A prognostic model to Assess Long-Term Survival of Patients on Antiretroviral Therapy: a 15-Year Retrospective Cohort Study in Southwestern China

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Summary

A prognostic model composed of fourteen variables is an effective tool for early assessing the prognosis of patients in antiretroviral therapy. A nomogram for the prognostic model could be printed on paper and it is especially suitable for physicians in rural southwestern China.
Abstract

Background: Due to no assessment tool for survival of HIV patients receiving antiretroviral therapy in rural southwestern China, we aimed to formulate and validate a simple-to-use model to predict long-term overall survival at the initiation of antiretroviral therapy (ART).

Methods: In total, 36268 eligible participants registered in Guangxi autonomous region between December 2003 and December 2018 were enrolled and randomized into development and validation cohorts. Predictive variables were determined based on Cox hazard models and specialists’ advice. Discrimination, calibration, and clinical utility were measured, respectively.

Results: The prognostic combined fourteen variables: sex, age, marital status, infectious route, opportunistic infection, AIDS-related symptoms, body mass index, CD$_4^+$ T-lymphocyte count, white blood cell, platelet, hemoglobin, serum creatinine, aspartate transaminase, and total bilirubin. Age, aspartate transaminase, and serum creatinine were assigned higher risk scores than that of CD$_4^+$ T-lymphocytopenia count and having opportunistic infections or AIDS-related symptoms. At three time points (1-, 3-, and 5-year), the area under the curve ranged from 0.75 to 0.81 and the Brier scores ranged from 0.03 to 0.07. The decision curve analysis curves showed an acceptable clinical net benefit.

Conclusions: The prognostic model incorporating routine baseline data can provide a useful tool for early risk appraisal and treatment management in ART in rural southwestern China. Moreover, our study underscores the role of non-AIDS-defining events in long-term survival in ART.

Keywords: prognostic model; HIV; antiretroviral therapy; survival
Introduction

Although the rapid scale-up of antiretroviral therapy (ART) has successfully reduced AIDS-related death, all-cause mortality in people with HIV (PWH) remains higher than that in the general population, which cannot be ignored [2-4]. Even in a resource-rich setting, currently available medications may not be sufficient for lifelong ART[5]. Therefore, prompt recognition of patients at high risk of poor survival can contribute to appropriately tailor care and burden reduction.

Some baseline characteristics, including demographic factors, clinical features, and laboratory parameters, can be used as independent predictive variables of adverse events[6-10], however, it is more convenient for physicians to use a simple-to-use prognostic model consisting of robust variables to comprehensively assess the risk of long-term mortality than to use a single variable. The performances of the existing prognostic models vary widely due to the differences in the HIV epidemic, status of care, and resource setting[11-13]. Briefly, the prognostic models developed in resource-limited settings mainly focused on short-term mortality and the contributions of AIDS-defining events to death. Whereas, the models developed in resource-rich settings primarily focused on long-term mortality and the risk factors of non-communicable diseases. In China, a prognostic model consisting of hemoglobin, viral load, and CD4 showed excellent internal validation in Wenzhou City[14], but poor external validation in Guangzhou City[15]. Therefore, we hypothesized that a new prognostic model developed based on the HIV epidemic, resource setting, and a large local cohort of antiretroviral therapy could present a higher accuracy and a more clinical benefit in southwestern China than those existing models.

According to the National HIV/AIDS epidemic estimation, there were 1.25 (95% CI 1.10–1.40) million PWH in China, as of 31 December 2018[16]. The distribution of PWH
varies significantly from region to region and the largest proportion of PWH was in Southwestern China. Yunnan and Sichuan had more than 100 thousand PWH each, followed by Guangxi, Guangdong, and Hennan with more than 50 thousand PWH each, in the same year[17]. China’s National Free Antiretroviral Therapy Program (NFATP) began in 2002. By the end of 2018, a total of 718499 registered patients were receiving ART in all 31 provinces, autonomous regions, and municipalities in mainland China[20]. Although overall mortality has dropped from 39.3/100 person-years in 2002 to 3.1/100 person-years in 2014, the mortality in southwestern regions is still higher than that in central and eastern regions[21]. Additionally, China Free Antiretroviral Therapy Manual recommends the standard regimen, the schedule of follow-up, and the frequency of testing, but the resource-rich areas have used several individual therapeutic planning, such as out-of-pocket medicine, pretreatment viral load, and pretreatment HIV drug resistance assay[22].

So far as we know, few studies have provided an applicable tool for physicians to calculate the risk scores of poor survival for individuals in the underdeveloped southwestern region in China. In this study, we aimed to construct and validate a prognostic model to predict long-term survival among PWH on ART in Guangxi, using longitudinal data from the National Free Antiretroviral Therapy (NFART) database.

