The Lancet Regional Health - Western Pacific 16 (2021) 100269

Contents lists available at ScienceDirect

The Lancet Regional Health - Western Pacific

journal homepage: www.elsevier.com/locate/lanwpc

Research paper

Development and external validation of a prognostic model for survival of people living with HIV/AIDS initiating antiretroviral therapy

Junfeng Wang[1,2,#], Tanwei Yuan[3,#], Haibo Ding[6,#], Junjie Xu[6,#], Willem R Keusters[1], Xuemei Ling[5], Leiwen Fu[3], Qiyu Zhu[4], Quanmin Li[5], Xiaoping Tang[5], Weiping Cai[5], Hong Shang[7,8,9,10,***], Linghua Li[5,**], Huachun Zou[3,11,12,*]

[1] *Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[2] *Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*
[3] *School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, China*
[4] *National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China*
[5] *Eighth People's Hospital, Guangzhou Medical University, Guangzhou, China*
[6] *NHC Key Laboratory of AIDS Immunology, Department of Laboratory Medicine, First Affiliated Hospital of China Medical University, Shenyang, China*
[7] *Key Laboratory of AIDS Immunology of National Health Commission, Department of Laboratory Medicine, the First Affiliated Hospital of China Medical University, Shenyang, China*
[8] *National Clinical Research Center for Laboratory Medicine, the First Affiliated Hospital of China Medical University, Shenyang, China*
[9] *Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China*
[10] *Key Laboratory of AIDS Immunology, Chinese Academy of Medical Sciences, Shenyang, Liaoning, China*
[11] *Kirby Institute, the University of New South Wales, Sydney, Australia*
[12] *School of Public Health, Shanghai Jiao Tong University, Shanghai, PR China*

ARTICLE INFO

Article history:
Received 11 June 2021
Revised 18 August 2021
Accepted 19 August 2021
Available online 7 September 2021

Keywords:
people living with HIV/AIDS
survival, prognostic model, antiretroviral therapy

ABSTRACT

Background: Most existing prognostic models for people living with HIV/AIDS (PLWHA) were derived from cohorts in high-income settings established a decade ago and may not be applicable for contemporary patients, especially for patients in developing settings. The aim of this study was to develop and externally validate a prognostic model for survival in PLWHA initiating ART based on a large population-based cohort in China.

Methods: We obtained data for patients from the Chinese National Free Antiretroviral Treatment Program database. The derivation cohort consisted of PLWHA treated between February 2004 and December 2019 in a tertiary center in Guangzhou, South China, and validation cohort of patients treated between February 2004 to December 2018 in another tertiary hospital in Shenyang, Northeast China. We included ART-naive patients aged above 16 who initiated a combination ART regimen containing at least three drugs and had at least one follow-up record. We assessed 20 candidate predictors including patient characteristics, disease characteristics, and laboratory tests for an endpoint of death from all causes. The prognostic model was developed from a multivariable cox regression model with predictors selected using the least absolute shrinkage and selection operator (Lasso). To assess the model's predictive ability, we quantified the discriminative power using the concordance (C) statistic and calibration accuracy by comparing predicted survival probabilities with observed survival probabilities estimated with the Kaplan–Meier method.

Findings: The derivation cohort included 16481 patients with a median follow-up of 3·41 years, among whom 735 died. The external validation cohort comprised 5751 participants with a median follow-up of 2·71 years, of whom 185 died. The final model included 10 predictors: age, body mass index, route of HIV acquisition, coinfection with tuberculosis, coinfection with hepatitis C virus, haemoglobin, CD4 cell count,

* Corresponding author: Prof Huachun Zou, Address: Room 107, Unit 3, Building 3, Gezhi Garden, 132 Waihuandong Road, School of Public Health (Shenzhen), Sun Yat-sen University, Panyu District, Guangzhou, Guangdong, China, 511431, Tel: +86 20 8733 5651
** Corresponding author: Dr Linghua Li, Address: No.627 Dongfeng Dong Road, Guangzhou, Guangdong 510060, China, Tel: +86 20-83710825, +86 13725297174
*** Corresponding author: Prof Hong Shang, Address: Key Laboratory of AIDS Immunology of National Health Commission, Department of Laboratory Medicine, the First Affiliated Hospital of China Medical University, No. 155, Nanjing North Street, Heping District, Shenyang, 110001, Liaoning, China, Tel: +86 24 83282634
E-mail addresses: hongshang100@hotmail.com (H. Shang), llheliza@126.com (L. Li), zouhuachun@mail.sysu.edu.cn (H. Zou).
# The authors contributed equally to this work.

https://doi.org/10.1016/j.lanwpc.2021.100269

platelet count, aspartate transaminase, and plasma glucose. The C-statistic was 0·84 (95% confidence interval 0·82–0·85) in internal validation after adjustment of optimism and 0·84 (0·82–0·87) in external validation, which remained consistently above 0·75 in all landmark time points within five years of follow up when using time-updated laboratory measurements. The calibration accuracy was satisfactory in both derivation and validation cohorts.

Interpretation: We have developed and externally validated a model to predict long-term survival in PLWHA on ART. This model could be applied to individualized patient counseling and management during treatment, and future innovative trial design.

Funding: Natural Science Foundation of China Excellent Young Scientists Fund, Natural Science Foundation of China International/Regional Research Collaboration Project, Natural Science Foundation of China Young Scientist Fund, the National Science and Technology Major Project of China,National Special Research Program of China for Important Infectious Diseases, 13th Five-Year Key Special Project of Ministry of Science and Technology, and the Joint-innovation Program in Healthcare for Special Scientific Research Projects of Guangzhou.

Research in context

Evidence before this study

We searched PubMed for publications in English from database inception until May 18, 2020, using the search terms (“HIV” [MeSH Terms] OR “acquired immunodeficiency syndrome” [MeSH Terms]) AND (“mortality”[MeSH Terms] OR “survival”[MeSH Terms]) AND ("risk score"[Title/Abstract] OR "nomogram*"[Title/Abstract] OR "prediction model"[Title/Abstract] OR "prognostic model”[Title/Abstract]). References of relevant articles and reviews were also screened for additional publications. Twelve studies about prediction of survival in people living with HIV/AIDS (PLWHA) were identified, and only five of them have been externally validated. These models were largely derived in cohorts from high-income regions and might not be applicable to patients from developing areas where medical resources are relatively insufficient. Moreover, most of these models were based on cohorts established over ten years ago, when antiretroviral therapy (ART) was less widely accessible, life expectancy of PLWHA was significantly shorter, and mortality from AIDS-related illness were higher compared with the present.

