BMC Infectious Diseases

RESEARCH

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Establishment and evaluation of a predictive model for immune reconstitution in people living with HIV after antiretroviral therapy

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Abstract

Background Achieving complete immune reconstitution (CIR) in people living with human immunodeficiency virus (PLWH) following antiretroviral therapy (ART) is essential for preventing acquired immunodeficiency syndrome (AIDS) progression and improving survival. However, there is a paucity of robust prediction models for determining the likelihood of CIR in PLWH after ART. We aimed to develop and validate a CIR prediction model utilizing baseline data.

Methods Baseline data including demographic information, immunological profiles, and routine laboratory test results, were collected from PLWH in Yunnan, China. Baseline referred to the first recorded results after HIV diagnosis but before initiating ART, and these initial measurements served as the baseline data for analysis. The participants were divided into training and validation sets (7:3 ratio). To construct the model and accompanying nomogram, univariable and multivariable Cox regression analyses were performed. The model was evaluated using the C-index, time-dependent receiver operating characteristic (ROC) curves, calibration curves, and clinical decision curves to assess discrimination, calibration, and clinical applicability.

Results Five thousand four hundred eight PLWH were included, with a CIR of 38.52%. Cox regression analysis revealed various independent factors associated with CIR, including infection route, baseline $CD4^+$T cell count, baseline CD4/CD8 ratio, interval from HIV diagnosis to ART initiation, and the level of PLT, Glu, Crea, HGB, ALT. A nomogram was formulated to predict the probability of achieving CIR at years 4, 5, and 6. The model demonstrated good performance, as evidenced by an AUC of 0.8 for both sets. Calibration curve analysis demonstrated a high level of agreement, and decision curve analysis revealed a significant positive yield.

Conclusions This study successfully developed a prediction model with robust performance. This model has considerable potential to aid clinicians in tailoring treatment strategies, which could enhance outcomes and quality of life for PLWH.

Keywords HIV, ART, Immune reconstitution, Predictive model, Nomogram, Model evaluation

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Introduction

Human immunodeficiency virus (HIV) infection remains a significant global health challenge [1]. The World Health Organization estimated that by the end of 2022, the population of people living with HIV (PLWH) would reach approximately 38 million, including the addition of 1.7 million new cases. The widespread implementation of "treat-all" antiretroviral therapy (ART) has greatly improved both the clinical prognosis and life expectancy of PLWH [2, 3]. ART is known to effectively suppress viral replication, restore immune function, and reduce the risk of acquired immunodeficiency syndrome (AIDS)-related complications [4–6]. However, despite these advances, a considerable proportion of PLWH (15%–30%) experience suboptimal recovery of immune function, referred to as immune unresponsiveness or incomplete immune reconstitution (IIR) [7].

There is still a lack of consensus and debate continues regarding the immunomodulatory mechanisms and therapeutic approaches for managing IIR. This condition, closely linked to diminished $CD4^+$T cell production in the bone marrow, reduced thymic output, persistent HIV replication, abnormal immune activation, disruptions in cytokine secretion, and specific genetic or metabolic characteristics in PLWH, increases their susceptibility to various complications, including both AIDS and non-AIDS events and is associated with elevated mortality rates [8, 9]. Therefore, identifying PLWH at risk of immune nonresponse is essential for personalized management and improved clinical outcomes.

Clinical prediction models are widely utilized in both medical research and practice to assess the likelihood of a specific clinical outcome within a study population. Typically, these models utilize various variables or predictors for comprehensive evaluation [10, 11]. However, there remains a notable scarcity of published research on models that effectively integrate multiple variables for accurately identifying complete immune reconstitution (CIR) in China. Most existing studies have focused on short-term outcomes, without in-depth analysis of long-term changes and trends in immune recovery following ART [12]. Studies with extended follow-up periods could provide a more accurate assessment of the CIR and the progression of adverse risks, especially given the existence of a plateau phase in immune recovery [13]. This lack of comprehensive long-term prediction models underscores the urgent need for the development of reliable, long-term clinical prediction models.

HIV continues to pose a significant challenge to global health, underscoring the urgent need for innovative approaches to enhance treatment outcomes and patient care. Given the notable differences in immune reconstitution among PLWH receiving ART, developing a predictive model that can identify the risk of inadequate immune reconstitution at an early stage is particularly crucial. The importance of constructing such a model for predicting CIR in PLWH following ART treatment is profound.The establishment of this predictive model will not only enable the accurate identification of patients at high risk for inadequate immune reconstitution at an early stage but also provide them with personalized and precise treatment options, which have the potential to significantly enhance patients' survival and quality of life. Furthermore, the model can generate tailored risk assessment reports based on patient-specific information, assisting physicians in selecting the most appropriate treatment pathways and aiding public health authorities in the efficient allocation of resources. Additionally, the development of this predictive model will contribute significantly to the advancement of personalized medicine, facilitating the customization of treatment plans, thereby improving outcomes and reducing the burden on patients. The primary objective of this study was to develop and evaluate a model designed to predict the likelihood of CIR in PLWH after 4, 5, and 6 years of ART. This model aims to provide clinicians with a straightforward and reliable tool for accurately identifying PLWH who may require additional monitoring and interventions, particularly during the initiation of ART, thus facilitating targeted, timely clinical interventions and personalized care.

Methods

The Transparent Reporting of a Multivariate Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist was used for the validation of the prediction model [14].

Study design and participants

This study involved participants who receiving ART at the Antiviral Outpatient Department of Yunnan Provincial Hospital of Infectious Diseases in Yunnan, China, between October 2004 and December 2020. Participant records were obtained by professional physicians from the National AIDS Integrated Prevention and Control Information System, and the data quality was thoroughly assessed. The inclusion criteria for participants were PLWH who were at least 18 years old at the time of study participation (during our data collection period from January 2024 to June 2024), had confirmed positive results for HIV antibodies in both primary screening and confirmatory tests, had undergone ART for a minimum of 3 years, and exhibited a viral load below the detection limit ($\leq$50 copies/mL) at the most recent follow-up. The exclusion criteria included participants who had

died, were lost to follow-up, discontinued medication, or lacked available demographic data.

Study outcomes

The primary outcome of our study was the rate of immune reconstitution in PLWH who had received ART for a minimum of 3 years and maintained a viral load below the limit of detection (≤50 copies/mL) at their most recent follow-up visit. The CIR was determined using binary indicators, specifically a $CD4^+$T cell count of ≥500 cells/μL and a CD4/CD8 ratio of ≥0.8, which are considered accurate measures of immune system function and status [15]. The determination of immunological reconstitution was based on the results from the latest recorded follow-up visit in the electronic case system.