Methods

Data source and study design

The database used in this study was downloaded from antiretroviral treatment for the adult information collection system, one of eight subsystems integrated into China’s HIV/AIDS Comprehensive Response Information Management System (CRIMS) [25]. The original database was comprised of electronic medical records of 91006 adolescents and adults registered in 109 designated clinical sites in 14 cities between December 2003 and
December 2018. Every patient would receive an ART regimen at the initial visit. Follow-up visits are scheduled at 2 weeks, 1, 2, 3 months, and then every 3 months thereafter. Based on this database, we performed a multicenter, retrospective cohort study. To make our prognostic model comparable with existing ones, we developed the following inclusion criteria and exclusion criteria referring to the previous studies\cite{11, 12, 14}. The inclusion criteria were: 1. age $\geq$ 15 years at treatment initiation, 2. previously naive to ART, 3. having at least one follow-up record including terminal outcomes. The exclusion criteria were: 1. pregnant women, 2. with missing baseline records. In total, 36268 participants were selected and randomized into a development cohort (n=25388) and a validation cohort (n=10880), at a ratio of 7:3 (Figure S1 in the supplementary materials described the participants’ selection process).

The development and validation procedures of the prognostic model were reported in concordance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement\cite{26}.

**Patient Consent Statement**

This study was approved by the Ethics Review Board of Guangxi Center for Disease Control and Prevention (Certificate No.: GXIRB2016-0047-1). Each patient signed an informed consent at the time of initiation of ART, allowing the use of the clinical records in future epidemiological studies. No additional informed consent was sought and all clinical records were de-identified before analysis. We signed a confidentiality agreement and were authorized to use the database for this study.
Variables and outcome

Baseline clinical characteristics previously reported to be associated with the overall survival of PWH were selected as candidate variables. The linearity assumption between continuous variables (e.g., age and laboratory results) and log relative hazard for overall survival were graphically examined using restricted cubic splines (RCS) regression\[27-29]. Since all continuous variables showed potential nonlinear effects, we converted them into categorical variables according to the China Free antiretroviral therapy Manual\[30\] and the physicians’ recommendations. For the categorical variables, plots of the Schoenfeld residuals were used to evaluate the proportional hazard (PH) assumption and to ensure that all variables fit the PH assumption. Continuous variable transformations were performed for age (<30, 30–39, 40–49, 50–59, 60–69 and ≥70 years), body mass index (BMI; <18.5, 18.5–23.9, 24–27.9 and ≥28 kg/m²), CD₄⁺ T lymphocytopenia count (CD4; <100, 100–199, 200–349 and ≥350 cells/μL), CD₈⁺ T lymphocytopenia count (CD8; <220, 220–1129 and ≥1130 cells/μL), White blood cell (WBC; <3.5, 3.5–9.5 and >9.5 ×10⁹/L), platelet count (PLT; <125, 125–350 and >350 ×10⁹/L), hemoglobin values (HB; <80, 80–109, 110–119 and ≥120 g/L), serum creatinine (Cr; <133, 133–177 and >177 μmol/L), aspartate transaminase (AST; <40, 40–99, 100–199, ≥200 U/L), alanine aminotransferase (ALT; <40, 40–99, 100–199 and ≥200 U/L), total cholesterol (TC; <5.0, 5.0–6.9 and ≥7.0 mmol/L), total bilirubin (TBIL; <34.0, 34.0–51.0 and >51.0 μmol/L), triglyceride (TG; <1.80, 1.80–2.83, 2.84–5.60 and >5.60 mmol/L) and fasting plasma glucose (FPG; <7.0 and ≥7.0 mmol/L). The outcome was defined as death from any cause after ART initiation, the date of death was obtained from the latest follow-up record. Survival time was measured from ART initiation to death or the last follow-up, patients were censored at the date of loss to follow-up, or study end (31 December 2018).
Prognostic model construction

The development cohort was used to construct the prognostic model in sequential steps. First, univariate Cox proportional hazard regression models (Cox model) were performed to identify those variables that achieved statistical significance at p-value < 0.1. Second, variables with statistical significance and clinical importance were entered into multivariate analyses. Finally, a multivariate Cox model containing optimal factors was established using backward stepwise processes with the Akaike information criterion (AIC) as the stopping rule. Interaction terms in the multivariate model were detected. None of the interaction terms were significant, and therefore none were addressed in our final model. To ensure adequate statistical power, we set 20 deaths per variable or more in the development and validation of the final multivariate model.

A nomogram was plotted as the graphical representation of the best fitting model. Risk scores of variable axes and survival probability at 1-, 3-, and 5-year were calculated by weighted regression coefficients and the baseline survival function[31].

