

Development and spatial validation of a prognostic model for poor immune reconstitution among the PLWHA in China

Jingwen Wang

Nanjing Municipal Center for Disease Control And Prevention

Zhijie Li

Sir Run Run Shaw Hospital

Yuan Dong

Shanghai Municipal Center For Disease Control Prevention

Xiaoyi Zhou

Nantong Municipal Center for Disease Control and Prevention

Xiaoshan Li

Wuxi People's Hospital

Yuanyuan Xu

Nanjing Municipal Center for Disease Control And Prevention

Ping Zhu

Nantong Municipal Center for Disease Control and Prevention

Hongli Xia

Nantong Municipal Center for Disease Control and Prevention

Wenbin Yang

Yangzhou Center for Disease Control and Prevention

Jincheng Li

Yangzhou Center for Disease Control and Prevention

Zhengping Zhu

zjp_njcdc@163.com

Nanjing Municipal Center for Disease Control And Prevention

Article

Keywords: Poor immune reconstitution, Persons living with HIV or AIDS, Clinical prognostic model, Internal validation, Spatial validation.

Posted Date: July 29th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9922519/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Importance:

This study aimed to develop and validate a clinical prognostic model for poor immune reconstitution in persons living with HIV or AIDS (PLWHA).

Method

Based on the AIDS Prevention and Control Information System, data of PLWHA from the CDC of four cities was used to build the model, and the evaluation of model performance was presented from discrimination, calibration, clinical benefit and risk stratification.

Result

A total of 6,878 participants were included in the study. Age of diagnosis, CD4⁺ T-lymphocyte count, Platelet, BMI, and First-time medication regimen were used to predict the risk of poor immune reconstitution. The AUC of the model in the internal validation was 0.76 (95%CI: 0.72–0.80). In the spatial validation datasets, the AUC was 0.82 (95%CI: 0.80–0.84), 0.81 (95%CI: 0.77–0.85), 0.72 (95%CI: 0.68–0.75). The calibration curve of internal and spatial validation indicated the good calibration. Regarding the clinical benefit of the model, the treatment based on the risk threshold of model has a certain clinical benefit. Additionally, the difference of poor immune reconstitution risk was significant among the PLWHA in different risk stratifications ($P < 0.001$). At last, a static nomogram and a website-based nomogram were completed to calculate the risk of poor immunity reconstruction of PLWHA.

Conclusion

The clinical prognostic model has good discrimination, calibration and clinical benefit in both internal validation and spatial validation. It is possible to find out the PLWHA with high risk of poor immune reconstitution and take health intervention measures in time, so as to improve the prognosis of PLWHA.

1. Introduction

Human Immunodeficiency Virus (HIV) pandemic has undoubtedly created a public health crisis. In 2022, an estimated 1.3 million people worldwide were newly infected with HIV and 630 thousand died from Acquired Immune Deficiency Syndrome-related illness (AIDS-related illness) [1]. With the spread of antiretroviral therapy (ART), AIDS has gradually become a chronic disease[2], which has prolonged the lives of many persons living with HIV or AIDS (PLWHA), resulting in a life expectancy comparable to that of a normal person. However, 10%-40% [3-5] of patients treated with ART have a low increase in CD4⁺ T-lymphocyte counts, referred to as poor immune reconstitution. It has been surfaced that poor immune

reconstitution is associated with an increased risk of opportunistic infections[6] and an elevated risk of AIDS-related deaths[7].

In order to control the spread of AIDS and improve the quality of life (QoL) of PLWHA, so as to achieve the goal of eliminating AIDS, the WHO has set three 95% targets: 95% of infected people are diagnosed, 95% of diagnosed people have access to ART, and 95% of people on treatment have viral suppression. However, even if the three 95% targets are achieved, the QoL of PLWHA will still be threatened when the poor immune reconstitution and its harms are not well addressed. Therefore, the tools identifying PLWHA received first time ART at high risk of poor immune reconstitution early and helping to take timely preventive measures to improve their quality of survival is necessary and critical. Current studies have shown that factors such as baseline CD4⁺ T-cell count[8], baseline viral load[9], HCV co-infection[10], BMI[11], HIV viral subtype[12], etc. are associated with poor immune reconstitution. However, it is difficult to predict a patient's risk based on a single factor, and a comprehensive tool is needed to help determine this.

The popularity of clinical predictive modeling has brought hope to the diagnosis and prognosis of diseases, which can combine multiple factors to predict the probability of current disease and prognosis and risk of disease for individuals in the future, and improve patient outcomes by allowing patients to receive medical treatment as early as possible[13]. Recently, the research of clinical predictive modeling of HIV is also increasing[14,15], but there are few prognostic models for poor immune reconstitution of PLWHA received first time ART. Hence, our team developed a prognostic model for predicting risk of poor immune reconstitution by using data from Nantong CDC, China. Meanwhile, three spatial validation datasets to validate and evaluate the performance of prognostic model. At last, a static nomogram with risk stratification and website-based dynamic nomogram were plotted and deployed.

2. Study design

2.1 Population

The data required for this study were obtained from AIDS Prevention and Control Information System (AIDS-PCIS), which is managed and widely used by CDCs in China to register, track and follow up PLWHA. The database contains a wide range of demographic information, laboratory test indicators and AIDS-specific indicators, and is uniform throughout the country. This provides great convenience for future validation and application of the model.

This study was approved by the Ethics Committee of Wuxi People's Hospital (approval number: KY24075) and registered in the medical research registration information system of the National Health Insurance Information Platform (pid: 237918) and the China Clinical Trial Registry (Number: ChiCTR2400089497). Informed consent has been waived by using cases and biological specimens obtained from previous clinical diagnoses and treatments. All personal data in the study have been anonymized during the data organization and statistical analysis stages to ensure participant privacy. No

compensation was provided to the participants. Methods are reported according to the Helsinki guidelines.