Candidate predictor variables

Potential predictor variables for the model were identified from the literature, and relevant variables were collected from the electronic medical records, including demographics, baseline immunological and laboratory tests, coinfections, and ART regimens. Baseline referred to the first recorded results before starting ART but after HIV diagnosis. The demographic data included age, sex, date of diagnosis, infection route, and marital status, with the latter two obtained from patient-initiated information or doctor–patient communication. Baseline immunological outcomes were assessed based on $CD4^+$ and $CD8^+$T cell counts and the CD4/CD8 ratio. The $CD4^+$ and $CD8^+$T cell counts were measured using Truecount™ Tubes (BD Biosciences, San Jose, CA, USA) and a FACSCalibur™ flow cytometer (BD Biosciences, San Jose, CA, USA).

Baseline laboratory test indicators included white blood cell count (WBC), hemoglobin (HGB), platelet (PLT), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Crea) levels; the creatinine clearance rate (Ccr); blood glucose (Glu), triglyceride (TG), and total cholesterol (CHO) levels. These parameters were analyzed using a DxH 800 hematology analyzer (Beckman Coulter, Miami, Florida, USA) and an automatic biochemical detector (Hitachi 7180, Tokyo, Japan).

Coinfection examination primarily focused on hepatitis B and C virus (HBV and HCV) infections, which were detected using HBV and HCV antibody diagnostic kits via enzyme-linked immunosorbent assay (ELISA) (Wantai BioPharm, Beijing, China). A positive result for anti-HBV or HCV surface antigen (HBsAg) indicated the presence of HBV or HCV infection.

ART regimens typically consist of a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) along with a nonnucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI) [16]. Thus, these regimens were categorized into three groups: 2NRTIs and NNRTI, or PI, or INSTI-containing regimens.

Sample size and missing data

Although no formal calculation of sample size was performed, the study adhered to the TRIPOD guidelines by including a minimum of 10 events per variable [14]. This necessitated the inclusion of at least 410 cases of CIR. To ensure adequate test efficiency, all 5,408 eligible participants who met the criteria during the study period were included. Among them, 2,083 belonged to the CIR category, exceeding the estimated minimum sample size. Missing data (with missing rates below 15%) were addressed through multiple imputation using the MICE package in R, assuming that missing data were random. We employed the standard multiple estimation analysis process. Initially, we utilized the VIM package to analyze the characteristics of the missing data (Figure S1A) and applied the MICE package to generate 5 complete estimation datasets. Subsequently, we used the with function to implement statistical models on each of the five interpolated datasets and employed the pool function to consolidate the analysis results from each dataset. Finally, we utilized density plots to compare the original and estimated data, thereby further validating the appropriateness of our estimation method. As shown in Figure S1 B, comparative analysis revealed that the distribution of the imputed data closely resembled that of the original data.

Statistical methods

Data collection and management were performed using Microsoft Office Excel 2011. Statistical analyses were performed using the R program (v 4.3.2). The R package "caret" was used to randomly divide participants into training and validation sets (at a 7:3 ratio). Continuous variables were transformed into categorical variables using X-tile software to determine optimal cutoff values. Categorical variables were compared using the chi-square test or Fishers exact probability method with the "tableone" package and are presented as frequencies (n) and proportions (%). Uivariable and multivariable Cox regression analyses ("survival" package) were conducted to construct the model. Variables with $P<0.2$ in univariable analyses were included in the multivariable analysis. The best model was selected using forward stepwise regression with the Akaike information criterion (AIC). Finally, the nomogram was created using the "rms" package. Model performance was assessed for discrimination, calibration, and clinical utility. Discrimination was evaluated using concordance statistics (C statistics) and time-dependent receiver operating characteristic (ROC)

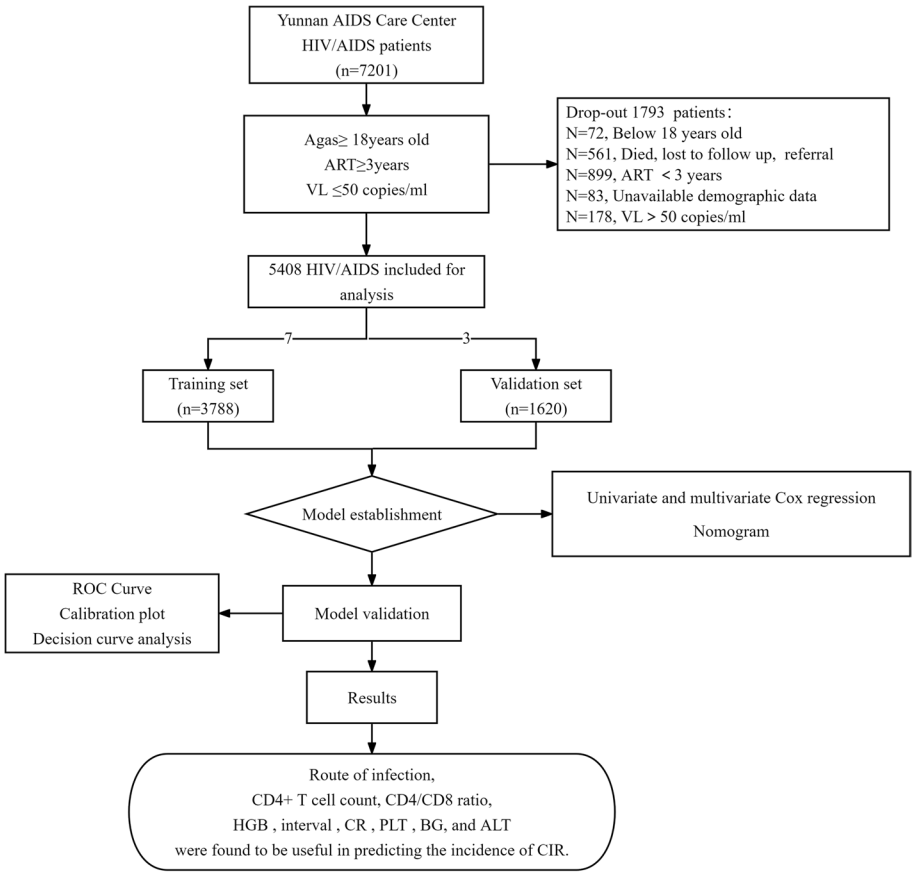

Fig. 1 Flowchart of the study. Flowchart of study selection for the present study

curves ("survival ROC" and "rms" packages). Internal verification and calibration curves were generated using the bootstrap resampling method, with 1,000 bootstrap repetitions. Clinical net benefit and DCA results were evaluated and plotted using the "rmda" package. Additionally, risk stratification analysis of all PLWH was conducted based on the prognosis index using Kaplan–Meier survival analysis and compared with the log-rank test, with the optimal cutoff value calculated using the "survminer" package. A statistical significance level of $P<0.05$ was applied.