Validation of the performance and clinical utility

A practical prognostic model should be characterized by accepted discrimination and calibration[32]. In this study, discrimination referred to the ability to separate participants who were alive from those who were dead at the observational time points after ART initiation. Discrimination was graphically presented by the receiver operating characteristic (ROC) curve and quantitatively measured by AUC. AUC ranges from 0 to 1, where 0.5 would indicate no discrimination, 0.7 to 0.9 would imply good discrimination and >0.9 would imply excellent discrimination[33]. Calibration indicated the agreement between the actual survival and the prediction at the observational time points. Calibration was visualized using
a bootstrapped calibration curve and quantified by the Brier score. Brier score ranges from 0 to 0.25, where smaller values indicate better calibration.

To assess the clinical utility of the model, we plotted decision curve analyses (DCA) curves to display the net benefit across a range of threshold probabilities[34].

**Statistical methods**

Statistical analyses were performed with R software (version 3.6.3, [https://www.r-project.org](https://www.r-project.org)). The ‘survival’ package was used to construct Cox models and calculate the baseline survival function. The ‘rms’ and ‘timeROC’ were used to plot the nomogram, ROC curves, and calibration curves. The ‘riskRegression’ package was used to calculate the AUC and the Brier score. The ‘stdca’ function (downloaded from [http://www.mskcc.org](http://www.mskcc.org)) was used to draw DCA curves. All statistical tests were two-sided and p<0.05 was considered statistically significant.

**Results**

**Baseline characteristics**

The baseline demographic, clinical features, and laboratory results of patients from the development cohort (n=25388) and validation cohort (n=10880) were summarized in Table 1. During the period of follow-up, 1548 patients in the development cohort and 637 patients in the validation cohort died. The all-cause mortality in the development cohort and validation cohort was 1.92/100 person-years (95% CI 1.83–2.02) and 1.85/100 person-years (95% CI 1.71–2.00), respectively.
Prognostic model construction

The univariate analysis showed that except for Hepatitis B and TG, other 21 candidate variables were associated with all-cause mortality. Subsequently, the multivariate analysis generated an adjusted model with a minimum AIC of 28679.49, which was composed of fifteen candidate variables (Table 2). To optimize the model, we remove hepatitis C (AHR for Negative vs Positive 0.82, 95% CI 0.65–1.04), and obtained the final model consisting of fourteen variables, namely sex, age, marital status (married not including same-sex marriage), infectious route, opportunistic infection, AIDS-related symptoms, BMI, CD4, WBC, PLT, HB, Cr, AST, and TBIL. The likelihood χ² statistic of the final model was 1409.0 (p< 0.001). The coefficients for building the model were shown in Table S1 in the supplementary materials. The baseline survival at 1-, 3-, and 5-year was 95.0%, 91.2%, and 87.9% (Table S2 in the supplementary materials.), respectively.

A nomogram that incorporated the significant variables was then created (Figure 1). The risk score of each variable derived from the scores bar at the top can be summed to generate the total scores and calculate the 1-, 3-, and 5-year overall survival probability, respectively. Moreover, we provided the instruction of the prognostic model in clinical practice in supplementary materials.

Discrimination and calibration of the prognostic model

In the development cohort, the C-index was 0.78 (95% CI 0.77–0.79). The AUC of 1-, 3-, and 5-year was 0.81 (95% CI 0.80–0.82), 0.79 (95% CI 0.77–0.81), and 0.76 (95% CI 0.69–0.83), respectively. In the validation cohort, the C-index was 0.78 (95% CI 0.76–0.80). The AUC of 1-, 3-, and 5-year was 0.81 (95% CI 0.79–0.83), 0.79 (95% CI 0.76–0.81), and 0.75 (95% CI 0.69–0.80), respectively. The ROC curves were shown in Figure 2.
Calibration tests showed that the Brier score of 1-, 3-, and 5-year in the development cohort was 0.03 (95% CI 0.03–0.04), 0.05 (95% CI 0.05–0.06), and 0.07 (95% CI 0.07–0.07), respectively. In the validation cohort, the Brier score at 1-, 3-, and 5-year was 0.03 (95% CI 0.03–0.03), 0.05 (95% CI 0.05–0.05), and 0.07 (95% CI 0.06–0.07), respectively. Figure 3 showed the calibration curves for the development and validation cohorts. Every curve was similar and close to the 45° diagonal, which indicated good concordance between the predicted and actual survival probabilities.

Decision curve analysis

The DCA curves (Figure 4) showed that when the threshold of predictive survival was 3% to 26% at 1-year, 5% to 37% at 3-year, or 8% to 30% at 5-year, the decision curve was higher than the two extreme curves representing all patients dying and all patients surviving, respectively. These results indicated that with our prognostic model, physicians could be more likely to identify patients at high risk of death.