The data used to develop the prognostic model were extracted from the AIDS - PCIS of Nantong CDC between 2005 to 2023. The observation end point was December 31, 2023. Data for the validation of this model were obtained from the CDC in Nanjing (2005-2021), Shanghai (2009-2019) and Yangzhou (2005-2022). The inclusion criteria included: (1) Newly diagnosed HIV-1 infected patients aged ≥ 18 years; (2) ART for at least 1 year; (3) At least once CD4 test after 1 year of ART. The exclusion criteria included: (1) ART has been interrupted during treatment; (2) Pregnant or breastfeeding women; (3) Patients with 50% missing variables or patients who cannot be tested for outcome indicators due to missing important indicators.

After inclusion and exclusion, a total of 2,292 patients were included in the Nantong data; 2,829 in the Nanjing data; 772 in the Shanghai data; and 985 in the Yangzhou data. The specific process of incorporating exclusions is shown in the Figure 1s (Supplementary material 1).

2.2 Candidate predictors

Candidate predictors were selected with reference to previous HIV clinical prediction models and the clinical experience of the co-authors. Eventually, 21 variables (demographic characteristics, epidemiologic characteristics, laboratory test indicators, initial medication regimen, and etc.) were selected as candidate predictors, and their explanations are provided in the supplementary material 2.

2.3 Definition of outcome

PLWHA with poor immune reconstitution were defined as: (1) PLWHA who have received ART for more than 1 year and less than 2 years with a CD4⁺ T-lymphocyte count < 200 cells/ μ L and a plasma virus load below the limit of detection; (2) CD4⁺T lymphocyte count < 350 cells/ μ L and plasma virus load below the limit of detection in patients who have received ART for more than 2 years; (3) After more than 4 years of ART, the CD4⁺T lymphocyte count does not exceed 500 cells/ μ L, and the plasma virus load is below the detection limit[16,17].

2.4 Sample size estimation

Prevalence of poor immune reconstitution was assumed to be 0.40 based on the incidence of the poor immune reconstitution in references and in our data. The number of parameters of candidate predictors was 30. Meanwhile, setting C-index of expected performance of this prognostic model as 0.70 as assumed, and a shrinkage as 0.9. Based on the sample size estimation method for clinical predictive models of Richard D Riley et al[18], the sample sizes based on the three criteria were 2177, 748 and 369, respectively. Thus, the minimum sample size required for the development of this prognostic model was 2177 cases.

2.5 Model development and validation

First, the missing value of the dataset for each region was described and a bar chart of the missing data was plotted in the supplementary material 3. Missing values of predictors were multiply imputed over 5 iterations. Then, candidate predictors were described and compared in terms of whether or not they were subgroups of poor immune reconstitution. For continuous, those conformed to normality were described using mean and standard deviation (*SD*), and two independent samples *t*-tests were used for between-group comparisons; those did not conform to normality were described using Median (Interquartile range), (*M (IQR)*), and the Mann Whitney *U* test was utilized for comparisons. For categorical variables, sample distributions were compared using the χ^2 test or Fisher's exact probability method, and variables with *P* values <0.1 were included in subsequent analyses.

Subsequently, the variables were furtherly screened using least absolute shrinkage and selection operator (lasso) regression. The linear relationship between the continuous variables and the risk of outcomes was assessed using restricted cubic spline, and those variables did not satisfy the linear relationship were converted into classified variables. Finally, the variables that are finally included in the model are determined by stepwise regression method.

The internal and spatial validation of the model consisted of discrimination described by the area under receiver operator characteristic curves (AUC), and calibration described by the calibration plot, the Hosmer-Lemeshow (HL) test and Brier scores. Benefits of the model are assessed through decision curves analysis (DCA).

2.6 Nomogram and risk stratifications

A static nomogram and website-based dynamic nomogram were plotted and deployed on the basis of this prognostic model. The total points of the static nomogram for individuals in training set and 3 spatial validation sets was calculated, and risk stratification was stratified by tertiles of total points of training set. The difference of incidence of poor immune reconstitution among risk stratifications was compared using Chi-square test, and the association between risk stratifications and risk of poor immune reconstitution was estimated using log-binomial regressions.. The steps of this study are showed in Figure 1.

3. Results

3.1 Baseline information

Comparative results between groups showed P-values of less than 0.1 for 15 variables, such as age of diagnosis, BMI, and WHO stage, which were included in the subsequent model analyses, as shown in the Table 1.

Table 1 Baseline statistical tables

Variable	n=2292	Poor immune reconstitution		Statistic	P-value
		No (n=1225)	Yes (n=1067)		
Gender				$\chi^2=1.717^1$	0.190
Male	1917 (83.64)	1013 (82.69)	904 (84.72)		
Female	375 (16.36)	212 (17.31)	163 (15.28)		
Age of diagnosis	43 (31, 54)	40 (29, 53)	46 (35, 55)	$Z=-6.580^2$	<0.001
Marital status				$\chi^2=32.090^1$	<0.001
Married	545 (23.78)	348 (28.41)	197 (18.46)		
Unmarried	1389 (60.60)	689 (56.24)	700 (65.60)		
Others	358 (15.62)	188 (15.35)	170 (15.93)		
Nationality				$\chi^2=0.531^1$	0.466
Han	2276 (99.30)	1215 (99.18)	1061 (99.44)		
Others	16 (0.70)	10 (0.82)	6 (0.56)		
Education				$\chi^2=31.068^1$	<0.001
Illiteracy	45 (1.96)	25 (2.04)	20 (1.87)		
Primary schools	308 (13.44)	155 (12.65)	153 (14.34)		
Junior high school	947 (41.32)	464 (37.88)	483 (45.27)		
Senior high school	541 (23.60)	290 (23.67)	251 (23.52)		
College	451 (19.68)	291 (23.76)	160 (15.00)		
History STD				$\chi^2=0.096^1$	0.757
No	1854 (80.89)	988 (80.65)	866 (81.16)		
Yes	438 (19.11)	237 (19.35)	201 (18.84)		
Route of infection				$\chi^2=5.661^1$	0.059
MSM	1206 (52.62)	669 (54.61)	537 (50.33)		
NMHR	1071 (46.73)	546 (44.57)	525 (49.20)		
Others	15 (0.65)	10 (0.82)	5 (0.47)		
Medication regimen				$\chi^2=45.641^1$	<0.001
NNRTIs	1985 (86.61)	1010 (82.45)	975 (91.38)		