Added value of this study

This study used two large independent contemporary cohorts of PLWHA in China to separately develop and validate, a prognostic model for survival of PLWHA initiating ART. This model was based on 10 clinical and laboratory predictors which are routinely collected and readily available. In external validation, the model showed good discriminative power and calibration accuracy, and the discriminative power remained satisfactory at different time points within five years of follow up when using time-updated laboratory predictors. We developed a free online calculator to make this model widely available and easily applicable in practical use. All parameters and equations of this model have been provided to allow further improvement of prediction.

Implications of all the available evidence

Our study identifies a range of independent predictors for long-term survival in PLWHA starting ART and provides a validated prognostic model. We encourage further external validation and improvement of our model in other patient cohorts. Our model could be implemented in clinical settings to facilitate individualized HIV counseling and management, and in innovative trial design by refining inclusion criteria, stratifying participants, and serving as a surrogate endpoint for deaths from all causes.

1. Introduction

The prognosis of people living with HIV/AIDS (PLWHA) has substantially improved thanks to the massive coverage of antiretroviral therapy (ART) on a global scale.[1,2] Nevertheless, HIV/AIDS remains a heavy disease burden worldwide.[3] Globally in 2019, 38 million people were living with HIV, and 690000 individuals died of HIV-related illness.[3] The increased life span of PLWHA also presents new challenges in caring for this increasingly expanding population: a growing body of evidence suggests that PLWHA tend to be at higher risk of chronic comorbidities compared with HIV-negative individuals,[4,5] contributing to a rise in non-AIDS related deaths.[6,7]

An ideal clinical prediction model could readily and reliably determine the prognosis of each PLWHA based on multiple individual patient characteristics.[8] It enables the planning of personalized treatment, disease management, and patient counselling, so as to improve treatment outcomes and optimize the use of medical resources.[8] In addition, the prognostic index (PI) for each patient derived from a prediction model could also be used to stratify the risk groups of patients for clinical trials,[8,9] and serve as a potential surrogate endpoint.

So far, thirteen prognostic models for PLWHA have been developed (appendix table1),[10-22] with age, sex, World Health Organization (WHO) clinical stage, body weight or body mass index (BMI), CD4 cell count, HIV viral load, and haemoglobin being commonly included as predictors. The majority of these models were developed based on datasets established a decade ago from well-resourced regions, including Europe,[13-15] North America,[11,12,14,15,19] and Australia.[18] These models might not be applicable to PLWHA in developing areas where the medical resources are inadequate and therefore the risk profile of patients could be disparate compared with that in high-income settings. Less attention has been paid to the development of prognostic models for PLWHA in developing regions, with only two models being developed for PLWHA in sub-Saharan Africa[10] and Haiti[21], respectively. A recent model based on PLWHA in Wenzhou city, China[20] was criticized for its high risk of bias in model development and poor model performance in external validation.[23]

The objective of this study was to develop and externally validate a prediction model for the long-term survival of PLWHA, based on two large population-based cohorts with more than ten years follow-up period in China.

2. Methods

2.1. Study design and participants

We conducted and reported this study in accordance with the guidance of Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Statement (TRIPOD),[8,24] and the completed checklist could be found in table2. For this prediction model development and validation study, we used data from the Chinese National HIV Free Antiretroviral Treatment Cohort, which has been described previously.[25] The national cohort was established and managed by each treatment site including designated HIV/AIDS treatment hospitals and Centers for Disease Control and Prevention. Measures were in place to control data quality, including real-time and time-elapsed data surveillance, routine quality reports, and nationwide on-site data validation.[25] The simplified ART cohort report recommended by WHO Patient Monitoring Guidelines for HIV Care and Antiretroviral therapy monitors cohort quality by tracking the proportion of patients who remain on treatment and their follow-up rates.[25] Each treatment site has access to data for its jurisdiction. For the derivation cohort, we included PLWHA treated in the Guangzhou Eighth People's Hospital, a tertiary referral center in Guangdong province, South China, between 10 February 2004 and 5 December 2019, and data were collected from 10 February 2004 up to 1 January 2020. For the external validation cohort, we included patients treated in the First Affiliated Hospital of China Medical University, a major tertiary hospital in Liaoning province, Northeast China, between 13 February 2004 to 13 December 2018, with patients being followed up to 28 December 2018.

Eligible patients were not previously exposed to ART, aged 16 years and over, initiated a combination ART regimen containing at least three drugs in the center, and had at least one follow-up record. The scheduled follow-up visits were 0·5, 1, 2, and 3 months after ART initiation and every 3 months thereafter. The outcome of interest for both derivation and validation cohort was all-cause deaths. This was determined by medical records for in-hospital patients. The death events of outpatients were determined by phone calls or physical visit to their households, or by checking the National Infectious Disease Surveillance System, which registered all available death cases of PLWHA in China. We chose candidate predictor variables based on their availability, reliability, and potential predictive ability judged by literature review and expert opinion (appendix p28). Variables with a missing value of above 50% were excluded from candidate predictors. We selected three demographic (age, sex, marital status), five clinical (route of HIV acquisition, WHO clinical staging of HIV disease, coinfection with tuberculosis, coinfection with hepatitis C virus [HCV], BMI), and 12 laboratory (CD4 cell counts, CD8 cell counts, white blood cell count, platelet count, haemoglobin, creatinine, triglyceride, total cholesterol, plasma glucose, aspartate transaminase, alanine aminotransferase, total bilirubin) candidate predictors. In both centers, healthcare providers collected patient-level data by standardized procedures and then completed standardized case report forms, which were uploaded to the central database.[25] Laboratory parameters were assessed in the central laboratory of centers by trained technicians blinded to standardized case report forms. Baseline information was collected within one week before ART initiation, and follow-up information was collected at scheduled follow-up visits.

This study was approved by the institutional review board of the Guangzhou Eighth People's Hospital and the First Affiliated Hospital of China Medical University.