Results

Characteristics and clinical features of participants

Between October 2022 and June 2023, a retrospective screening was conducted on 7 201 PLWH under ART. Among these participants, 1793were excluded from the study due to various factors, such as age, length of treatment, viral load, and unavailability of data. Ultimately, a total of 5 408 PLWH were enrolled based on the inclusion criteria (Fig. 1). The cohort predominantly consisted of males (66.79%), with a majority being middle-aged (59.93% aged 42 years or older) and unmarried (51.31%). The primary mode of HIV transmission was sexual contact. Approximately 47.95% of participants had initial $CD4^+T$ cell counts ranging from 187 to 459 cells/μL and $CD8^+T$ cell counts ranging from 751 to 1 499 cells/μL. As a result, 40.16% of participants had a CD4/CD8 ratio ≤ 0.2. NNRTIs and NRTIs were the main components, accounting for 92.86% of the initial regimens and 60.67% of the current regimens. The cohort also included 2083 participants with CIR and 3325 participants with IIR. The overall rate of CIR, as defined, was 38.52%. Significant differences were observed between the CIR and IIR cohorts in certain baseline data, including sex, age, and interval from diagnosis to treatment ($P<0.001$). The baseline characteristics of the training cohort ($n=3,788$) and the validation cohort ($n=1,620$) after random allocation are presented in Table 1. With the exception of age at diagnosis and age at treatment initiation, which were significantly different between the two cohort, the other characteristics did not show significant differences between the training and validation sets. Therefore, the basic characteristics of the PLWH were relatively balanced across both the training and validation sets.

Table 1 Characteristics of the 5408 patients in the study according to IIR/CIR and randomization to the training and validation sets

	Total patient cohort ($n=5408$)	IIR ($n=3325$)	CIR ($n=2083$)	*P* value	Training set ($n=3788$)	Validation set ($n=1620$)	*P* value
Sex							
Male	3612 (66.79)	2377 (71.49)	1235 (59.29)	< 0.001	2538 (67.00)	1074 (66.30)	0.637
Female	1796 (33.21)	948 (28.51)	848 (40.71)		1250 (33.00)	546 (33.70)	
Current age (year)							
≤ 35	1105 (20.43)	637 (19.16)	468 (22.47)	< 0.001	784 (20.70)	321 (19.81)	0.758
35–41	1062 (19.64)	617 (18.56)	445 (21.36)		740 (19.54)	322 (19.88)	
≥ 42	3241 (59.93)	2071 (62.29)	1170 (56.17)		2264 (59.77)	977 (60.31)	
Age at diagnosis (year)							
≤ 46	4422 (81.77)	2653 (79.79)	1769 (84.93)	< 0.001	3134 (82.73)	1288 (79.51)	0.006
> 46	986 (18.23)	672 (20.21)	314 (15.07)		654 (17.27)	332 (20.49)	
Age at initial ART (year)							
≤ 45	4241 (78.42)	2545 (76.54)	1696 (81.42)	< 0.001	3004 (79.30)	1237 (76.36)	0.018
> 45	1167 (21.58)	780 (23.46)	387 (18.58)		784 (20.70)	383 (23.64)	
Marital status							
Married	2101 (38.85)	1300 (39.10)	801 (38.45)	0.649	1481 (39.10)	620 (38.27)	0.830
Unmarried	2775 (51.31)	1691 (50.86)	1084 (52.04)		1938 (51.16)	837 (51.67)	
Divorced or widowed	532 (9.84)	334 (10.05)	198 (9.51)		369 (9.74)	163 (10.06)	
Infection route							
Heterosexual	2881 (53.27)	1763 (53.02)	1118 (53.67)	0.067	2006 (52.96)	875 (54.01)	0.506
Homosexual	1272 (23.52)	766 (23.04)	506 (24.29)		892 (23.55)	380 (23.46)	
Intravenous drug use	515 (9.52)	344 (10.35)	171 (8.21)		355 (9.37)	160 (9.88)	
Other/Unclea[a]	740 (13.68)	452 (13.59)	288 (13.83)		535 (14.12)	205 (12.65)	
Weight (kg)							
≤ 54	1902 (35.17)	1183 (35.58)	719 (34.52)	0.501	1350 (35.64)	552 (34.07)	0.116
55–64	1975 (36.52)	1219 (36.66)	756 (36.29)		1397 (36.88)	578 (35.68)	
≥ 65	1531 (28.31)	923 (27.76)	608 (29.19)		1041 (27.48)	490 (30.25)	
Anti-HBsAg							
Negative	5129 (94.84)	3150 (94.74)	1979 (95.01)	0.708	3591 (94.80)	1538 (94.94)	0.885
Positive	279 (5.16)	175 (5.26)	104 (4.99)		197 (5.20)	82 (5.06)	
Anti-HCV							
Negative	4803 (88.81)	2936 (88.30)	1867 (89.63)	0.143	3365 (88.83)	1438 (88.77)	0.980
Positive	605 (11.19)	389 (11.70)	216 (10.37)		423 (11.17)	182 (11.23)	
Diagnosis treatment interval (month)							
≤ 0.7	1978 (36.58)	1245 (37.44)	733 (35.19)	0.001	1353 (35.72)	625 (38.58)	0.135
0.8–1.6	1340 (24.78)	860 (25.86)	480 (23.04)		951 (25.11)	389 (24.01)	
≥ 1.7	2090 (38.65)	1220 (36.69)	870 (41.77)		1484 (39.18)	606 (37.41)	
$CD4^+$T cell counts (cells/μL)							
≤ 186	2051 (37.93)	1652 (49.68)	399 (19.16)	< 0.001	1454 (38.38)	597 (36.85)	0.292
187–459	2593 (47.95)	1416 (42.59)	1177 (56.51)		1790 (47.25)	803 (49.57)	
≥ 460	764 (14.13)	257 (7.73)	507 (24.34)		544 (14.36)	220 (13.58)	
$CD8^+$T cell counts (cells/μL)							
≤ 750	1966 (36.35)	1233 (37.08)	733 (35.19)	< 0.001	1359 (35.88)	607 (37.47)	0.498
751–1499	2547 (47.10)	1494 (44.93)	1053 (50.55)		1802 (47.57)	745 (45.99)	
≥ 1500	895 (16.55)	598 (17.98)	297 (14.26)		627 (16.55)	268 (16.54)	
CD4/CD8							
≤ 0.20	2172 (40.16)	1755 (52.78)	417 (20.02)	< 0.001	1541 (40.68)	631 (38.95)	0.475
0.21–0.39	2027 (37.48)	1197 (36.00)	830 (39.85)		1411 (37.25)	616 (38.02)	
≥ 0.40	1209 (22.36)	373 (11.22)	836 (40.13)		836 (22.07)	373 (23.02)	
WBC (× 109/L)							
≤ 3.7	1280 (23.67)	897 (26.98)	383 (18.39)	< 0.001	886 (23.39)	394 (24.32)	0.320

Table 1 (continued)