Variable	n=2292	Poor immune reconstitution		Statistic	P-value
		No (n=1225)	Yes (n=1067)		
NRTIs	21 (0.92)	11 (0.90)	10 (0.94)		
PIs	37 (1.61)	21 (1.71)	16 (1.50)		
INSTIs	249 (10.86)	183 (14.94)	66 (6.19)		
CD4 ⁺ T-lymphocyte count (cells/ μ L)	224.00 (94.75, 327.00)	286.00 (201.00, 390.00)	149.00 (41.00, 250.50)	Z=19.637 ²	<0.001
WHO stage				Z=-4.544 ²	<0.001
I	1089 (47.51)	632 (51.59)	457 (42.83)		
II	262 (11.43)	153 (12.49)	109 (10.22)		
III	478 (20.86)	214 (17.47)	264 (24.74)		
IV	463 (20.20)	226 (18.45)	237 (22.21)		
White blood cell (10^9 /L)	4.90 (3.81, 6.10)	5.10 (4.10, 6.30)	4.63 (3.50, 5.83)	Z=7.128 ²	<0.001
Platelet (10^9 /L)	177.00 (142.75, 220.00)	185.00 (149.00, 226.00)	167.00 (132.50, 215.00)	Z=6.286 ²	<0.001
Haemoglobin (g/L)	136.75 $\pm$ 22.11	140.09 $\pm$ 20.58	132.91 $\pm$ 23.16	t=7.790 ³	<0.001
Blood creatinine (μ mol/L)	66.08 $\pm$ 20.59	66.22 $\pm$ 20.31	65.92 $\pm$ 20.91	t=0.341 ⁴	0.733
Triglyceride (mmol/L)	1.31 (1.01, 1.86)	1.32 (1.01, 1.89)	1.31 (1.01, 1.82)	Z=0.538 ²	0.591
Total cholesterol (mmol/L)	4.08 $\pm$ 0.98	4.15 $\pm$ 0.99	4.00 $\pm$ 0.96	t=3.611 ⁴	<0.001
Glucose (mmol/L)	5.87 $\pm$ 1.69	5.85 $\pm$ 1.67	5.89 $\pm$ 1.72	t=-0.466 ³	0.641
Alanine aminotransferase (U/L)	23 (16, 36)	23 (16, 35)	24 (16, 38)	Z=-2.309 ²	0.021
Aspartate transaminase (U/L)	27 (23, 36)	26 (22, 34)	29 (23, 38)	Z=-5.120 ²	<0.001
Total bilirubin (μ mol/L)	10.4 (7.7, 14.0)	10.9 (8.4, 14.6)	9.80 (7.2, 13.3)	Z=6.368 ²	<0.001
BMI (Kg/m ²)	22.18 $\pm$ 3.08	22.59 $\pm$ 3.16	21.71 $\pm$ 2.92	t=6.878 ³	<0.001

Notes: 1. Pearson χ^2 test; 2. Mann Whitney U test; 3. variance-corrected independent samples t test; 4. independent samples t test.

3.2 Development of the model

3.2.1 Lasso regression analysis

Based on the above table of baseline characteristics, those predictors with a P-value ≤ 0.1 were included in subsequent analyses, and Lasso regression was used to further screen for factors that might contribute to the outcome variables. The results showed that as λ increased, the factors that had less impact on the risk of adverse immune reconstitution were compressed to 0 earlier, and the number of variables gradually decreased (Figure 6sA). When λ was 0.0047, a total of 10 predictors were screened; the value of λ was optimal ($\lambda = 0.0230$) when it continued to increase by 1 standard error, at which point a total of 5 variables were screened, namely age at diagnosis, baseline CD4⁺ T-lymphocyte counts, platelets, BMI and medication regimen, as detailed in Supplementary material 4.

3.2.2 Restricted cubic spline plots

Linear relationships between continuous variables and outcomes were assessed using restricted cubic spline, and it was found that age at diagnosis did not satisfy the linear relationship with outcomes, and were converted to categorical variables based on restricted cubic spline plots. Specific classification criteria are shown in the Supplementary Material 5.

3.2.3 Binary logistic regression model construction

The variables obtained above were incorporated into a dichotomous logistic model using stepwise regression to obtain the final model as shown in the **Table 2**.

Table 2 Binary logistic regression model

Variable	β	<i>Sd</i>	<i>Z</i>	<i>P</i> -value	OR(95%CI)
Age of diagnosis					
<43 years old	Ref				
≥43 years old	0.508	0.096	5.286	<0.001	0.602(0.498~0.726)
CD4 ⁺ T-lymphocyte count	-0.006	0.001	-16.783	<0.001	0.994(0.993~0.995)
Platelet	-0.002	0.001	-3.287	0.001	0.998(0.996~0.999)
BMI	-0.05	0.016	-3.091	0.002	0.951(0.921~0.982)
First-time medication regimen					
NNRTIs	Ref.				
NRTIs	-0.909	0.468	-1.943	0.052	0.403(0.159~1.015)
PIs	-0.417	0.375	-1.112	0.266	0.659(0.313~1.376)
INSTIs	-1.351	0.169	-8.013	<0.001	0.259(0.185~0.359)
Intercept	2.672	0.388	6.886	<0.001	-

3.3 Internal validation and spatial validation of the model

Data from the Nanjing, Shanghai and Yangzhou CDC were used for spatial validation, which also included discrimination, calibration and clinical benefit. The results of the homogeneity test for the training set and validation set are in Supplementary Material 6.