2.2. Statistical analysis

We did not formally calculate sample size, but used event per variable to assess the data sufficiency.[8] All available data on the database of centers during the study period were used to maximize the statistical power and generalizability of the results. Patient characteristics were summarized as median and interquartile range for continuous variables, or as count and percentage for categorical variables. Survival was determined as time between ART initiation and death, or last follow-up visit, or end of the study data collection, whichever came first. All-cause deaths were presented by Kaplan-Meier curves. Median follow-up time was computed using the reverse Kaplan-Meier method.[8]

We used multiple imputation by chained equations to impute (10 times) missing values of baseline variables and laboratory parameters collected during follow up.[26,27] The number of iterations in each imputation was set at five. Variables used in the multiple imputation model included the 20 candidate predictors, auxiliary variables and the outcome (i.e., the Nelson-Aalen estimator of the baseline cumulative hazard, and the outcome indicator).[28,29] Since continuous laboratory parameters can only have positive values and were possibly skewed, they were all logarithmically transformed before being included in the multiple imputation model. The multiple imputation created 10 imputed datasets with identical known values but with differences in imputed values to account for the uncertainty associated with missing values. The 10 imputed datasets were analyzed in parallel, and results obtained from each dataset were combined with Rubin's rule.[30,31] This model was developed based on predictors collected at ART initiation. The distribution of candidate predictors before multiple imputation was compared with that after imputation.

The linear relationships between continuous predictors (e.g., age, CD4 cell counts) and the risk of death were examined by restricted cubic splines in univariate Cox models.[32] When strong non-linear effects were shown, additional variable transformation was performed until the relationship between the transformed variable and outcome was linear. Predictor selection was performed by fitting all the candidate predictors in a multivariable Cox regression model via the least absolute shrinkage and selection operator (Lasso). Lasso's penalty parameter 'lambda' was chosen as the largest value of lambda so that the mean cross-validated error was within one standard error of the minimum (the one standard error rule[33]). We selected those predictors that were consistently retained in all 10 models calculated from the ten imputed datasets. The clinical validity of selected predictors was approved by an expert panel consisting of clinicians, epidemiologists and statisticians (appendix p31). Additionally, in order to reduce model overfitting and any optimism in the final prediction model, we derived an adjustment factor from the bootstrap validation approach (100 resamples).[8] The final regression coefficient of each selected predictors was the original one multiplied by the adjustment factor.[8] We did not address interaction terms in this prediction model. Adherence to the proportional hazard assumption was assessed by inspecting the plot of the Schoenfeld residuals.

We assessed the model performance by examining measures of discrimination and calibration. Internal validation was performed by a bootstrap procedure (100 resamples) to account for optimism.[8] Discrimination (i.e., the ability of a model to differentiate between high-risk patients and low-risk patients) was calculated with Harrell's overall concordance (C) statistic, ranging from 0·5 (no predictive discrimination) to 1·0 (perfect discrimination).[34]

Additionally, we plotted cumulative/dynamic time-dependent receiver operating characteristic (ROC) curves at 2, 5, and 10 years after ART initiation to assess the discriminative power of the model in different time horizon.[35,36] Calibration refers to the agreement between the predicted and observed risk of deaths. To evaluate the calibration accuracy, we divided patients into three risk groups based on their PI calculated from the prediction model, with cut-off points at the 1st and 2nd tertiles in the derivation cohort, respectively.[37] We then compared the averaged predicted survival probability curves with the observed Kaplan-Meier survival probability curves in the three risk groups. We also assessed calibration with calibration plots in which patients were evenly divided into ten groups and the predicted survival probability (x-axis) was compared against the observed survival probability (y-axis) at 2, 5, and 10 years after ART initiation, respectively. A 45° diagonal line represents perfect calibration, while deviation below or above this line implies overestimation or underestimation ofsurvival.

We also estimated the calibration slope and cumulative baseline hazard (i.e., the calibration intercept in Cox models) in external validation to determine whether we need to recalibrate coefficients, baseline hazard, or both.[38]

In order to assess the dynamic discriminative power of the model, we performed a landmarking analysis by calculating C-statistics at 0·5, 1, 2, 3, 4, and 5 years after ART initiation using updated laboratory measurements with the last observation carried forward method. In addition, according to HIV treatment guidelines, HIV viral load, CD4 cell counts, and CD4/CD8 ratio are recommended as major indicators to assess a patient's treatment outcomes and prognosis;[39,40] to examine whether the discriminative power of the model is consistently superior to these commonly used individual prognostic factors, we also compared the C-statistic of the model with that of CD4 cell counts and that of CD4/CD8 ratio.

Statistical analyses were performed using R version 4.0.2, and packages MICE, rms, glmnet, riskRegression, timeROC, survival, survminer, and ggplot2. R code used for this study is provided in appendix p32 -75.

2.3. Role of the funding source

All funding parties did not have any role in the in study design, data collection, data analysis, interpretation, or writing of the report.

3. Results

The flow diagram of patient selection is shown in appendix figure 1, and patient characteristics are summarized in Table 1. The derivation cohort included 16481 eligible patients. A total of 735 patients in the derivation cohort died during 63648 person-years of follow-up (mortality 11·55 per 1000 person-years, 95% confidence interval [CI]: 10·73 -12·41), with a median follow-up of 3·41 years (IQR [interquartile range] 1·67 - 5·60). The event per variable in the model derivation was 37 (735/20), which indicated reasonable number of events compared to the number of candidate predictors.[37] The validation cohort comprised 5751 participants, of whom 185 died during 17336 person-years of follow-up (mortality 10·67, 9·19 - 12·32), and the median follow-up was 2·71 years (IQR 1·28 - 4·33). The cumulative mortality rate of patients included in the derivation cohort was slightly higher compared with that in the validation cohort (appendix figure 2). Correspondingly, compared with patients included in the validation cohort, a higher proportion of patients in the derivation cohort were clinically-advanced (WHO stage III/IV 95·2% vs 29·7%), and had a lower median CD4 cell count (208 vs 256 cells/μL) and CD8 cell count (786 vs 942 cells/μL) at ART initiation. We observed high percentages of missing values for HIV viral load in both cohorts, and this figure was relatively higher in derivation cohort (85·6%) than that in validation cohort (55·7%). The percentages of missing values remained high in both derivation cohort (above 80%) and validation cohort (above 40%) in recent years, and there was no temporal trend in the percentage of missingness (appendix figure3). All eligible patients were included for model development or validation after imputing missing values.