	Total patient cohort (*n* = 5408)	IIR (*n* = 3325)	CIR (*n* = 2083)	*P* value	Training set (*n* = 3788)	Validation set (*n* = 1620)	*P* value
3.8–4.7	1361 (25.17)	844 (25.38)	517 (24.82)		975 (25.74)	386 (23.83)	
≥ 4.8	2767 (51.16)	1584 (47.64)	1183 (56.79)		1927 (50.87)	840 (51.85)	
PLT (× 109/L)							
≤ 186	2473 (45.73)	1630 (49.02)	843 (40.47)	< 0.001	1730 (45.67)	743 (45.86)	0.919
> 186	2935 (54.27)	1695 (50.98)	1240 (59.53)		2058 (54.33)	877 (54.14)	
HGB (g/L)							
≤ 134	1850 (34.21)	1209 (36.36)	641 (30.77)	< 0.001	1271 (33.55)	579 (35.74)	0.257
135–154	1656 (30.62)	1002 (30.14)	654 (31.40)		1179 (31.12)	477 (29.44)	
≥ 155	1902 (35.17)	1114 (33.50)	788 (37.83)		1338 (35.32)	564 (34.81)	
Crea (μmol/L)							
≤ 58	1480 (27.37)	813 (24.45)	667 (32.02)	< 0.001	1043 (27.53)	437 (26.98)	0.533
59–65	735 (13.59)	455 (13.68)	280 (13.44)		502 (13.25)	233 (14.38)	
≥ 65	3193 (59.04)	2057 (61.86)	1136 (54.54)		2243 (59.21)	950 (58.64)	
Ccr (mL/min)							
≤ 140	4723 (87.33)	2958 (88.96)	1765 (84.73)	< 0.001	3301 (87.14)	1422 (87.78)	0.550
> 140	685 (12.67)	367 (11.04)	318 (15.27)		487 (12.86)	198 (12.22)	
CHO (mmol/L)							
≤ 4	1588 (29.36)	1043 (31.37)	545 (26.16)	< 0.001	1099 (29.01)	489 (30.19)	0.642
4.01–5.62	2543 (47.02)	1549 (46.59)	994 (47.72)		1795 (47.39)	748 (46.17)	
≥ 5.63	1277 (23.61)	733 (22.05)	544 (26.12)		894 (23.60)	383 (23.64)	
TG (mmol/L)							
≤ 2.6	4635 (85.71)	2866 (86.20)	1769 (84.93)	0.208	3245 (85.67)	1390 (85.80)	0.929
> 2.6	773 (14.29)	459 (13.80)	314 (15.07)		543 (14.33)	230 (14.20)	
Glu (mmol/L)							
≤ 4.5	975 (18.03)	579 (17.41)	396 (19.01)	0.147	677 (17.87)	298 (18.40)	0.675
> 4.5	4433 (81.97)	2746 (82.59)	1687 (80.99)		3111 (82.13)	1322 (81.60)	
ALT (U/L)							
< 23	2268 (41.94)	1359 (40.87)	909 (43.64)	0.048	1599 (42.21)	669 (41.30)	0.552
≥ 23	3140 (58.06)	1966 (59.13)	1174 (56.36)		2189 (57.79)	951 (58.70)	
AST (U/L)							
< 25	2696 (49.85)	1635 (49.17)	1061 (50.94)	0.217	1912 (50.48)	784 (48.40)	0.170
≥ 25	2712 (50.15)	1690 (50.83)	1022 (49.06)		1876 (49.52)	836 (51.60)	
TBIL (μmol/L)							
< 8.5	2232 (41.27)	1405 (42.26)	827 (39.70)	0.068	1551 (40.95)	681 (42.04)	0.473
≥ 8.5	3176 (58.73)	1920 (57.74)	1256 (60.30)		2237 (59.05)	939 (57.96)	
Initial ART regimen							
NNRTIs	5022 (92.86)	3090 (92.93)	1932 (92.75)	< 0.001	3533 (93.27)	1489 (91.91)	0.077
PIs	306 (5.66)	169 (5.08)	137 (6.58)		197 (5.20)	109 (6.73)	
INSTIs	80 (1.48)	66 (1.98)	14 (0.67)		58 (1.53)	22 (1.36)	
Current ART regimen							
NNRTIs	3281 (60.67)	1983 (59.64)	1298 (62.31)	0.143	2318 (61.19)	963 (59.44)	0.303
PIs	747 (13.81)	469 (14.11)	278 (13.35)		526 (13.89)	221 (13.64)	
INSTIs	1380 (25.52)	873 (26.26)	507 (24.34)		944 (24.92)	436 (26.91)	

Categorical data are presented as n (%)

IIR incomplete immune reconstitution, *CIR* complete immune reconstitution, *ART* antiretroviral treatment, *HBsAg* hepatitis B surface antigen, *Anti-HCV* antibodies against the hepatitis C virus, *WBC* white blood cell count, *PLT* platelet, *HGB* hemoglobin, *CR* creatinine, *Ccr* creatinine clearance rate, *CHO* cholesterol, *TG* triglycerides, *Glu* blood glucose, *ALT* alanine transaminase, *AST* aspartate transaminase, *TBIL* total bilirubin, *NNRTIs* nonnucleoside reverse transcriptase inhibitors, *PIs* protease inhibitors, *INSTI* integrase strand transfer inhibitors

[a] Others/Unclear included blood transfusion, mother-to-child transmission, and unknown

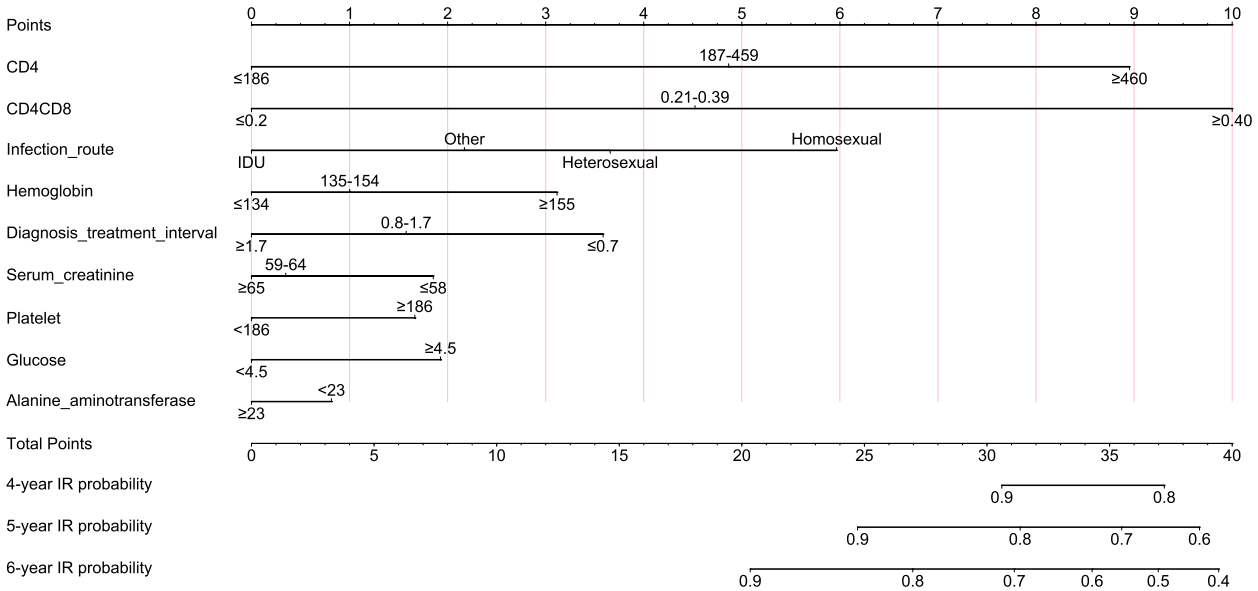

Fig. 2 The nomogram for predicting the CIR of PLWH. A nomogram was established based on univariable and multivariable Cox regression analyses. Significant predictors included the interval from HIV diagnosis to ART initiation, infection route, baseline $CD4^+$T cell count, baseline CD4/CD8 ratio, platelet count, glucose, creatinine, hemoglobin, and alanine aminotransferase level