3.3.1 Validation of model differentiation

We used the Bootstrap method to resample 500 times in order to plot the ROC curve and obtain the area under the curve to evaluate the discrimination of the model. The results (Figure 8s, Supplementary Material 7) show that in the internal validation of the Nantong data, the AUC is 0.76 (95% *CI*: 0.72-0.80); while in the spatial validation of the remaining three regions, the model performs better in the Nanjing and Shanghai data, with AUCs of 0.82 (95% *CI*: 0.80-0.84) and 0.81 (95% *CI*: 0.77-0.85), respectively, while in the Yangzhou data the model performance was average with an AUC of 0.72 (95% *CI*: 0.68-0.75). Overall, the discriminatory power of this constructed model performed well in both internal and spatial validation datasets.

3.3.2 Validation of model calibration

For the evaluation of the calibration of the model, we integrated the plotting of the calibration curve, the HL test, in addition, due to the high sensitivity of the HL test for large samples, which is prone to draw conclusions that are not statistically significant, we additionally utilized the brier scores to further evaluate the calibration of the model, and used the brier < 0.25 as the criterion for good calibration.

In the internal validation of the Nantong data, the HL test $\chi^2=6.783$, $P=0.560$, Brier score=0.195. The brier scores of Nanjing, Shanghai and Yangzhou were 0.159, 0.184 and 0.213, respectively.

The brier scores of Nanjing, Shanghai and Yangzhou were 0.159, 0.184 and 0.213, respectively. Combined with the fact that the calibration curves in Figure 9s (Supplementary Material 7) are all closer to the diagonal, the calibration of the model can be considered to be good.

3.3.3 Decision curve

Decision curves (Figure 10s, Supplementary Material 7) were constructed based on the constructed model and validation set. The results of the internal validation showed that the intervention was beneficial at risk thresholds of 0.23-0.75 or cost-benefit ratios of 23:77-3:1; whereas in the spatially validated Nanjing dataset, the intervention was beneficial at risk thresholds of 0.11-0.47 or cost-benefit ratios of 11:89-47:53; in the Shanghai dataset, the intervention was beneficial at risk thresholds of 0.09-0.39 or The intervention was beneficial when the cost-benefit ratio was 9:91- 39:61; in the Yangzhou dataset, the intervention was beneficial when the risk threshold was 0.36-0.67 or the cost-benefit ratio was 9:16- 67:33.

3.4 Static and dynamic nomograms

The prognostic model is made into an actionable tool: a static nomogram (Figure 2). Meanwhile, total points of nomogram for individuals were calculated and risk stratification with three categories: low (<144.06), medium (144.06-154.14) and high (≥ 154.15) was stratified according to the tertiles of that. Moreover, to facilitate the dissemination and utilization of the model, we constructed an online nomogram, published on https://lee478474.shinyapps.io/Poor_immune_reconstitution_Clinical_prediction_model/.

3. 5Classification of risk group

PLWHA from 3 spatial validation sets were also classified into 3 groups (low, medium and high risk) based on the tertiles of the total points of nomogram representing the risk of poor immune reconstitution, respectively. As Table 6s (Supplementary material 8) showed, the difference of the incidence of poor immune reconstitution among 3 groups was significant (all $P<0.001$). Additionally, the association between risk stratification and poor immune reconstitution was estimated (**Figure 3 and Table 7s**), which demonstrated the risk of poor immune reconstitution in medium and high risk stratification were higher than that of low risk stratification (all $P<0.001$). Above all, the risk stratification based on the total points and threshold of the nomogram can effectively distinguish the risk degree of poor immune reconstitution among PLWHA in the future.

3.6Sensitivity analyses

CD4⁺ T-lymphocyte count , Platelet, and BMI were transformed into categorical variables, and the above analysis was repeated to evaluate the stability of the model, and the results showed that in internal

validation, the AUC was 0.74 (0.72-0.76), the Brier score was 0.205, and the intervention was beneficial at risk thresholds of 0.32-0.73 or cost-benefit ratios of 8:17-73:27; in the spatial validation, the model continued to show good discrimination, calibration and clinical benefit, and the detailed results are shown in Supplementary Material 9.

4. Discussion

With the advent of antiretroviral therapy, mortality and morbidity from HIV infection have declined significantly[19], but this has been hampered by poor immune reconstitution. Several studies have shown that poor immune reconstitution has a negative impact on patient prognosis[19,20]. Therefore, there is an urgent need for a tool that can be used to predict the risk of poor immune reconstitution. In this study, we constructed a clinical prediction model about poor immune reconstitution in AIDS based on the Nantong CDC PLWH population data, and the meaningful variables in the model included Age of diagnosis, BMI, Platelet, CD4⁺ T-lymphocyte count, and first-time medication regimen. The model was spatially validated based on three CDCs' data from different regions, and the results showed that our model is well differentiated and calibrated.

In the model, age at diagnosis was seen as one of the predictors of poor immune reconstitution, with patients older than 43 having a higher risk of poor immune reconstitution than those younger than 43, and a study found similar results[21]. However, some studies have also shown that immune reconstitution in older HIV-infected patients is similar to that in younger patients[22], therefore more research is needed to verify the causal association between them.

A growing number of studies have demonstrated a significant association between higher BMI and CD4⁺ T-cell count recovery[11,23-25] and although the rationale for this has not been elucidated, there is no doubt that body weight is a non-negligible factor during antiretroviral therapy for HIV patients. Fortunately, our model used body weight as one of the predictors and the risk of poor immune reconstitution decreased with increasing body weight, consistent with the findings of the above study.

The HIV virus mainly attacks the body's CD4⁺ T-lymphocyte, and the reduction of CD4⁺ T-lymphocyte in the later stages of the disease reduces the body's immunity, which can lead to a variety of malignant cancers or infectious diseases. Many studies have shown that baseline CD4⁺ T-lymphocyte count is one of the most important factors affecting patients' immune reconstitution[26,27] and the higher the baseline CD4⁺ T-lymphocyte count, the lower the risk of poor immune reconstitution in patients. In the model, patients with high CD4⁺ T lymphocyte counts (CD4>326) had a reduced risk of poor immune reconstitution to 0.299 (0.255-0.349) times the risk of poor immune reconstitution compared to patients with low counts (CD4≤326).