The distribution of all candidate variables after multiple imputation was comparable to that before imputation (appendix table3). The relationship between deaths and eight logarithmically-transformed continuous predictors (white blood cell count, platelet, creatinine, triglyceride, plasma glucose, alanine aminotransferase, total bilirubin, total cholesterol) followed a V-shaped pattern (appendix figure4). Therefore, values for these variables were further transformed by taking the absolute distance from the value that was at the turning point of the curve. For categorical predictors, dummy variables were created. Detailed coding of all candidate predictors can be found in appendix table4.

The final model included 10 predictors: age, BMI, route of HIV acquisition, coinfection with tuberculosis, coinfection with HCV, haemoglobin, CD4 cell count, platelet count, aspartate transaminase, and plasma glucose. Age, haemoglobin, coinfection with HCV, and CD4 cell count were the top four important predictors. Selection and importance rank of predictors can be found in appendix figure5. The adjustment factors for overfitting ranged from 0·98 to 0·99 in ten imputed datasets. Based on the coefficients and adjustment factors obtained from all imputed datasets, the final PI is structured as

PI= Infection route score + Tuberculosis score + HCV score + 0·053 *Age -0·070*BMI+ 0·238* log(Aspartate transaminase) - 0·662*log(Haemoglobin) - 0·200* log(CD4 cell count) + 0·778*abs (log(Plasma glucose)-1·66) + 0·340*abs(log(Platelet count)-5·27) in which:

- Infection route score: men who have sex with men = 0; injection drug use = 1·074; heterosexual transmission = 0·537; other = 0·929
- Tuberculosis score: negative = 0; positive = 0·455
- HCV score: negative = 0; positive = 0·611;
- Age is in years, Aspartate transaminase is in U/L, Haemoglobin is in g/L, CD4 cell count is in cells/μL, Total bilirubin is in μmol/L, Plasma glucose is in mmol/L, and Platelet is in 10^9/L
- "Abs" stands for absolute value, and "log" stands for natural logarithm

The distribution of the final PI in the derivation and validation cohort is shown in appendix figure6. Baseline survival probabilities of the derivation cohort are shown in appendix table 5, which can be used to calculate the survival probability for an individual patient at any year (up to 15 year) after ART initiation. An example of how to use this model to predict the survival probability of a patient is provided in appendix p29-30. This calculation can also be done by an online calculator (appendix figure7): https://jwang7.shinyapps.io/presurvhiv/

In internal validation, the apparent discriminative power (overall C-statistic) of the model was 0·85 (95%CI 0·83 - 0·86), and the value after adjustment of optimism (optimism=0.01, calculated with bootstrapping method) was 0·84 (0·82 - 0·85). In terms of calibration accuracy, the observed Kaplan-Meier survival curves of the three risk groups that we defined (appendix table 6) were all close to the mean predicted survival curves (Figure 1A). In addition, the Kaplan-Meier survival curves of the three risk groups were all separated, which further corroborated the high discriminative power of the model.

In external validation cohort, the C-statistic of the model remained high 0·84 (0·82 - 0·87). The calibration slope was 1·01

Table 1
Patient characteristics*

	Derivation cohort Total (n=16481)	Missing values,n (%)	Validation cohort Total (n=5751)	Missing values,n (%)
Age (years)	34·2 [27·1, 43·9]	0 (0·0)	32·0 [26·4, 43·5]	0 (0·0)
Sex				
Male	13462 (81·7)	0 (0·0)	5420 (94·2)	0 (0·0)
Female	3019 (18·3)		331 (5·8)	
Marital status				
Married	7807 (47·7)	105 (0·6)	1637 (28·5)	13 (0·2)
Unmarried	8569 (52·3)		4101 (71·5)	
HIV exposure group				
MSM	7213 (43·8)	0 (0·0)	4246 (73·8)	0 (0·0)
Heterosexual transmission	7327 (44·5)		779 (13·5)	
Injection drug use	1125 (6·8)		44 (0·8)	
Other	816 (4·9)		682 (11·9)	
Coinfection with hepatitis C virus				
Positive	887 (6·6)	2970 (18·0)	91 (1·7)	478 (8·3)
Negative	12624 (93·4)		5182 (98·3)	
Coinfection with tuberculosis				
Yes	1081 (6·6)	13 (0·1)	358 (6·2)	5 (0·1)
No	15387 (93·4)		5388 (93·8)	
WHO stage				
I	411 (2·5)	13 (0·1)	3339 (58·1)	5 (0·1)
II	391 (2·4)		697 (12·1)	
III	15276 (92·8)		641 (11·1)	
IV	390 (2·4)		1069 (18·6)	
ART initiation year‡				
2004-2007	519 (3·2)	0 (0·0)	25 (0·4)	0 (0·0)
2008-2011	2182 (13·2)		449 (7·8)	
2012-2015	5755 (34·9)		2458 (42·7)	
2016-2019	8025 (48·7)		2819 (49·0)	
Body mass index, kg/m^2†	20·8 [19·0, 22·9]	2565 (15·6)	21·8 [19·9, 24·1]	172 (3·0)
CD4 cell count, cells/μL	208·0 [71·0, 319·0]	156 (0·9)	257·0 [136·0, 370·0]	74 (1·3)
CD8 cell count, cells/μL	786·0 [520·0, 1121·0]	392 (2·4)	942·0 [635·0, 1316·0]	283 (4·9)
HIV viral load, copies/mL	65550·0 [17750·0, 221750·0]	14115 (85·6)	41200·0 [14900·0, 110000·0]	3201 (55·7)
White blood cell, 10^9/L	5·1 [4·0, 6·4]	208 (1·3)	5·1 [4·1, 6·2]	73 (1·3)
Platelet count, 10^9/L	200·0 [160·0, 242·0]	216 (1·3)	196·0 [164·0, 232·0]	76 (1·3)
Haemoglobin, g/L	137·0 [116·0, 150·0]	224 (1·4)	150·0 [136·0, 159·0]	82 (1·4)
Creatinine, μmol/L	74·0 [63·9, 84·0]	479 (2·9)	68·0 [60·0, 76·0]	185 (3·2)
Triglyceride, mmol/L	1·3 [0·9, 1·8]	2463 (14·9)	1·2 [0·9, 1·8]	484 (8·4)
Total cholesterol, mmol/L	4·0 [3·4, 4·6]	2468 (15·0)	4·0 [3·4, 4·5]	498 (8·7)
Plasma glucose, mmol/L	5·2 [4·7, 5·7]	1388 (8·4)	5·1 [4·8, 5·5]	412 (7·2)
Aspartate transaminase, U/L	23·0 [19·0, 32·0]	235 (1·4)	22·5 [18·4, 29·0]	228 (4·0)
Alanine aminotransferase, U/L	23·0 [16·0, 36·0]	219 (1·3)	22·0 [15·0, 34·0]	112 (1·9)
Total bilirubin, μmol/L	9·8 [7·2, 13·0]	336 (2·0)	11·6 [8·7, 15·1]	133 (2·3)
Median follow-up (years)	3·4 (1·7, 5·6)		2·7 (1·3, 4·3)	
Number of deaths	735		185	
Follow-up period (person-years)	63648		17336	
Mortality per 1000 person-years	11·6 (10·7, 12·4)		10·7 (9·2, 12·3)	