Construction of a prediction model for the CIR in PLWH based on the training set

Univariable and multivariable Cox regression analyses were performed to identify potential predictors of CIR in PLWH. Table S1 presents the results of the univariable analysis of all 24 candidate predictors individually. Based on these results, 20 predictors were included in the multivariable Cox regression analyses. Six factors with $P \geq 0.2$ were excluded from the analysis: CHO, age at HIV diagnosis, age at initiation of ART, sex, coinfection with hepatitis B, and TG. Multivariable Cox regression analysis identified the following independent predictors for CIR: interval from HIV diagnosis to ART initiation, infection route, baseline $CD4^+$T cell count, baseline CD4/CD8 ratio, and the level of PLT, Glu, Crea, HGB, ALT. Consequently, a nomogram was constructed using the multivariable analysis results, as shown in Fig. 2. Total points were obtained by summing the corresponding points of each index value and then converted into the probability of CIR incidence at 4, 5, and 6 years according to the nomogram.

Evaluation and evaluation of the prediction models

The discrimination capacity of the prediction model was evaluated using C-indices and time-ROC curves. The model achieved a C-index of 0.78 (95% CI, 0.77–0.79), and internal validation yielded a similar C-index of 0.76 (95% CI, 0.74–0.78). The time-dependent ROC curves for predicting the CIR at 4, 5, and 6 years are shown in Fig. 3. The areas under the ROC curve (AUCs) reached 0.781 at 4 years, 0.809 at 5 years, and 0.816 at 6 years in the training cohort. The AUCs of the validation set reached 0.777 at 4 years, 0.808 at 5 years, and 0.792 at 6 years. These results indicate that the model achieved good predictive performance.

Calibration curves are used to compare observed outcomes with model predictions, providing a measure of model accuracy in estimating absolute risk. The agreement between the predicted and observed values is evaluated by the degree of alignment between the calibration curve and diagonal line [17]. In this study, the prediction results strongly agreed with the actual observations in both the training and validation sets, suggesting that the model accurately and effectively captured the actual values (Fig. 4).

Furthermore, DCA was employed to evaluate the clinical utility of the prediction model [18], including both the training and validation sets. As shown in Fig. 5, the model provided a net benefit, ranging from approximately 5% to 50%, in both the training and validation sets. These results indicated that the model is advantageous for making decisions in clinical settings, particularly for scenarios in the sixth year.

To assess the predictive effectiveness of the model, the study participants were divided into two risk groups based on their calculated risk scores from the nomogram: a low-scoring group (total score < 19.9) and a high-scoring group (total score ≥ 19.9). As shown in Fig. 6, the Kaplan–Meier curves for both the training and validation sets clearly demonstrated that the model

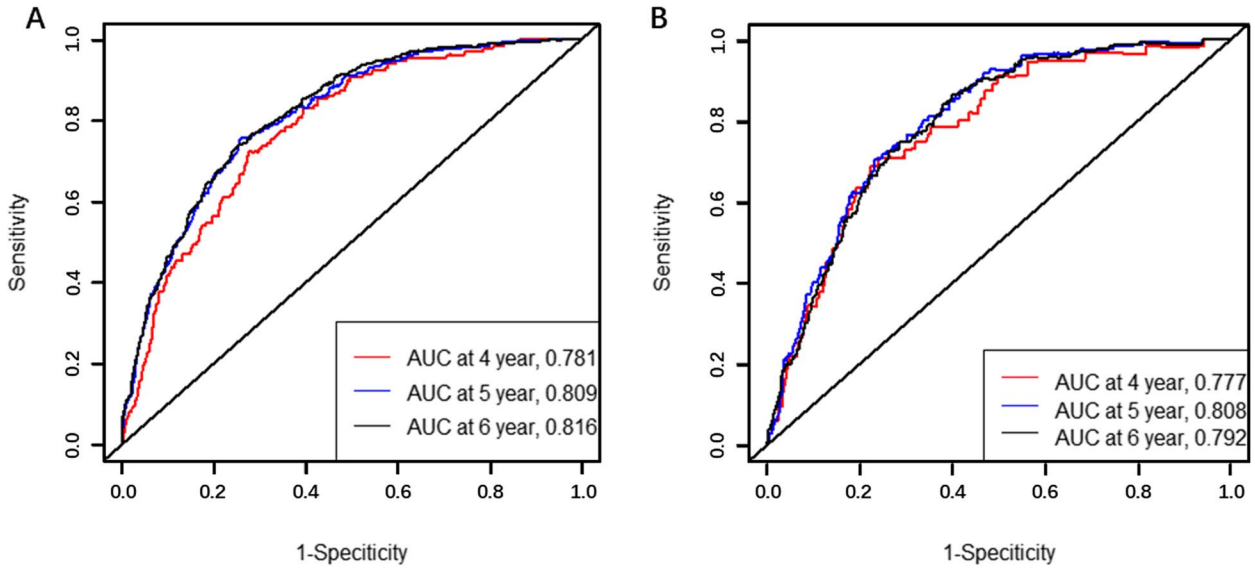

Fig. 3 Time-dependent ROC analysis for 4, 5, and 6 years of CIR for PLWH after ART. Training set (**A**) and the validation set (**B**). The red curve represents the ROC for 4-year survival, the blue curve represents the ROC for 5-year survival, and the black curve represents the ROC for 6-year survival. The x-axis represents the false positive rate (1-specificity), while the y-axis shows the true positive rate (sensitivity). An AUC value of 1 indicates perfect discrimination, while a value of 0.5 suggests no discriminative ability. The closer the AUC is to 1, the better the model's performance

