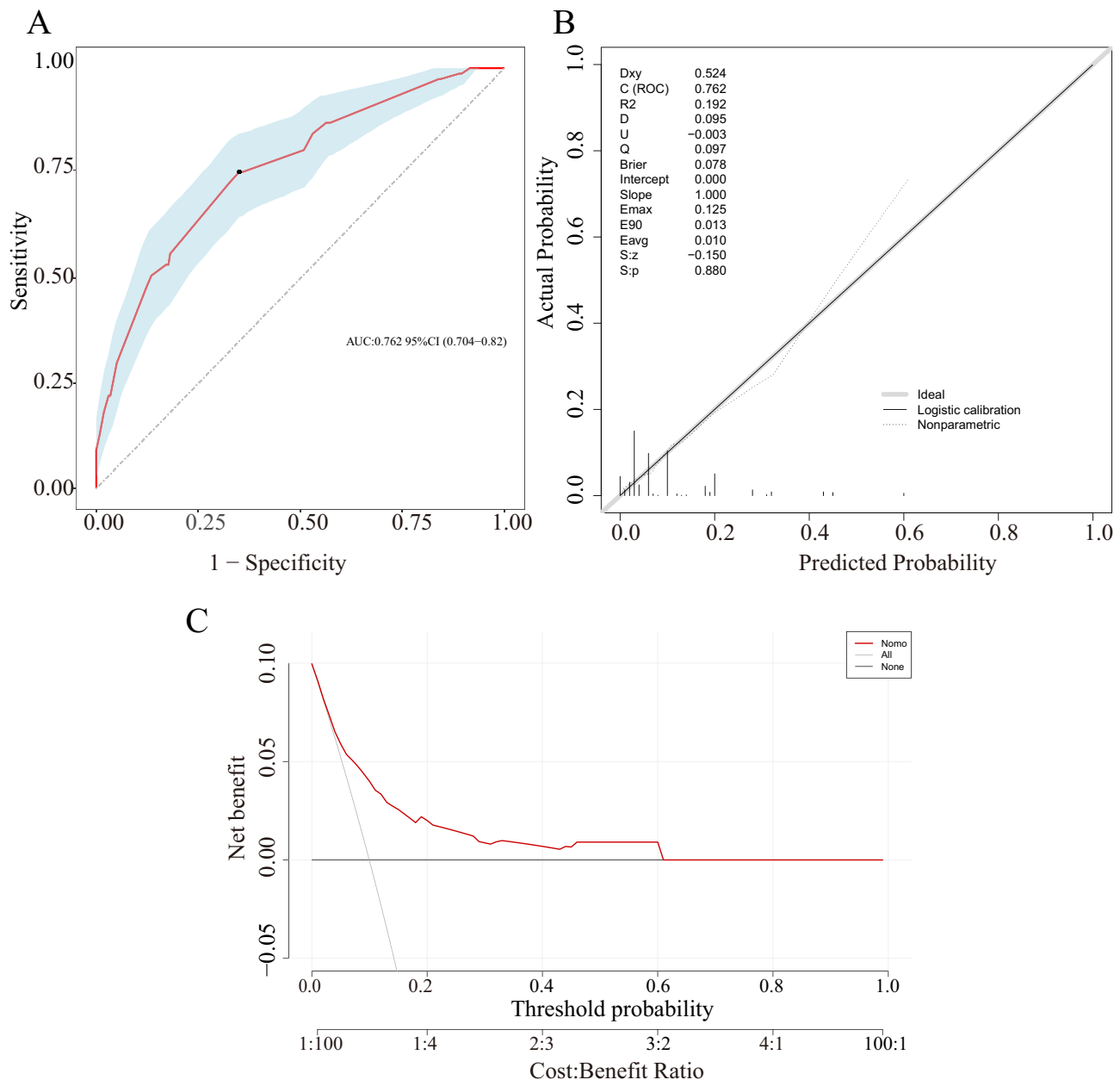

Figure 4 Performance assessment of the predictive model for virological failure in low-level viremia. (**A**) ROC curve (AUC = 0.762) indicates good discriminative power. (**B**) Calibration plot shows excellent agreement between predicted and observed outcomes. (**C**) Decision curve analysis confirms clinical utility of the model.

virological failure risk in patients with LLV following ART. Calibration curve and the DCA curve demonstrated excellent discriminative ability and calibration accuracy of the model. Internal validation further confirmed its clinical applicability across the intended patient populations, confirming its readiness for real-world implementation. The core clinical value of this tool lies in its ability to stratify patients by risk, thereby enabling healthcare providers to prioritize limited medical resources for managing high-risk individuals. Specifically, clinicians can use this scoring system to early identify patients prone to treatment failure and implement targeted interventions, ultimately maximizing the benefits of individualized treatment management and public health prevention.