Discussion

Early risk assessment for survival probability of PWH will lead to better individual therapeutic regimens. Using the routine clinical data from NFART, we developed and validated a prognostic model with satisfactory predictive accuracy and acceptable clinical net benefit. Compared with existing models, the physicians can directly read the risk score according to the reference range of the variable instead of a continuous scale which may hide the U-shaped or non-linear relationship between variables and risk score[35]. Besides, we deliberately did not classify the total risk scores into low-risk and high-risk groups, because it would be impractical to categorize patients by risk scores alone. A low-risk score does not mean a zero risk of mortality in reality. We believe that physicians will find out the optimal
cut-off of total risk scores and choose the individual intervention based on available resources.

A practical prognostic model could provide not only risk assessment information but also the potential intervention during follow-up. In resource-rich areas, the dominant causes of death during ART have shifted from AIDS-defining events to non-AIDS-defining events, including non-AIDS-related cancers, liver diseases, cardiovascular diseases, renal dysfunction diseases, invasive bacterial infection, suicide, and drug toxicity[36, 37]. A recent study based on the largest consortium of HIV cohorts in the USA and Canada revealed that preventing elevated total cholesterol would avoid 44% of myocardial infarctions while preventing elevated total cholesterol, viral suppression and low CD4 would avoid 22%, 19%, and 13% of real diseases. So, the potential intervention in these areas could focus on traditional risk factors for non-communicable diseases[38]. Whereas, a similar study in Guangdong province, a relatively resource-rich area in China, also revealed that the contribution of traditional risk for non-AIDS-defining events outweighed the HIV-related risk factors. However, the population-attributable fractions were lower than that in the USA and Canada[39]. In our study, age was assigned the highest risk score, followed by AST, Cr, CD4, TBIL, infectious route, BMI, HB, WBC, sex, PLT, marital status, AIDS-related symptoms, and opportunistic infection. This result highlighted the geriatric-HIV medicine during ART[40] and emphasized the importance of preventing the risk factors of liver diseases and renal diseases over the traditional HIV-related factors such as CD4, AIDS-related symptoms, and the opportunistic infection in Guangxi in China. Additionally, our model showed that male, single, and injecting drug users were associated with high risk scores, which might indicate poor adherence in these populations[41]. Interestingly, advanced WHO clinical stage, tuberculosis, hepatitis B and C did not integrate into our model. This is probably because that the China Free Antiretroviral Therapy Manual recommends aggressive regimens for special patients.
with complications and co-infection. This is consistent with a prior study in Guangxi, which reported that the diagnosis of tuberculosis was a beneficial factor for the survival of hospitalized HIV/AIDS patients[42].

This study has some limitations. First, although it is a 15-year retrospective study based on the NFART database which provides us with a large sample size, the analyses for available factors were limited by the unified data framework. Additional factors could be accounted for in a prospective study. Second, the changes of standard regimen over time may affect mortality which is a common limitation in existing models. But the first-line regimen in China is composed of two nucleoside reverse transcriptase inhibitors and one nonnucleoside reverse transcriptase inhibitor. The first-line regimen accounts for approximately 80% of the free regimen in China[48], which would weaken this impact to some extent. Third, our prognostic model was validated only in the PWH from Guangxi, which may potentially limit the generalizability in other regions of China. Therefore, we report the baseline survival at each time point, and further studies can refine our model and perform external validation in an independent dataset.

Conclusion

It remains challenging to perform an early risk assessment and develop personalized treatment for PWH on ART. A simple-to-use prognostic model that combines with weighted baseline clinical information may provide a robust and useful tool for the individualized treatment plan and health resource utilization.
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Contributions

H.J., Q.Z. G.L., H.L., and Y.S. take responsibility for the study design and result interpretation. H.J., J.H., Z.Y and X.Z. analyzed the data. H.J. drafted the manuscript. Q.Z., Y.F, Y.S., G.L., and H.L. review the manuscript. All authors approved the final version for submission.

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Conflict of Interest statement

H.J., Q.Z., Y.F., J.H., Z.Y., X.Z., G.L., H.L., and Y.S. declare that there are no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
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Table 1. Baseline characteristics of patients in the development cohort and validation cohort