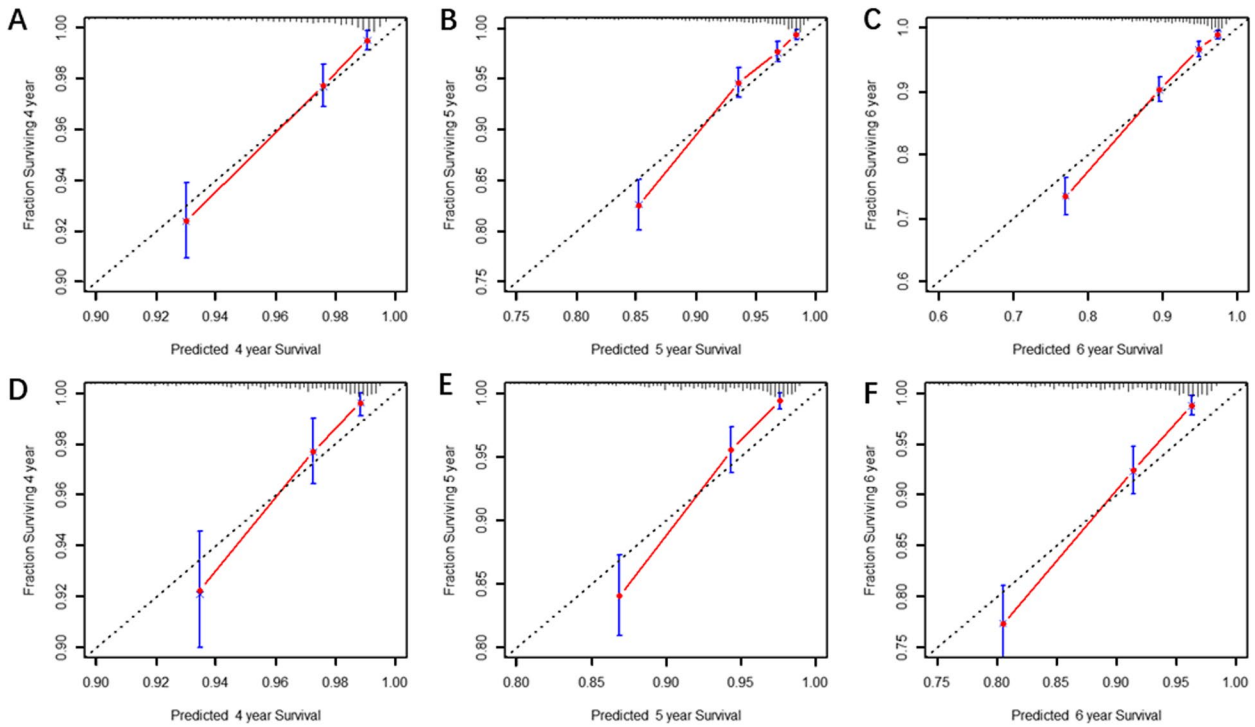

Fig. 4 Calibration curves of the prognostic nomogram for 4-, 5- and 6-year survival after ART. Training set (**A**-**C**) and the validation set (**D**-**F**). The calibration curves illustrate the agreement between the predicted and observed survival probabilities at 4, 5, and 6 years post-ART initiation. The x-axis represents the predicted survival probability, while the y-axis shows the actual observed survival probability. The dashed line indicates the ideal calibration where predicted probabilities perfectly match observed probabilities. The closer the calibration curve is to the dashed line, the better the model's predictive accuracy

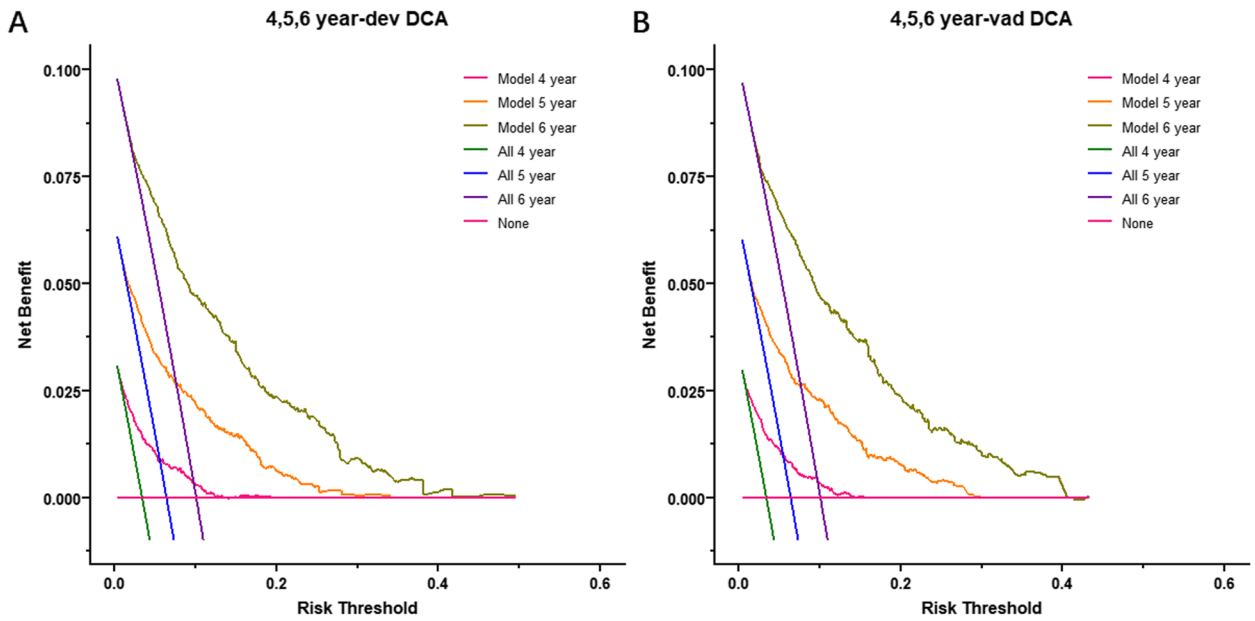

Fig. 5 Decision curve analysis (DCA) curve of the nomogram. **A** DCA curve for the training set. **B** DCA curve for the validation set. The DCA evaluates the clinical utility of the nomogram by quantifying the net benefit of using the model across different threshold probabilities. The x-axis represents the threshold probability, which reflects the minimum probability at which a patient would opt for a specific intervention. The y-axis represents the net benefit, which balances the true positive rate against the false positive rate, weighted by the threshold probability. A higher net benefit indicates greater clinical utility of the nomogram