MSM=men who have sex with men. WHO=world health organization. ART=antiretroviral therapy
* Categorical variables are presented as n (%), and continuous variables are presented as median (interquartile range).
† Body mass index= body weight/height^2
‡ Cut-off values of years were determined by changes in Chinese national guidelines for the treatment of HIV/AIDS regarding the threshold of CD4+ cell counts for initiating ART. Prior to 2007, HIV-infected patients with a CD4+ count $\leq$ 200 cells per μL or those who had been diagnosed with an AIDS-defining illness were eligible for ART initiation. The treatment initiation threshold was raised to 350 cells per μL in 2008 and then to 500 cells per μL in 2012. Since 2016 all PLWHA have been eligible for ART regardless of CD4+ count.

(0·90-1·12). The external calibration accuracy of the model of baseline survival was desirable. The observed Kaplan-Meier survival curves of the three risk groups created based on the same thresholds as used in the derivation cohort were close to the mean predicted survival curves (Figure 1B). In addition, the calibration plots also indicate good agreement between predicted and observed survival probability at 2, 5, and 10 year after ART initiation (appendix figure8). According to the time-dependent ROC curves (appendix figure9), our model demonstrated consistently high discriminative power with large area under the curve (78 - 86) at 2, 5, and 10 years after ART initiation in both derivation and validation cohorts.

The C-statistics of the model based on data at 0·5, 1, 2, 3, 4, and 5 years of follow-up were mostly above 0·75, consistently higher than that of CD4 cell counts or that of CD4/CD8 ratio (Figure 2).

4. Discussion

This study develops a model for prediction of survival in PLWHA on the basis of a large population-based HIV cohort from China. External validation of the model in an independent cohort showed its good discrimination and calibration. The model incorporates 10 items: age, BMI, route of HIV acquisition, coinfection with tuberculosis, coinfection with HCV, haemoglobin, CD4 cell count, platelet count, aspartate transaminase, and plasma glucose. Essential parameters that were objectively measured, readily available and routinely monitored, as recommended by current HIV treatment and management guidelines, were included in our model.[41,42]

The majority of predictors included in our model have also been included in existing models (appendix table1). Compared with

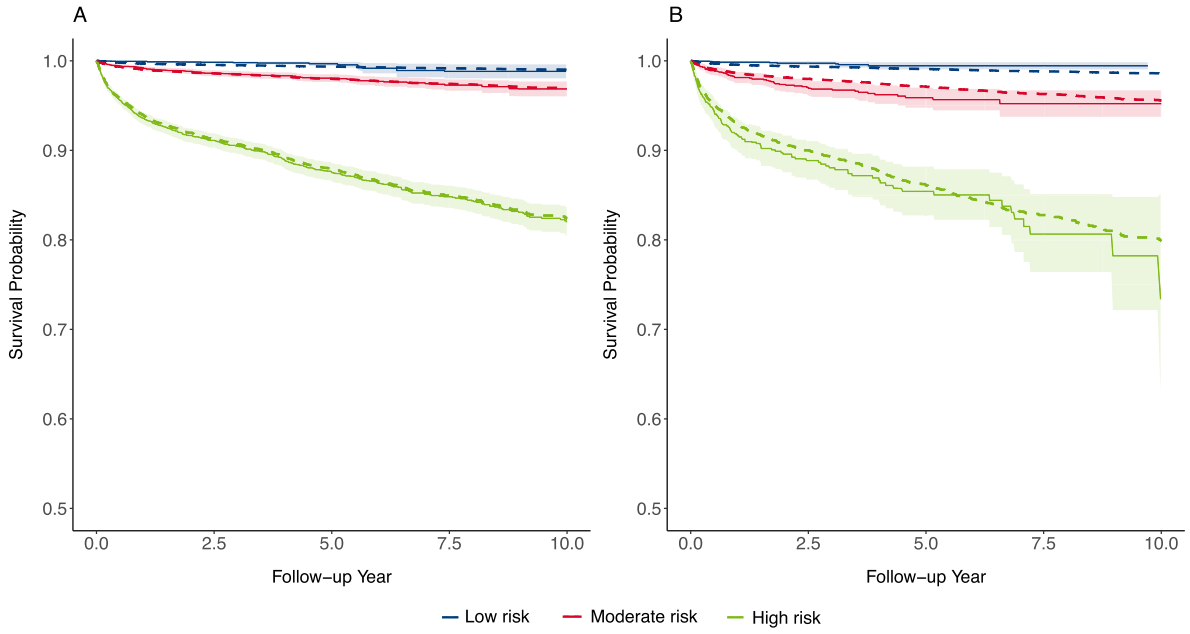

Figure 1. Predicted versus observed survival probability per risk group in derivation cohort (A) and external validation cohort (B). Solid line: Observed Kaplan-Meier Curve; Dashed line: Mean predicted survival curves; Shaded areas: 95% confidence interval of observed survival probability.