| Characteristic       | Development cohort (n=25388) | validation cohort (n=10880) |
|----------------------|-----------------------------|-----------------------------|
| No. (%)              |                             |                             |
| Sex                  |                             |                             |
| Male                 | 17241 (67.9)                | 7392 (67.9)                 |
| Female               | 8147 (32.1)                 | 3488 (32.1)                 |
| Age, years           |                             |                             |
| <30                  | 3643 (14.3)                 | 1589 (14.6)                 |
| 30–39                | 5819 (22.9)                 | 2488 (22.9)                 |
| 40–49                | 5471 (21.6)                 | 2313 (21.3)                 |
| 50–59                | 4815 (19.0)                 | 2050 (18.8)                 |
| 60–69                | 4247 (16.7)                 | 1843 (16.9)                 |
| ≥70                  | 1393 (5.5)                  | 597 (5.5)                   |
| Marital status       |                             |                             |
| Single               | 4820 (19.0)                 | 2042 (18.8)                 |
| Married*             | 16002 (63.0)                | 6886 (63.3)                 |
| Divorced/widowed     | 4566 (18.0)                 | 1952 (17.9)                 |
| Infectious route     |                             |                             |
| Condition                              | Yes      | No        |
|----------------------------------------|----------|-----------|
| Sexual/others                          | 24122 (95.0) | 10323 (94.9) |
| Injecting drug use                     | 1266 (5.0)    | 557 (5.1)     |
| Tuberculosis                           |          |           |
| Yes                                    | 2791 (11.0) | 1155 (10.6) |
| No                                     | 22597 (89.0) | 9725 (89.4)  |
| Opportunistic infection                |          |           |
| Yes                                    | 8851 (34.9) | 3824 (35.1) |
| No                                     | 16537 (65.1) | 7056 (64.9)  |
| AIDS-related symptoms                  |          |           |
| Yes                                    | 4326 (17.0) | 1829 (16.8) |
| No                                     | 21062 (83.0) | 9051 (83.2)  |
| WHO clinical stage                     |          |           |
| I                                      | 11882 (46.8) | 5105 (46.9) |
| II                                     | 3668 (14.4) | 1522 (14.0) |
| III                                    | 3958 (15.6) | 1742 (16.0) |
| IV                                     | 5880 (23.2) | 2511 (23.1) |
| Hepatitis B                            |          |           |
| Positive                               | 3175 (12.5) | 1344 (12.4) |
|                      | Value 1 | Value 2 |
|----------------------|---------|---------|
| **Hepatitis C**      |         |         |
| Positive             | 1778 (7.0) | 742 (6.8) |
| Negative             | 23610 (93.0) | 10138 (93.2) |
| **Body mass index, kg/m²** |         |         |
| <18.5                | 5835 (23.0) | 2511 (23.1) |
| 18.5–23.9            | 16259 (64.0) | 6966 (64.0) |
| 24.0–27.9            | 2849 (11.2) | 1235 (11.4) |
| ≥28                  | 445 (1.8) | 168 (1.5) |
| **CD₄⁺ T-lymphocyte count, cells/μL** |         |         |
| <100                 | 8442 (33.3) | 3634 (33.4) |
| 100–199              | 4553 (17.9) | 2018 (18.5) |
| 200–349              | 7418 (29.2) | 3107 (28.6) |
| ≥350                 | 4975 (19.6) | 2121 (19.5) |
| **CD₈⁺ T-lymphocyte count, cells/μL** |         |         |
| <220                 | 1337 (5.3) | 566 (5.2) |
| 220–1129             | 17078 (67.2) | 7363 (67.7) |
| ≥1130                | 6973 (27.5) | 2951 (27.1) |
| **White blood cell, 10⁹/L** |     |     |
|---------------------------|-----|-----|
| <3.5                      | 4022 (15.8) | 1711 (15.7) |
| 3.5–9.5                   | 20479 (80.7) | 8769 (80.6) |
| >9.5                      | 887 (3.5) | 400 (3.7) |
| **Platelet, 10⁹/L**       |     |     |
| <125                      | 2756 (10.9) | 1173 (10.8) |
| 125–350                   | 21335 (84.0) | 9169 (84.3) |
| >350                      | 1297 (5.1) | 538 (4.9) |
| **Hemoglobin, g/L**       |     |     |
| <80                       | 1069 (4.2) | 479 (4.4) |
| 80–109                    | 5471 (21.6) | 2352 (21.6) |
| 109–119                   | 3895 (15.3) | 1700 (15.6) |
| ≥120                      | 14953 (58.9) | 6349 (58.4) |
| **Serum creatinine, μmol/L** |     |     |
| <133                      | 24940 (98.2) | 10682 (98.2) |
| 133–177                   | 319 (1.3) | 138 (1.3) |
| >177                      | 129 (0.5) | 60 (0.6) |
| **Aspartate transaminase, U/L** |     |     |
|                | <40            | 40–99          | 100–199         | ≥200          |
|----------------|---------------|----------------|----------------|---------------|
| Alanine aminotransferase, U/L |               |                |                |               |
| <40            | 20626 (81.2)  | 4233 (16.7)    | 448 (1.8)      | 81 (0.3)      |
| 40–99          | 20656 (81.3)  | 4211 (16.6)    | 452 (1.8)      | 69 (0.3)      |
| 100–199        | 20453 (80.6)  | 4631 (18.2)    | 304 (1.2)      | 304 (1.2)     |
| ≥200           | 25138 (99.0)  | 60 (0.6)       | 115 (0.5)      | 115 (0.5)     |
| Total cholesterol, mmol/L |                |                |                |               |
| <5.0           | 8810 (81.0)   | 1873 (17.2)    | 162 (1.5)      | 35 (0.3)      |
| 5.0–6.9        | 8737 (81.5)   | 1759 (16.2)    | 220 (2.0)      | 220 (2.0)     |
| ≥7.0           | 10778 (99.0)  | 2003 (18.4)    | 140 (1.3)      | 140 (1.3)     |
| Total bilirubin, μmol/L |                |                |                |               |
| <34.0          | 10778 (99.0)  | 10778 (99.0)   | 10778 (99.0)   | 10778 (99.0)  |
| 34.0–51.0      | 60 (0.6)      | 60 (0.6)       | 60 (0.6)       | 60 (0.6)      |
| >51.0          | 42 (0.4)      | 42 (0.4)       | 42 (0.4)       | 42 (0.4)      |
| Triglyceride, mmol/L |                |                |                |               |