We established that higher viral loads during LLV episodes significantly increased virological failure susceptibility in PLWH. This aligned with a Beijing cohort study attributing the phenomenon to LLV-induced systemic immune activation and accelerated drug resistance development.[31] A previous finding from a single-center cohort study demonstrated a 4.76-fold

increased risk of virological failure among individuals with a VL of 500–999 copies/mL.[32] Some investigators posit that heightened systemic immune activation may mechanistically impair CD4+ T-cell reconstitution, thereby predisposing PLWH to virological failure.[33] Higher viral load is closely associated with the accumulation of drug-resistant mutations, and sustained accumulation of these mutations may increase the risk of virological failure in the future.[34]

A northeastern China study found elevated virologic failure risk in LLV patients receiving NVP/3TC/AZT.[3] Compared with alternative antiretroviral regimens, the NVP/3TC/AZT regimen demonstrates a heightened burden of long-term toxicities, predominantly manifesting as gastrointestinal disturbances, neuropsychiatric disorders, and musculoskeletal complications.[35] Studies have shown that the NVP/3TC/AZT regimen is associated with an elevated risk of severe hepatotoxicity, predominantly presenting as increased ALP levels.[36] NVP demonstrates a higher incidence of cutaneous reactions than other non-nucleoside reverse transcriptase inhibitors within the ART regimen, with its risk profile being notably elevated relative to this drug class.[37] Other studies have also yielded similar results.[38,39] AZT can cause hematological disorders, including various adverse reactions such as neutropenia and anemia. With prolonged therapy or higher dosing, this may progress to severe complications including bone marrow suppression.[40] In addition, some studies have found that a small number of patients taking zidovudine developed peripheral nervous system lesions.[41] 3TC demonstrates a comparatively favorable toxicity profile. Clinical studies have documented its association with mild-to-moderate adverse effects including fatigue, headache, nausea, and cutaneous rash.[42–44] These effects may compromise medication adherence and foster treatment reluctance, potentially culminating in therapeutic failure.[10,45] NVP and 3TC have relatively low resistance barriers, and sustained LLV replication may still trigger resistance mutations, ultimately leading to treatment failure.

Our study found that WHO stage 1 was a protective factor for virologic treatment failure in patients with LLV. These clinically stable patients typically exhibit preserved immune function with higher CD4+ T-lymphocyte counts and absence of AIDS-defining conditions or opportunistic infections, thus demonstrating a lower risk of virologic failure.[46] This is similar to the results of the current study.[47]

These three predictors demonstrate strong associations with virological failure in LLV patients, a finding substantiated by our dataset in alignment with prior evidence. Our study newly identifies ART delay and triglyceride as novel independent predictors of virological failure in LLV.As evidenced by current research, ART delay extends the untreated infection period, promotes accumulation of latently infected CD4+ T cells, and consequently expands the HIV viral reservoir.[48] This leads to elevated viral loads, compromises immune function integrity, and ultimately culminates in virological failure. Dyslipidemia in PLWH may associate with persistent immune activation and inflammation during infection. Studies have shown elevated inflammatory biomarkers correlate positively with triglyceride levels in chronic HIV infection.[49] Despite effective suppressive antiretroviral therapy, latently infected cells may undergo reactivation to produce new virions, thereby sustaining viral reservoir persistence and fostering ongoing viral replication.[50]

This study is characterized by several salient strengths. First, we developed the first nomogram to predict virological failure risk among PLWH who develop LLV following ART initiation. This predictive model was subsequently operationalized into a points-based risk stratification system, distinguished by its methodological parsimony, low resource dependency, and implementation feasibility within resource-constrained primary care environments. Second, the scoring system exhibits intrinsic operational simplicity and pragmatic utility, specifically designed to enhance clinical decision-making efficiency for frontline clinicians in resource-limited primary care settings. However, three principal limitations merit discussion. First, the monocentric design and limited sample size constrain the external validity of our findings, necessitating verification through prospective, multi-center cohort studies with adequate statistical power. Second, approximately 5–10% of sociodemographic and laboratory data were incomplete, while key biomarkers (eg, immune cell subsets) in LLV patients remained unassessed, gaps requiring resolution in future studies. Finally, we were unable to systematically collect or control for data on patients' medication adherence and viral drug resistance. To address this limitation, future studies could systematically integrate adherence assessments (eg, via pill counts, electronic drug monitoring, or plasma drug concentration measurements) and baseline resistance testing within a prospectively designed cohort. Furthermore, exploring the use of indirect indicators from routine medical data, such as appointment adherence and prescription refill intervals, to construct proxy measures for adherence represents a highly valuable direction for further research.

Collectively, the novel scoring system demonstrated excellent calibration and discriminative performance in predicting virological failure among patients with low-level viremia. This tool incorporates five clinically accessible parameters

readily implementable in primary care settings, enabling accurate identification of individuals at heightened risk of treatment failure who may benefit from targeted interventions.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality reasons. Data can be made available upon reasonable request from Lianguo Ruan (2020jy0004@hust.edu.cn).

Ethics Approval and Consent to Participate

The Declaration of Helsinki was followed in the conduct of this study. The Huazhong University of Science and Technology's Tongji Medical College's ethics committee at Wuhan Jinyintan Hospital gave its approval to the study protocol (KY-2022-13). All participants provided informed consent to take part at the beginning of the process as part of the online survey.

Author Contributions

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

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Disclosure

The authors declare that they have no competing interests.

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