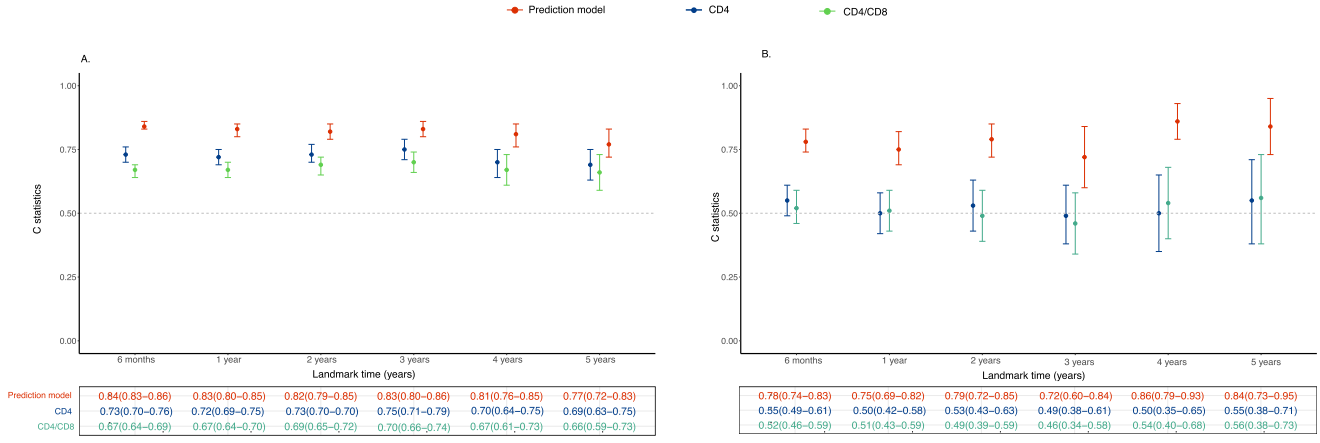

Figure 2. Comparison of the C-statistics between prediction model, CD4 cell count, and CD4/CD8 ratio at different landmark time. (A) Derivation cohort (B) Validation cohort.

previously developed models, our model includes a comparatively larger set of variables that are not traditional HIV-related factors. This may be because the endpoint used in the present study was all-cause deaths, instead of HIV-related death or the composite endpoint of progression to AIDS or death used in nearly half (6/13, 46%) of the existing models. Another factor that may contribute to this difference is that we used relatively new patient cohorts with follow-up period from 2004 to 2019, during which there has been a global trend of a rise in non-AIDS-related deaths in PLWHA on ART.[6,7] Therefore, it is justifiable and important to include coinfections and biochemistry parameters that reflect chronic co-morbidities in our model, since these comorbidities increasingly account for non-AIDS-related deaths in PLWHA. For example, the predictor of plasma glucose is a marker for diabetes, and results from a multinational cohort study suggested that diabetes and prediabetes were associated with mortality in PLWHA.[43]

Previous systematic reviews and meta-analyses found a significantly increased risk of all-cause mortality among HIV-infected men compared with women,[44-46] and similar results have been reported from studies conducted in China.[47,48] Nevertheless, sex was not identified as a predictor in this study. This might be explained by the fact that route of HIV acquisition differentiating MSM, heterosexual individuals, and injection drug users, is more sensitive in predicting mortality than sex. In fact, different patterns of HIV acquisition between men and women could account for the sex difference in mortality. For example, many studies reported a higher proportion of men than women infected with HIV via injection drug use,[49,50] a behavior that has been associated with higher mortality in PLWHA.[51,52] Our model is also in line with our recent finding that HIV-infected MSM had better survival compared with heterosexual individuals, probably because of early diagnosis as a result of active HIV testing at earlier stages and good adherence to HIV treatment and management.[53] For practical reasons of computing a prediction model, we did not further divide men and women under the groups of heterosexual individuals and injection drug users. Nevertheless, in our sensitivity analysis, the model performance remained satisfactory in both male and female groups (appendix figure9-10).

This study has several strengths. First, this model was developed based on a large patient cohort, predicted a longer survival interval up to 15 years, validated model performance in an independent dataset, and carefully followed established recommendations (TRIPOD) for model development and validation.[8] The recent updated VACS Index (VACS 2.0) from the US also included many of the same clinical biomarkers of general health to estimate all-cause mortality in PLWHA.[22] This model has been validated in large diverse samples in North America and Europe, but has not been validated in resource limited settings. Thus, there a necessity of a model developed based on local settings, rather than having a one-size-fits-all global model. Based on a large sample, by using Lasso for predictor selection and incorporating optimism adjustment, our model minimized statistical overfitting, a common methodological problem in prediction model development studies.[8] The endpoint of all-cause deaths is particularly relevant given the rise of non-AIDS-defining deaths in this population.[6,7] Moreover, our sensitivity analyses showed that our model still had very good model performance in subgroups by gender, patients who initiated ART under the latest treatment guideline, and elderly patients aged above 50 (appendix figure9-12), which could ensure that the model will perform well in future use. Lastly, our model performance was externally validated, which ensures its potential generalizability.