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| Fasting plasma glucose, mmol/L | <1.80 | 17515 (69.0) | 7512 (69.0) |
|-------------------------------|-----------------|-----------------|-----------------|
| 1.8–2.83                     | 5720 (22.5)     | 2463 (22.6)     |
| 2.84–5.60                    | 1848 (7.3)      | 770 (7.1)       |
| >5.60                        | 305 (1.2)       | 135 (1.3)       |

* Married does not include same-sex marriage.
Table 2. Univariable and multivariable analysis of overall survival in the development cohort

| Variable       | Univariable HR for mortality (95% CI) | p-value | Multivariable HR for mortality (95% CI) | p-value |
|----------------|-------------------------------------|---------|----------------------------------------|---------|
| Sex            |                                     |         |                                        |         |
| Male           | 1 (ref)                             |         | 1 (ref)                                |         |
| Female         | 0.47 (0.41–0.53)                    | <0.00   | 0.64 (0.56–0.73)                       | <0.00   |
| Age, years     |                                     |         |                                        |         |
| <30            | 1 (ref)                             |         | 1 (ref)                                |         |
| 30–39          | 1.98 (1.54–2.55)                    | <0.00   | 1.63 (1.26–2.11)                       | <0.00   |
| 40–49          | 2.72 (2.12–3.49)                    | <0.00   | 2.34 (1.80–3.03)                       | <0.00   |
| 50–59          | 3.20 (2.45–4.11)                    | <0.00   | 3.39 (2.60–4.42)                       | <0.00   |
| 60–69          | 5.15 (4.04–6.56)                    | <0.00   | 5.47 (4.21–7.12)                       | <0.00   |
| ≥70            | 9.97 (7.70–12.91)                   | <0.00   | 9.86 (7.43–13.09)                      | <0.00   |
| Marital status |                                     |         |                                        |         |
| Marital Status       | Odds Ratio (95% CI) | p-value | 95% CI  |
|----------------------|---------------------|---------|---------|
| Single               | 1 (ref)             |         |         |
| Married *            | 1.12 (0.97–1.29)    | 0.11    | 0.78 (0.66–0.91) |
| Divorce d/widowed    | 1.42 (1.20–1.69)    | <0.00   | 0.77 (0.64–0.93) |
|                      |                     |         |         |
| Infectious route     |                     |         |         |
| Sexual/others        | 1 (ref)             | 1 (ref) |         |
| Injecting drug use   | 1.52 (1.26–1.83)    | <0.00   | 1.70 (1.30–2.22) |
|                      |                     |         |         |
| Tuberculosis         |                     |         |         |
| Yes                  | 1 (ref)             |         |         |
| No                   | 0.60 (0.52–0.68)    | <0.00   | 1       |
|                      |                     |         |         |
| Opportunistic infection |                   |         |         |
| yes                  | 1 (ref)             |         | 1 (ref) |
| No                   | 0.42 (0.38–0.47)    | <0.00   | 0.87 (0.77–0.98) |
|                      |                     |         |         |
| **AIDS-related complications** |  |  |  |
|-----------------------------|--|--|--|
| Yes | 1 (ref) | 1 (ref) |  |
| No | 0.50 (0.45–0.56) | <0.00 | 0.77 (0.69–0.87) | <0.01 |

| **WHO clinical stage** |  |  |  |
|-----------------------|--|--|--|
| I | 1 (ref) |  |  |
| II | 1.56 (1.32–1.84) | <0.00 | 1 |  |
| III | 2.62 (2.28–3.02) | <0.00 | 1 |  |
| IV | 2.76 (2.43–3.14) | <0.00 | 1 |  |

| **Hepatitis B** |  |  |  |
|-----------------|--|--|--|
| Positive | 1 (ref) |  |  |
| Negative | 0.91 (0.79–1.05) | 0.19 |  |