Platelets, as a common indicator in blood counts, are very easy to obtain and were also included in this clinical prediction model for poor immune reconstitution, which helps in the practice of this model. In this study, the lower the baseline platelet counts, the higher the risk of poor immune reconstitution.

Some studies have shown that HIV infection can affect hematopoiesis and that poor immune reconstitution is associated with hematopoietic depletion in patients[28,29]. KYEYUNE found that the lower the number of CD4⁺ T lymphocytes, the higher the rate of thrombocytopenia in humans, suggesting that thrombocytopenia in HIV/AIDS patients is directly related to the body's immune function[30]. In China, both white blood cells and haemoglobin are easily accessible laboratory indicators for AIDS patients, and both are retained as predictors in the model.

In our study, we analyzed the effect of type of first medication on poor immune reconstitution by roughly dividing the type of medication into 5 categories[31]. Fortunately, this factor was eventually included as a predictor in the model, which showed that compared to patients treated with NNRTIs, those treated with PIs (OR: 0.517, 95%CI: 0.296-0.883) and INSTIs (OR: 0.319, 95%CI: 0.251-0.404) had a lower risk of poor immune reconstitution. Martin et al. in a study of HIV-infected patients treated with ART between 1997-2010 found that PIs first-line regimens immune reconstitution was superior to NNRTIs-based based regimens, which is entirely consistent with our findings[32]. Wijting et al. found that INSTIs-based regimens induced a rapid decline in viral load as well as restoration of CD4⁺ T-lymphocytes in a study targeting patients with advanced HIV-1, both of which provide evidence for our study[33].

There are some limitations in the study. First of all, we only used the baseline information to predict the future risk of poor immune reconstitution, but some factors such as CD4⁺ T-lymphocytes will continue to change with the duration of treatment, and the treatment regimen will also change with the patient's condition. Due to the complexity of the analysis, we did not take into account the dynamics of these factors in this study, and we look forward to adding these dynamics to better predict the risk of the patients in the future studies. Second, there is no more uniform definition of poor immune reconstitution internationally; the definition of poor immune reconstitution in this study is the result of our synthesis of various literatures, and it may be inconvenient for the user to be consistent with our definition of poor immune reconstitution if our model were to be used; Third, the participants in the study were all from China, and the generalization of the conclusions to the entire population of PLWH may have some limitations.

Strengths of the study include that our study is the first poor immune reconstitution model with spatial validation, and we performed internal and spatial validation in terms of discrimination, calibration, and clinical benefit, all of which showed that the model had good performance in all three regions. All variables included in this study were obtained from the AIDS-PCIS system, which is widely used in China for the management of HIV/AIDS patients, and the data contained in this database are consistent across the country, which greatly facilitates the validation and application of the model in China. In addition, we constructed a webpage nomogram of the poor immune reconstitution prediction model for HIV/AIDS patients to self-assess their risk of poor immune reconstitution, in the hope that this will serve as a warning to patients at high risk.

In conclusion, our study illustrates that the constructed model plays an important role in the prediction of poor immune reconstitution, and with our model, patients at higher risk of poor immune reconstitution

can be identified at an early stage at a very small cost, and early health interventions can be made to improve the prognosis of HIV/AIDS patients.

Declarations

Acknowledgments

The authors sincerely acknowledge the contributors for collecting the research data, and also thank all the participants and investigators involved in the China's AIDS Prevention and Control Information System (AIDS-PCIS).

ORCID ID

Jingwen Wang <https://orcid.org/0009-0007-5916-6071>

Data Availability

The data required for this study were obtained from China's AIDS Prevention and Control Information System (AIDS-PCIS).

Ethical Considerations

This study was approved by the Ethics Committee of Wuxi People's Hospital (approval number: KY24075) and registered in the medical research registration information system of the National Health Insurance Information Platform (pid:237918) and the China Clinical Trial Registry (Number: ChiCTR2400089497).

Funding

This work was supported by National Natural Science Foundation of China (Grant no. 82103896), Nanjing Medical Science and Technology Development Project (ZKX23059, YKK23192) and Nanjing Center for Disease Control and Prevention Young Talents Research and Development Team Project (NPY2307).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. UNAIDS. Global HIV&AIDS statistics—Fact sheet. <https://www.unaids.org/en/resources/fact-sheet>
2. Simon, V. & Ho, D. D. Abdool Karim, Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* **368**, 489–504. [https://doi.org/10.1016/s0140-6736\(06\)69157-5](https://doi.org/10.1016/s0140-6736(06)69157-5) (2006).