Our study has several limitations. First, as an inherent drawback of retrospective data collection, data on some predictors in our model were missing for many patients. In order to avoid selection bias and increase model applicability, we used multiple imputation to impute missing data so as to include all eligible patients.[8,54] For the same patient, we also included their biochemical parameters collected during follow-up, thereby further improving the validity of the results.[54] However, these missing predictors might not limit the prospective use of the model in clinical practice, since they are all readily available and easy to access. If clinicians encountered the situation where one or several required predictors are missing for a single patient, it would not be difficult to ask for more information at a patient visit. Second, we did not include HIV viral load as a candidate predictor in our model due to its high percentage of missing values. This is largely caused by limited medical resources coupled with prohibitive costs of HIV viral load testing. We found that the percentages of missing values remained high in both derivation cohort and validation cohort in recent years, so HIV viral load is less likely to be available in most patients in the near future. Moreover, we performed a range of sensitivity analyses (appendix table 7 and 8) to ensure that not selecting HIV viral load tend not to significantly reduce the model performance a lot. Many ART programs in resource-limited areas such as sub-Saharan Africa also do not have the resources to routinely monitor HIV viral load in all patients.[10] Exclusion of HIV viral load could be partly compensated by the inclusion of CD4 cell count, which is recommended by the WHO to diagnose treatment failure among PLWHA in resource-limited settings.[55] The incremental predictive value of HIV viral load needs to be investigated in future studies for further improvement of the current model. Third, we analyzed mortality from all-causes rather than HIV-related deaths because of a lack of reliable information on causes of deaths, though the endpoint of all-cause deaths might be more pertinent given the growing role of non-AIDS-related deaths.[6,7] Fourth, in spite of various methods in place to control data quality, it is still challenging to have unbiased and reasonably complete mortality ascertainment in resource-limited settings. Potential incomplete mortality ascertainment in our model derivation cohort might hinder our model from performing well on future patients. Fifth, the predictive accuracy of a model hinges on the accurate information of predictors. Although the majority of predictors included in our model could be objectively measured, route of HIV acquisition is reported by patients, which might be subject to self-reporting bias. Sixth, our model is somewhat complex, given that a total of 10 predictors were included in the final model and data transformations were applied to several of them. Nevertheless, we tried to find a balance between the model's simplicity and methodological soundness. Therefore, only the most important predictors were selected and and data transformation was only applied when necessary. In order to reduce the difficulty incurred by model complexity in clinical application, we developed a user-friendly online calculator which only requires the input of a few of parameters, and all data transformations and calculations were build-in in the system. Additionally, although laboratory parameters included in the model generally change with the course of disease, as with previous models, our model is only based on data collected at time of ART initiation, rather than incorporating measurements collected during follow-up. Nevertheless, we assessed the dynamic discriminative power of the model, and our model demonstrated consistently satisfactory discriminative power (C-statistics $>0{\cdot}75$) compared with CD4 cell count or CD4/CD8 ratio alone when using updated laboratory parameters at a follow-up of 0·5, 1, 2, 3, 4, and 5 years. This suggests that the model might have the potential for dynamic prediction of survival for PLWHA on ART. Lastly, the generalizability of the model requires further verification given that it is based on cohorts from a single hospital in an upper-middle-income country, though the Guangzhou Eighth People's Hospital is one of the largest designated hospitals for HIV/AIDS treatment in China and delivers HIV treatment for over one third of PLHIV in the Guangdong province. In our study, we have provided all parameters and equations of our model to allow further recalibration or revision of the current model. This should also facilitate more validations of the model in external cohorts from different settings, and different independent research groups.

Our prognostic model has several practical applications. Healthcare providers can use our model in a freely available online tool to calculate estimates of survival for individual PLWHA, either at ART initiation or during follow-up. This could help healthcare providers identify patients at high risk of death in a timely and straightforward manner, and determine the intensity of care and adopt personalized care.[8] Additionally, the model might upgrade innovative trial design in three ways. First, the predicted survival could be used as an inclusion criterion.[56] Targeted inclusion of patients at high risk of deaths can be cost-effective as the required sample size can be reduced.[56] Second, the model could be used to stratify participants according to their PIs. Compared with using a limited set of prognostic variables for stratification, this approach could create more homogeneous strata, leading to a greater statistical power to detect an effect.[9] Third, the PI for each patient calculated by our model could also serve as a surrogate endpoint for all-cause deaths, thereby reducing required follow-up time and financial budget.

In conclusion, we have developed and externally validated a model consisting of 10 clinical and biochemical variables for accurate prediction of long-term survival probabilities of PLWHA on ART. The prediction model has the potential to facilitate tailored HIV disease management, which might help improve the life expectancy and quality of life of PLWHA patients in the era of highly active antiretroviral therapy and precision medicine.

Contributors

JW and HZ designed the study. JW and TY performed statistical analysis, made the tables and figures, and wrote the manuscript. HD and JX contribute significantly to data collection and data analysis. WK contributed to the shiny app. HD, JX, LL, XL, QL, XT and WC provided data and clinical input. JW, HZ, LL, and HS supervised the study. All authors critically reviewed and agreed on the manuscript.

Acknowledgment

This study was supported by the Natural Science Foundation of China Excellent Young Scientists Fund [grant ID: 82022064], Natural Science Foundation of China International/Regional Research Collaboration Project [grant ID: 72061137001], Natural Science Foundation of China Young Scientist Fund [grant ID: 81703278], the National Science and Technology Major Project of China [grant ID: 2018ZX10721102], the National Special Research Program of China for Important Infectious Diseases (grant ID: 2018ZX10302103-002), the 13th Five-Year Key Special Project of Ministry of Science and Technology (grant ID: 2018ZX10715004), and the Joint-innovation Program in Healthcare for Special Scientific Research Projects of Guangzhou (grant ID: 201803040002). All funding parties did not have any role in the design of the study or in the explanation of the data.

Data sharing policy

The dataset used for the current study is not publicly available due to restrictions from the China Center for Disease Control and Prevention.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100269.