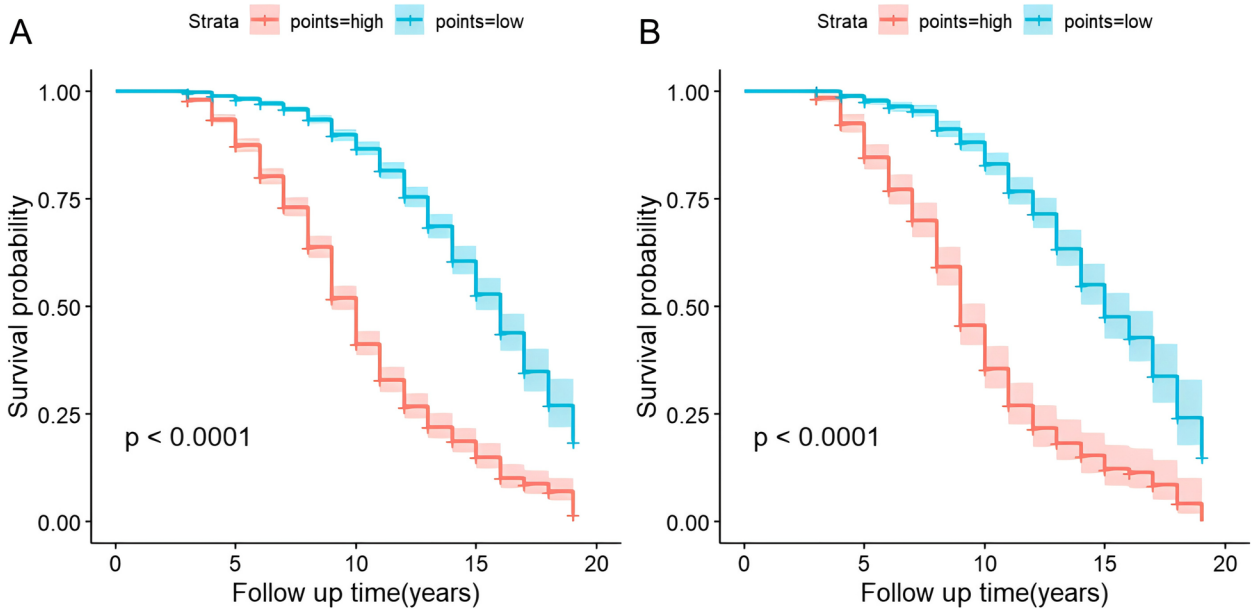

Fig. 6 Kaplan–Meier curve of the nomogram model. **A** Kaplan–Meier curve of the training set. **B** Kaplan–Meier curve of the validation set. The Kaplan-Meier curves visually demonstrate the ability of the nomogram model to stratify patients into distinct risk groups with significantly different survival outcomes. The curve illustrates the survival probability over time for patients in the training set, stratified by risk groups based on the nomogram model. The x-axis represents the time (in years) after ART initiation, and the y-axis represents the cumulative survival probability. The log-rank test was used to compare survival differences between risk groups, with a *p*-value of <0.001 indicating significant stratification

effectively distinguished between the high- and low-risk groups (log-rank test, $P < 0.05$).

Discussion

Accurate assessment of the potential for CIR following ART is crucial for improving prognosis and guiding treatment decisions for PLWH. This study aimed to develop and validate a prediction model to determine the likelihood of PLWH achieving CIR at years 4, 5, and 6 after initiating ART. Participant data for model development were derived from initial routine laboratory tests performed post-HIV diagnosis, selected for their affordability, ease of collection, and broad applicability.

Direct comparison of our model with others is challenging due to differences in CIR definitions. In contrast to the findings of Zhang et al. [12], our CIR criteria were more stringent, defining the CIR as a $CD4^+$T cell count ≥ 500 cells/μL and a CD4/CD8 ratio ≥ 0.8, which has been proven to more accurately evaluate the extent of immune restoration in the "treat all" era [15]. Longitudinal research has suggested a gradual CIR process following ART, often exhibiting a prolonged plateau phase. Studies have indicated that total $CD4^+$T and $CD8^+$T cell turnover rates tend to stabilize after 12–36 months of ART and reach a plateau after 3–4 years of suppressive treatment [19, 20]. The Multicenter AIDS Cohort Study, which involved 314 PLWH, revealed no increase in $CD4^+$T cell counts after 2–3 years of ART [21]. Similarly, the AIDS Clinical Trials Group (ACTG) study revealed that most changes in $CD4^+$T cell counts occur within the first year of ART, with no significant increases in the second or third year of therapy [22]. Based on these findings, our model was constructed using data from PLWH who had undergone ART for a minimum of 3 years, aiming to forecast CIR at 4, 5, and 6 years post-ART initiation.

In this study, we identified several factors influencing the CIR, including diagnosis-treatment interval, infection route, baseline $CD4^+$T cell count, CD4/CD8 ratio, and various hematological and biochemical parameters. The significance of baseline $CD4^+$T cell counts and the CD4/CD8 ratio in immune recovery has been extensively studied [15, 23–28]. For instance, among PLWH with baseline $CD4^+$T cell counts of less than 50, 50–199, 200–349, and 350–499 cells/μL, the probabilities of achieving $CD4^+$T cell counts of 500 cells/μL or higher after ART vary considerably, ranging from 1.97%, 7.84%, 62.85%, and 71.07%, respectively [15]. Similarly, among PLWH who started ART with less than 200 cells/μL, 57% did not reach 600 cells/μL after 7 years, while those with baseline counts of 200–349 $CD4^+$T cells/μL achieved this count in less than 2 years [23]. Previous studies have also demonstrated that the time required to achieve a 90% probability of CIR after two years of ART is significantly longer for PLWH with a CD4/CD8 ratio less than 0.5 compared to those with a ratio greater than 0.5 [29] These studies consistently demonstrated that higher baseline $CD4^+$T cell counts and CD4/CD8 ratioplay a crucial role in determining the rate and extent of immune recovery after ART, underscoring the importance of initiating ART at higher $CD4^+$T cell counts. Additionally, homosexual transmission was significantly associated with a lower rate of CIR. The impact of different infection routes on immune reconstitution is complex, with factors such as viral tropism, intestinal flora, and coreceptor switching linked to CIR in men who have sex with men (MSM) [30–32]. Research has indicated that only 60.5% of Chinese MSM have undergone HIV testing [33], which is attributed to limited awareness, social discrimination, and concealment of sexual orientation. Consequently, approximately 50% of Chinese MSM living with HIV are unaware of their serostatus, impacting timely diagnosis and access to treatment, which are crucial for effective immune reconstitution [33, 34]. In deciding on medication use, physicians consider various factors, including $CD4^+$T cell counts, virological efficacy, and drug tolerability. Preference is often given to more potent ART regimens when $CD4^+$T cell counts are low. In our cohort, participants who were initially prescribed INSTI-based regimens had average baseline $CD4^+$T cell counts of only 230 cells/μL. In contrast, those on NNRTI-based regimens had average baseline $CD4^+$T cell counts of 265 cells/μL, while those on PI-based regimens had average baseline $CD4^+$T cell counts of 320 cells/μL.

Regarding other influential factors, both a longer interval between HIV diagnosis was associated with lower baseline $CD4^+$T cell counts. An extended interval between diagnosis and treatment can lead to increased HIV replication, more severe immune system damage, and an increased incidence of opportunistic infections. Previous studies have shown positive correlations between the length of the diagnosis-to-treatment interval and the progression of AIDS and mortality [35]. This study also revealed associations between immune reconstitution and various hematological and blood biochemical parameters, including HGB, Crea, PLT, Glu, and ALT. Previous research has demonstrated that PLWH with suboptimal $CD4^+$T cell recovery often have elevated platelet counts [36]. This could be attributed to the ability of platelets to directly interact with HIV, facilitating viral binding and entry into cells, with platelets further acting as a reservoir for the virus during chronic infection. In addition, platelet-$CD4^+$T cell aggregates display increased levels of activation, depletion, and apoptotic markers, suggesting a potential role for platelets in $CD4^+$T cell depletion [37]. However, further research is

needed to clarify the relationships between the CIR and other blood biochemical parameters.