| **Hepatitis C** |  |  |  |
|-----------------|--|--|--|
| Positive | 1 (ref) | 1 (ref) |  |
|                              | Mean (95% CI)   | P       | Mean (95% CI)   | P       |
|------------------------------|----------------|---------|----------------|---------|
| Negative                     | 0.72 (0.61–0.85) | <0.00   | 0.82 (0.65–1.04) | 0.10    |
| Body mass index, kg/m²       |                |         |                |         |
| >18.5–23.9                   | 0.52 (0.47–0.58) | <0.00   | 0.72 (0.65–0.81) | <0.001  |
| 24–27.9                      | 0.30 (0.24–0.38) | <0.00   | 0.56 (0.44–0.71) | <0.001  |
| ≥28                          | 0.28 (0.16–0.49) | <0.00   | 0.61 (0.34–1.08) | <0.001  |
| CD₄⁺ T-lymphocyte count, cells/μL |                |         |                |         |
| <100                         | 1 (ref)         |         | 1 (ref)         |         |
| 100–199                      | 0.55 (0.48–0.63) | <0.00   | 0.66 (0.57–0.77) | <0.001  |
| 200–349                      | 0.39 (0.35–0.45) | <0.00   | 0.63 (0.54–0.74) | <0.001  |
| ≥350                         | 0.25 (0.21–0.31) | <0.00   | 0.48 (0.38–0.59) | <0.001  |
|                          | 01         | 01         |
|--------------------------|------------|------------|
| **CD8⁺ T-lymphocyte count, cells/µL** |            |            |
| <220                     | 1 (ref)    |            |
| 220–1129                 | 0.51 (0.43–0.61) | <0.00 1 |
| ≥1130                    | 0.38 (0.31–0.46) | <0.00 1 |

**White blood cell, 10⁹/L**

|          | 01         | 01         |
|----------|------------|------------|
| <3.5     | 1 (ref)    | 1 (ref)    |
| 3.5–9.5  | 0.59 (0.53–0.67) | <0.00 1 | 1.06 (0.93–1.20) | 0.43 |
| >9.5     | 1.08 (0.84–1.37) | 0.55 | 1.68 (1.31–2.16) | <0.0 1 |

**Platelet, 10⁹/L**

|       | 01         | 01         |
|-------|------------|------------|
| <125  | 1 (ref)    | 1 (ref)    |
| Value         | $H_{\text{emol}}$, g/L | $\text{s}_{\text{erum}}$, μmol/L | | |
|---------------|-------------------------|----------------------------------|---|---|
| $125–350$     | $0.48 (0.42–0.55)$      | $<0.00$                          | $0.78 (0.68–0.89)$ | $<0.001$ |
| $>350$        | $0.86 (0.69–1.07)$      | $0.17$                           | $1.05 (0.84–1.32)$ | $0.66$   |
| Hemoglobin, g/L |                         |                                  |               |          |
| $<80$         | $1$ (ref)               |                                  | $1$ (ref)     |          |
| $80–109$      | $0.72 (0.60–0.87)$      | $0.001$                          | $0.85 (0.70–1.02)$ | $0.09$   |
| $109–119$     | $0.49 (0.40–0.60)$      | $<0.001$                         | $0.73 (0.59–0.90)$ | $0.003$  |
| $\geq 120$   | $0.27 (0.22–0.33)$      | $<0.001$                         | $0.56 (0.45–0.69)$ | $<0.001$ |
| Serum creatinine, μmol/L |                   |                                  |               |          |
| $<133$        | $1$ (ref)               |                                  | $1$ (ref)     |          |
| $133–177$     | $2.19 (1.60–3.02)$      | $<0.001$                         | $1.10 (0.80–1.52)$ | $0.55$   |
| $>177$        | $4.22 (2.84–6.27)$      | $<0.001$                         | $2.68 (1.80–4.00)$ | $<0.001$ |
| Aspartate transaminase, |                          |                                  |               |          |
| U/L               | [123,456] | [789,012] | [345,678] |
|------------------|----------|-----------|-----------|
| <40              | 1 (ref)  | 1 (ref)   |           |
| 40–99            | 1.96 (1.75–2.19) | <0.00 |
|                  |          | 1.45 (1.29–1.63) | <0.0 |
|                  |          | 1         | 01        |
| 100–199          | 3.38 (2.67–4.28) | <0.00 |
|                  |          | 2.19 (1.71–2.82) | <0.0 |
|                  |          | 1         | 01        |
| ≥200             | 4.81 (2.94–7.89) | <0.00 |
|                  |          | 3.73 (2.24–6.19) | <0.0 |
|                  |          | 1         | 01        |
| Alanine aminotransferase, U/L | | | |
| <40              | 1 (ref)  |           |           |
| 40–99            | 1.38 (1.22–1.56) | <0.00 |
|                  |          | 1         |           |
| 100–199          | 1.56 (1.13–2.15) | 0.006 |
|                  |          |           |           |
| ≥200             | 2.50 (1.30–4.81) | 0.006 |
| Total cholesterol, mmol/L | | | |
| <5.0             | 1 (ref)  |           |           |
| Bilirubin Range | Mean (95% CI) | p-Value | OR (95% CI) |
|-----------------|---------------|---------|-------------|
| 5.0–6.9         | 0.66 (0.57–0.77) | <0.001 | 1 (ref)     |
| ≥7.0            | 0.82 (0.50–1.34)  | 0.43    | 1 (ref)     |
| **Total**       |               |         |             |
| <34.0           | 1 (ref)                   | 1 (ref) |
| 34.0–51.0       | 2.48 (1.56–3.94)    | <0.001 | 1.38 (0.86–2.21) | 0.18 |
| >51.0           | 4.19 (2.80–6.28)    | <0.001 | 1.97 (1.29–3.01) | 0.002 |
| **Triglyceride**|               |         |             |
| <1.80           | 1 (ref)                   |         |             |
| 1.80–2.83       | 1.05 (0.93–1.18)    | 0.46    |             |
| 2.84–5.60       | 0.89 (0.72–1.09)    | 0.24    |             |
| >5.60           | 0.81 (0.49–1.35)    | 0.43    |             |
| **Fasting**     |               |         |             |
| **plasma**      |               |         |             |
| glucose, mmol/L |        |        |
|----------------|--------|--------|
| <7.0           | 1 (ref)|        |
| ≥7.0           | 1.38 (1.17–1.62) | <0.00 1 |