3. Zhang, W. & Ruan, L. Recent advances in poor HIV immune reconstitution: what will the future look like? *Front. Microbiol.* **14**, 1236460. <https://doi.org/10.3389/fmicb.2023.1236460> (2023).
4. Negash, H. et al. The effect of tuberculosis on immune reconstitution among HIV patients on highly active antiretroviral therapy in Adigrat general hospital, eastern Tigray, Ethiopia; 2019: a retrospective follow up study. *BMC Immunol.* **20**, 45. <https://doi.org/10.1186/s12865-019-0327-7> (2019).
5. Bayarsaikhan, S., Jagdagsuren, D., Gunchin, B., Sandag, T. & Survival CD4 T lymphocyte count recovery and immune reconstitution pattern during the first-line combination antiretroviral therapy in patients with HIV-1 infection in Mongolia. *PLoS One.* **16**, e0247929. <https://doi.org/10.1371/journal.pone.0247929> (2021).
6. Shete, A. et al. Incomplete functional T-cell reconstitution in immunological non- responders at one year after initiation of antiretroviral therapy possibly predisposes them to infectious diseases. *Int. J. Infect. Dis.* **81**, 114–122. <https://doi.org/10.1016/j.ijid.2019.01.017> (2019).
7. Loutfy, M. R. et al. A CD4 + cell count < 200 cells per cubic millimeter at 2 years after initiation of combination antiretroviral therapy is associated with increased mortality in HIV-infected individuals with viral suppression. *J. Acquir. Immune Defic. Syndr.* **55**, 451–459. <https://doi.org/10.1097/qai.0b013e3181ec28ff> (2010).
8. D'Amico, R. et al. Lower CD4 + T lymphocyte nadirs may indicate limited immune reconstitution in HIV-1 infected individuals on potent antiretroviral therapy: analysis of immunophenotypic marker results of AACTG 5067. *J. Clin. Immunol.* **25**, 106–115. <https://doi.org/10.1007/s10875-005-2816-0> (2005).
9. Chen, S. et al. Very high baseline HIV viremia impairs efficacy of non-nucleoside reverse transcriptase inhibitor-based ART: a long-term observation in treatment- naive patients. *Infect. Dis. Poverty.* **9**, 75. <https://doi.org/10.1186/s40249-020-00700-8> (2020).
10. Santin, M. et al. Impact of hepatitis C virus coinfection on immune restoration during successful antiretroviral therapy in chronic human immunodeficiency virus type 1 disease. *Eur. J. Clin. Microbiol. Infect. Dis.* **27**, 65–73. <https://doi.org/10.1007/s10096-007-0384-3> (2008).
11. Li, X. et al. Predictive effects of body mass index on immune reconstitution among HIV- infected HAART users in China. *BMC Infect. Dis.* **19**, 373. <https://doi.org/10.1186/s12879-019-3991-6> (2019).
12. Ge, Y. et al. The Molecular Epidemiological and Immunological Characteristics of HIV-1 CRF01_AE/B Recombinants in Nanjing, China. *Front. Microbiol.* **13**, 936502. <https://doi.org/10.3389/fmicb.2022.936502> (2022).
13. Steyerberg, E. W. et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med.* **10**, e1001381. <https://doi.org/10.1371/journal.pmed.1001381> (2013).
14. Hou, X. et al. Development and validation of a prognostic nomogram for HIV/AIDS patients who underwent antiretroviral therapy: Data from a China population-based cohort. *EBioMedicine* **48**, 414–424. <https://doi.org/10.1016/j.ebiom.2019.09.031> (2019).
15. Jiang, F. et al. Construction and validation of a prognostic nomogram for predicting the survival of HIV/AIDS adults who received antiretroviral therapy: a cohort between 2003 and 2019 in Nanjing.

- BMC Public Health*. **22**, 30. <https://doi.org/10.1186/s12889-021-12249-8> (2022).
16. Li, T. et al. Reduced thymic output is a major mechanism of immune reconstitution failure in HIV-infected patients after long-term antiretroviral therapy. *Clin. Infect. Dis.* **53**, 944–951. <https://doi.org/10.1093/cid/cir552> (2011).
 17. Guidelines for the use of antiretroviral agents. in HIV-infected adults and adolescents, January 28, 2000 by the Panel on Clinical Practices for Treatment of HIV Infection. *HIV Clin. Trials*. **1**, 60–110. <https://doi.org/10.1310/hct.2000.1.1.008> (2000).
 18. Riley, R. D. et al. Calculating the sample size required for developing a clinical prediction model. *Bmj* **368**, m441 (2020). <https://doi.org/10.1136/bmj.m441>
 19. Guihot, A., Bourgarit, A., Carcelain, G. & Autran, B. Immune reconstitution after a decade of combined antiretroviral therapies for human immunodeficiency virus. *Trends Immunol.* **32**, 131–137. <https://doi.org/10.1016/j.it.2010.12.002> (2011).
 20. Engsig, F. N. et al. Long-term mortality in HIV-positive individuals virally suppressed for > 3 years with incomplete CD4 recovery. *Clin. Infect. Dis.* **58**, 1312–1321. <https://doi.org/10.1093/cid/ciu038> (2014).
 21. Chen, J. et al. The effect of age on CD4 + T-cell recovery in HIV-suppressed adult participants: a sub-study from AIDS Clinical Trial Group (ACTG) A5321 and the Bone Loss and Immune Reconstitution (BLIR) study. *Immun. Ageing*. **19**, 4. <https://doi.org/10.1186/s12979-021-00260-x> (2022).
 22. Jourjy, J., Dahl, K. & Huesgen, E. Antiretroviral Treatment Efficacy and Safety in Older HIV-Infected Adults. *Pharmacotherapy* **35**, 1140–1151. <https://doi.org/10.1002/phar.1670> (2015).
 23. Han, W. M. et al. Association of body mass index with immune recovery, virological failure and cardiovascular disease risk among people living with HIV. *HIV Med.* **22**, 294–306. <https://doi.org/10.1111/hiv.13017> (2021).
 24. Kiweewa, F. et al. HIV virologic failure and its predictors among HIV-infected adults on antiretroviral therapy in the African Cohort Study. *PLoS One*. **14**, e0211344. <https://doi.org/10.1371/journal.pone.0211344> (2019).
 25. Koethe, J. R. et al. Higher Time-Updated Body Mass Index: Association With Improved CD4 + Cell Recovery on HIV Treatment. *J. Acquir. Immune Defic. Syndr.* **73**, 197–204. <https://doi.org/10.1097/qai.0000000000001035> (2016).
 26. Roul, H. et al. CD4 + cell count recovery after combined antiretroviral therapy in the modern combined antiretroviral therapy era. *Aids* **32**, 2605–2614. <https://doi.org/10.1097/qad.0000000000002010> (2018).
 27. Garcia, F. et al. Long-term CD4 + T-cell response to highly active antiretroviral therapy according to baseline CD4 + T-cell count. *J. Acquir. Immune Defic. Syndr.* **36**, 702–713. <https://doi.org/10.1097/00126334-200406010-00007> (2004).
 28. Carter, C. C. et al. HIV-1 infects multipotent progenitor cells causing cell death and establishing latent cellular reservoirs. *Nat. Med.* **16**, 446–451. <https://doi.org/10.1038/nm.2109> (2010).