References

[1] Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr Opin HIV AIDS 2016;11(5):492–500.
[2] Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV 2017;4(8):e349–ee56.
[3] Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020(20):30750–9 **S0140-6736**.
[4] Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis 2011;53(11):1120–6.
[5] Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis 2011;53(11):1130–9.
[6] Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43(1):27–34.
[7] Grinsztejn B, Luz PM, Pacheco AG, et al. Changing mortality profile among HIV-infected patients in Rio de Janeiro, Brazil: shifting from AIDS to non-AIDS related conditions in the HAART era. PLoS One 2013;8(4):e59768.
[8] Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162(1):W1–73.
[9] Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 2006;6:18.
[10] May M, Boulle A, Phiri S, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet 2010;376(9739):449–57.
[11] Blatt SP, McCarthy WF, Bucko-Krasnicka B, et al. Multivariate models for predicting progression to AIDS and survival in human immunodeficiency virus-infected persons. J Infect Dis 1995;171(4):837–44.
[12] Roussanov BV, Taylor JM, Giorgi JV. Calculation and use of an HIV-1 disease progression score. AIDS 2000;14(17):2715–22.
[13] Lundgren JD, Mocroft A, Gatell JM, et al. A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. J Infect Dis 2002;185(2):178–87.
[14] Egger M, May M, Chêne G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002;360(9327):119–29.
[15] May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. AIDS 2007;21(9):1185–97.
[16] Zhou J, Kumarasamy N. Predicting short-term disease progression among HIV-infected patients in Asia and the Pacific region: preliminary results from the TREAT Asia HIV Observational Database (TAHOD). HIV Med 2005;6(3):216–23.
[17] Mocroft A, Ledergerber B, Zilmer K, et al. Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk-score. AIDS 2007;21(14):1867–75.
[18] Nakhaee F, Law M. Parametric modelling of survival following HIV and AIDS in the era of highly active antiretroviral therapy: data from Australia. East Mediterr Health J 2011;17(3):231–7.
[19] Tate JP, Justice AC, Hughes MD, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS 2013;27(4):563–72.
[20] Hou X, Wang D, Zuo J, 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 2019;48:414–24.
[21] McNairy ML, Jannat-Khah D, Pape JW, et al. Predicting death and lost to follow-up among adults initiating antiretroviral therapy in resource-limited settings: Derivation and external validation of a risk score in Haiti. PLoS One 2018;13(8):e0201945.
[22] Tate JP, Sterne JAC, Justice AC. Albumin, white blood cell count, and body mass index improve discrimination of mortality in HIV-positive individuals. AIDS 2019;33(5):903–12.
[23] Wang J, Yuan T, Ling X, et al. Critical appraisal and external validation of a prognostic model for survival of people living with HIV/AIDS who underwent antiretroviral therapy. Diagnostic and Prognostic Research 2020;4(1):19.
[24] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ (Clinical research ed) 2015;350:g7594.
[25] Ma Y, Zhang F, Zhao Y, et al. Cohort profile: the Chinese national free antiretroviral treatment cohort. International journal of epidemiology 2010;39(4):973–9.
[26] Buuren Stef van. Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw 2011;45(3):1–68.
[27] Murad H, Dankner R, Berlin A, Olmer L, Freedman LS. Imputing missing time-dependent covariate values for the discrete time Cox model. Statistical methods in medical research 2020;29(8):2074–86.
[28] Moons KG, Donders RA, Stijnen T, Harrell FE Jr. Using the outcome for imputation of missing predictor values was preferred. Journal of clinical epidemiology 2006;59(10):1092–101.
[29] White IR, Royston P. Imputing missing covariate values for the Cox model. Statistics in medicine 2009;28(15):1982–98.
[30] D R. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
[31] Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.
[32] Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Springer; 2015.
[33] Hastie T, R Tibshirani, Friedman J. The Elements of Statistical Learning. 2nd ed. Springer; 2009.
[34] Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Statistics in medicine 1996;15(4):361–87.
[35] Bansal A, Heagerty PJ. A comparison of landmark methods and time-dependent ROC methods to evaluate the time-varying performance of prognostic markers for survival outcomes. Diagn Progn Res 2019;3:14.
[36] Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. Biometrics 2005;61(1):92–105.
[37] Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. BMC Med Res Methodol 2013;13:33.
[38] Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW. Calibration: the Achilles heel of predictive analytics. BMC medicine 2019;17(1):230.
[39] Chinese Center for Disease Control and Prevention China free antiretroviral therapy manual. 4th edition; 2016 http://www.sxcdc.com/uploadfiles/files/2017071711372183.pdf (accessed November 26 2020).
[40] European AIDS Clinical society guidelines Version 10.1; 2020. https://www.eacsociety.org/files/guidelines-10.1.finalsept2020.pdf. (accessed November 26 2020).
[41] Chinese Center for Disease Control and Prevention China Free Antiretroviral Therapy Manual; 2016. 2016 edn. http://www.sxcdc.com/uploadfiles/files/2017071711372183.pdf (accessed December 25, 2020).
[42] Chinese Center for Disease Control and Prevention Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services; 2020. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. (accessed December 25.
[43] Bijker R, Kumarasamy N, Kiertiburanakul S, et al. Diabetes, mortality and glucose monitoring rates in the TREAT Asia HIV Observational Database Low Intensity Transfer (TAHOD-LITE) study. HIV Med 2019;20(9):615–23.
[44] Castilho JL, Melekhin VV, Sterling TR. Sex differences in HIV outcomes in the highly active antiretroviral therapy era: a systematic review. AIDS Res Hum Retroviruses 2014(30):446–56.
[45] Beckham SW, Beyrer C, Luckow P, Doherty M, Negussie EK, Baral SD. Marked sex differences in all-cause mortality on antiretroviral therapy in low- and middle-income countries: a systematic review and meta-analysis. J Int AIDS Soc 2016;19(1):21106.
[46] Abioye AI, Soipe AI, Salako AA, et al. Are there differences in disease progression and mortality among male and female HIV patients on antiretroviral therapy? A meta-analysis of observational cohorts. AIDS Care 2015;27(12):1468–86.

[47] Dou Z, Xu J, Jiao JH, et al. Gender difference in 2-year mortality and immunological response to ART in an HIV-infected Chinese population, 2006-2008. PLoS One 2011;6(8):e22707.
[48] Chen M, Dou Z, Wang L, et al. Gender Differences in Outcomes of Antiretroviral Treatment Among HIV-Infected Patients in China: A Retrospective Cohort Study, 2010-2015. J Acquir Immune Defic Syndr 2017;76(3):281–8.
[49] Collazos J, Asensi V, Carton JA. Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART. AIDS 2007;21(7):835–43.
[50] Nicastri E, Angeletti C, Palmisano L, et al. Gender differences in clinical progression of HIV-1-infected individuals during long-term highly active antiretroviral therapy. AIDS 2005;19(6):577–83.
[51] Perez-Hoyos S, del Amo J, Muga R, et al. Effectiveness of highly active antiretroviral therapy in Spanish cohorts of HIV seroconverters: differences by transmission category. AIDS 2003;17(3):353–9.
[52] Zhang G, Gong Y, Wang Q, et al. Outcomes and factors associated with survival of patients with HIV/AIDS initiating antiretroviral treatment in Liangshan Prefecture, southwest of China: A retrospective cohort study from 2005 to 2013. Medicine (Baltimore) 2016;95(27):e3969.
[53] Li L, Yuan T, Wang J, et al. Sex differences in HIV treatment outcomes and adherence by exposure groups among adults in Guangdong, China: A retrospective observational cohort study. EClinicalMedicine 2020;22:100351.
[54] Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.
[55] World Health Organization. What's new in treatment monitoring: Viral load and CD4 cell testing, updated July 2017. https://apps.who.int/iris/bitstream/handle/10665/255891/WHO-HIV-2017.22-eng.pdf;jsessionid=132F516827ECBBFCDA4BBCD51F961404?sequence=1 (accessed December 26 2020).
[56] Galovic M, Döhler N, Erdélyi-Canavese B, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. The Lancet Neurology 2018;17(2):143–52.