*Married does not include same-sex marriage.*
Figure legends

Figure 1. Nomogram for calculating 1-, 3-, and 5-year overall survival probabilities at the initiation of ART

Abbreviations: OI, opportunistic infection; BMI, body mass index; CD4, CD4+ T-lymphocyte count; WBC, white blood cell; PLT, platelet; HB, hemoglobin; Cr, serum creatinine; TBIL, total bilirubin.

Instruction: (1) Read the risk scores from the top reference scores bar. The right side of the scores bar indicates higher risk scores than the left side. (2) Add up these scores and plot the sum on the total scores bar. (3) Translate the total scores to the probabilities of 1-, 3-, and 5-year survival.

Figure 2. The receiver operating characteristic (ROC) curves and the area under the ROC curves (AUC) to predict survival at 1-year (a), 3-year (b), and 5-year (c) in the development cohort and 1-year (d), 3-year (e), and 5-year (f) in the validation cohort.

Figure 3. 1-year (a), 3-year (b), and 5-year (c) calibration curves in the development cohort; 1-year (d), 3-year (e), and 5-year (f) calibration curves in the validation cohort.

Figure 4. Decision curve analysis (DCA) curves for the prognostic model at 1-year (a), 3-year (b), and 5-year (c).
Figure 1

| Reference | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|-----------|---|----|----|----|----|----|----|----|----|----|-----|
| Sex       |   | Male | Female | | | | | | | | |
| Age       | <30 | 30-39 | 40-49 | 50-59 | 60-69 | ≥70 | | | | | |
| Marital   |   | Married | Divorced/Widowed | Single | | | | | | | |
| Route     |   | Sexual/Others | IDU | | | | | | | | |
| GI        |   | Yes | No | | | | | | | | |
| Symptom   |   | Yes | No | | | | | | | | |
| BMI       | ≥28 | <18.5 | 24-27.0 | 18.5-23.9 | | | | | | |
| CD4       | ≥500 | 200-349 | <100 | | | | | | | |
| WBC       | ≥3.5 | <8.5 | >3.5 | | | | | | | |
| PLT       | ≥125 | <125 | 125-350 | >350 | | | | | | |
| HB        | ≥120 | 100-119 | <50 | | | | | | | |
| AST       | ≥40 | 40-90 | 100-199 | ≥200 | | | | | | |
| Cr        | ≥133 | 133-177 | >177 | | | | | | | |
| TBIL      | ≥34 | 34-51 | >51 | | | | | | | |
| Total     |   |   |   |   |   |   |   |   |   |   |   |
| 1-Y survival | 0.99 | 0.95 | 0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 |   |
| 3-Y survival | 0.99 | 0.95 | 0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 | 0.1 |
| 5-Y survival | 0.99 | 0.95 | 0.9 | 0.8 | 0.7 | 0.6 | 0.5 | 0.4 | 0.3 | 0.2 | 0.1 |
Figure 3

(a) Actual 1-year Survival vs. Predicted 1-year Survival
(b) Actual 3-year Survival vs. Predicted 3-year Survival
(c) Actual 5-year Survival vs. Predicted 5-year Survival
(d) Actual 1-year Survival vs. Predicted 1-year Survival
(e) Actual 3-year Survival vs. Predicted 3-year Survival
(f) Actual 5-year Survival vs. Predicted 5-year Survival
Figure 4

(a) 

(b) 

(c) 

Net benefit

Threshold probability

Net benefit

Threshold probability

Net benefit

Threshold probability

None

Model

None

Model

None

Model