Given the complexity and importance of immune reconstitution, various studies have examined adjuvant therapeutic strategies to enhance CIR, including interleukin 2 (IL-2), statins, metformin, and other immunomodulators [38–40]. Furthermore, various immunotherapeutic approaches, such as broadly neutralizing antibodies, stem cell transplants, and therapeutic vaccines, are currently under investigation [41–43]. Recent clinical trials have shown the potential of (5R)−5-hydroxytriptolide to promote $CD4^+$T cell recovery and reduce inflammation in PLWH, suggesting that this is a new approach for the treatment of IIR [44]. Despite these developments, many current clinical trials and research initiatives have yet to achieve success, spurring ongoing efforts to develop more efficient immunomodulators and therapeutic strategies.

Our study is distinguished by a relatively large sample size ($N=5\,408$) and extended follow-up period, with 85.11% of participants monitored for more than 5 years. However, several limitations should be considered. First, the retrospective nature of the study inherently limited the scope of the analysis and may have introduced biases. Furthermore, as the study was conducted at a single center without external evaluation, the generalizability of the findings may be limited. Therefore, caution should be exercised when extrapolating the results to other populations or regions. Of particular note is the selection of PLWH treated for more than three years in our inclusion criteria. This selection was primarily based on our objective to accurately determine whether PLWH achieved CIR based on long-term treatment outcomes. However, this inclusion criterion inevitably limits the applicability of the model, particularly for patients who were lost to follow-up or discontinued treatment within the first three years of initiating ART. We clarify that our model is specifically designed for patients who remain on treatment and survive, which may be particularly relevant for guiding long-term management strategies in stable patient populations. Simultaneously, we recognize that future studies will need to incorporate factors such as early mortality and loss to follow-up into predictive models to more comprehensively assess the long-term immune recovery of patients after ART. Second, the study primarily focused on PLWH examination results at baseline and at the most recent follow-up. The predictors were derived from the initial test results following diagnosis, while the outcome indicators were based on the most recent test results. It is important to note that all immunological, virological, blood biochemical, and relevant indicators of routine laboratory tests in PLWH change over time. Our study did not consider these dynamic changes during ART, which are crucial for a comprehensive understanding of the CIR, potentially leading to inaccurate estimations of the true risk of IIR in PLWH. Finally, the absence of data on baseline viral load, viral load rebound, comorbidities, coinfections, treatment adherence, drug resistance, adverse effects, and changes in ART regimens for most participants is a significant limitation, as these factors could differentially impact the CIR but were not considered in our analysis.

Recent advances in medical research have deepened our understanding of HIV and the human immune system. Novel indicators, such as the percentage of naïve $CD4^+$T cells prior to ART in PLWH, the ratio of naïve/effective memory $CD4^+$T cells [45], and the activity of the immunomodulatory kynurenine pathway in tryptophan catabolism, have emerged. These metrics show promise in predicting the normalization of $CD4^+$T cell counts. Although the current evidence remains inconclusive, these findings offer new possibilities for diagnosis and prediction. Additionally, advancements in artificial intelligence and machine learning are expected to yield new models and algorithms that can adapt to the dynamic shifts in PLWH metrics, aiding healthcare professionals in making more informed decisions and improving longevity and quality of life for PLWH.

Conclusion

This study successfully developed a prediction model with robust performance, identifying interval from HIV diagnosis to ART initiation, infection route, baseline $CD4^+$T cell count, baseline CD4/CD8 ratio, platelet, glucose, creatinine, hemoglobin, and alanine aminotransferase level as independent predictors for CIR in PLWH after ART. The prediction model developed in this study, derived from baseline data, effectively predicted the probability of CIR in PLWH undergoing ART. The model demonstrated high accuracy and discriminatory power during internal evaluation, and the clinical utility of the nomogram was evaluated and confirmed using DCA. Based on our findings, we recommend the adoption of the model as a diagnostic tool to facilitate timely provision of appropriate therapeutic interventions, adjustment of ART regimens, precise and individualized management of PLWH, and optimization of cost-effectiveness.

Abbreviations

CIR	Complete immune reconstitution
PLWH	People living with human immunodeficiency virus
ART	Antiretroviral therapy
AIDS	Acquired immunodeficiency syndrome
ROC	Receiver operating characteristic
HIV	Human immunodeficiency virus
IRR	Incomplete immune reconstitution
DCA	Decision curve analyses
TRIPOD	Transparent Reporting of a Multivariate Prediction Model for Individual Prognosis or Diagnosis
WBC	White blood cell count

HGB	Hemoglobin
PLT	Platelet
TBIL	Total bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Crea	Creatinine
Ccr	Creatinine clearance rate
Glu	Blood glucose
TG	Triglyceride
CHO	Total cholesterol
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ELISA	Enzyme-linked immunosorbent assay
HBsAg	Anti-HBV or HCV surface antigen
NRTIs	Nucleoside reverse transcriptase inhibitors
NNRTIs	Nonnucleoside reverse transcriptase inhibitors
PIs	Protease inhibitors
INSTIs	Integrase strand transfer inhibitor
AIC	Akaike information criterion
C statistics	Concordance statistics
AUCs	Areas under the ROC curve
ACTG	AIDS Clinical Trials Group
MSM	Men who have sex with men
IL-2	Interleukin 2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10673-4.

Supplementary Material 1.

Acknowledgements
We are sincerely grateful for the support and assistance received for this study. We would like to thank all the medical staff and colleagues who were involved in the data collection and analysis for their support and assistance. Importantly, we express our gratitude to all the anonymous participants who participated in this study. Furthermore, our sincere gratitude goes to Yunnan Infectious Disease Hospital for providing valuable data resources that enabled us to conduct this study.

Authors' contributions
The authors' contributions in this study are as follows: Profs. Z-Q Shen and Y-T Zheng proposed the initial conception and design of the study and provided important guidance throughout its design and implementation. Profs. X-Q Dong and H-Q Li managed the study, including data collection and coordination, and provided the source of clinical data. Na Li and Rui Li were responsible for the data analysis, graphical presentation of the results, and writing of the first draft of the paper. Authors H-Y Zheng and R-R Tian conducted a comprehensive literature review and made substantial revisions to the paper. W-Q He, R-F Duan, and Xia Li carefully checked the clinical data and the reasonableness of the corresponding statistical methods. All authors read and approved the final manuscript.

Funding
This work was supported by grants from the National Key R & D Program of China (2023YFC2306700), the National Natural Science Foundation of China (U23A20473), the Yunnan Key R & D Program (202403AC100011), and the Key Laboratory of Bioactive Peptides of Yunnan Province (HXDT-2022–3).

Data availability
Data requests can be addressed to the corresponding author.

Declarations

Ethics approval consent to participate
This study was approved by the Ethics Committee of Yunnan Infectious Disease Hospital (approval No. Ke2024005), and informed consent from the participants was waived due to the use of anonymous data. The study was conducted in accordance with the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 9 August 2024 Accepted: 18 February 2025
Published online: 24 February 2025

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