29. Sauce, D. et al. HIV disease progression despite suppression of viral replication is associated with exhaustion of lymphopoiesis. *Blood* **117**, 5142–5151. <https://doi.org/10.1182/blood-2011-01-331306> (2011).
30. Kyeyune, R. et al. Prevalence and correlates of cytopenias in HIV-infected adults initiating highly active antiretroviral therapy in Uganda. *BMC Infect. Dis.* **14**, 496. <https://doi.org/10.1186/1471-2334-14-496> (2014).
31. Tate, D. L. et al. Comparison of two combined antiretroviral treatment regimens in the management of HIV in pregnancy: an observational study. *J. Matern Fetal Neonatal Med.* **34**, 3723–3729. <https://doi.org/10.1080/14767058.2019.1691987> (2021).
32. Martin, D. A. et al. Improved virologic outcomes over time for HIV-infected patients on antiretroviral therapy in a cohort from Rio de Janeiro, 1997–2011. *BMC Infect. Dis.* **14**, 322. <https://doi.org/10.1186/1471-2334-14-322> (2014).
33. Wijting, I. E. A. et al. Immune reconstitution inflammatory syndrome in HIV infected late presenters starting integrase inhibitor containing antiretroviral therapy. *EClinicalMedicine* **17**, 100210. <https://doi.org/10.1016/j.eclinm.2019.11.003> (2019).

Figures

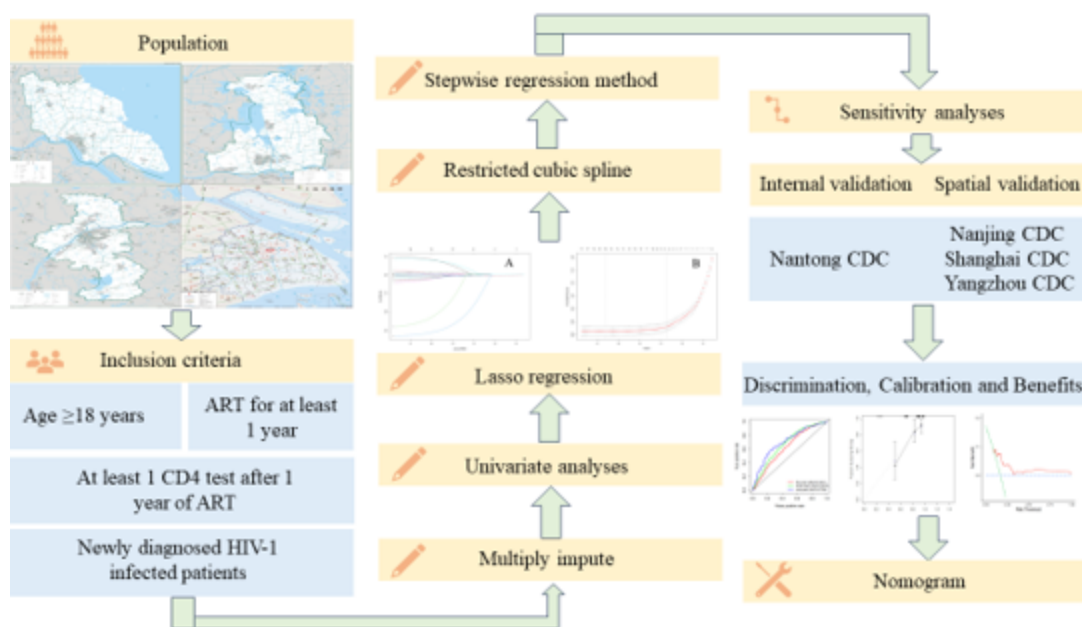


Figure 1

Flowchart of the study

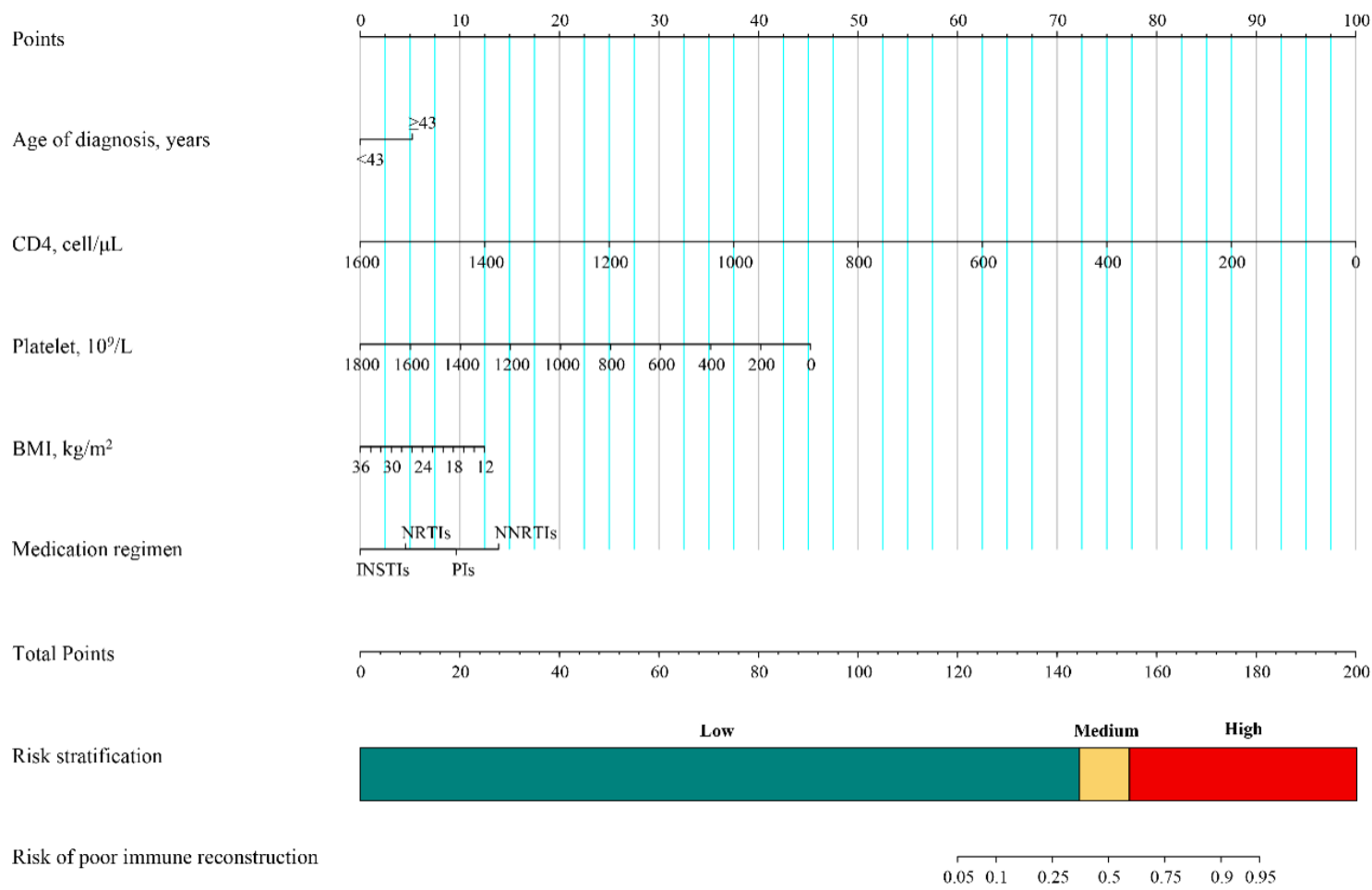


Figure 2

Static nomogram of predictive models regarding poor immune reconstitution

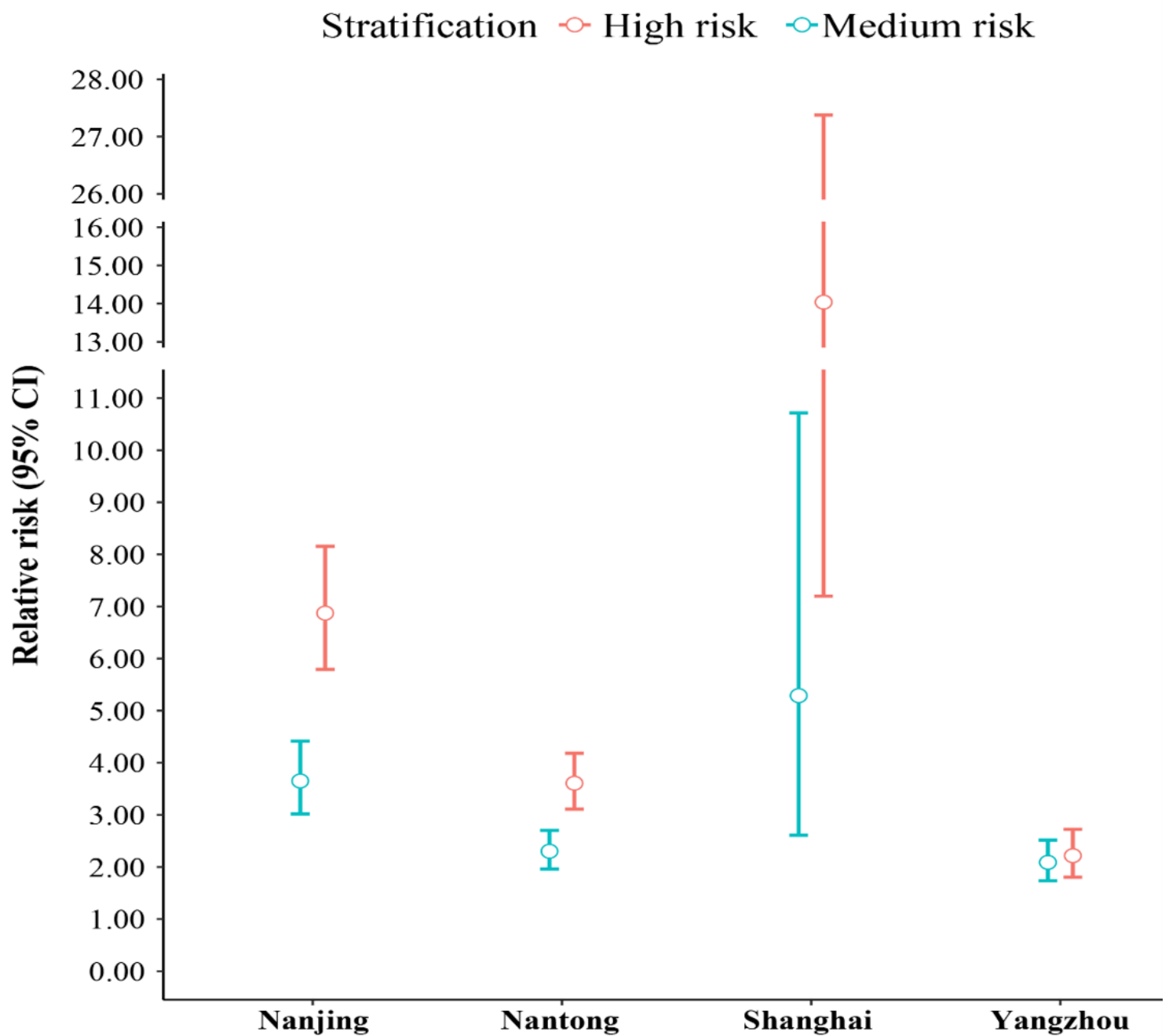


Figure 3

The association between risk stratification and risk of poor immune reconstitution in Nanjing, Nantong, Shanghai and Yangzhou

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplemntaryMaterial.docx](#)