A Clinical scoring model to predict mortality in HIV/TB co-infected patients at end stage of AIDS in China: An observational cohort study

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Summary

We construct and validate a non-invasive clinical scoring model to predict mortality in HIV/TB patients at end stage of AIDS in China. There were 1,007 HIV/TB patients admitted to Beijing Ditan Hospital from August 2009 to January 2018 included in this study, who were randomly assigned to form derivation cohort and validation cohort. A clinical scoring model was developed based on predictors associated with mortality identified with Cox proportional hazard models. The discrimination and accuracy of model were further validated using the area under the ROC curves. The derivation and validation cohort consisted of 807 and 200 patients in 8:2 ratio, respectively. In derivation cohort, anemia (HGB < 90g/L), tuberculous meningitis, severe pneumonia, hypoalbuminemia, unexplained infections or space-occupying lesions, and malignancies remained independent risk factors of mortality in HIV/TB co-infected patients, and included in this clinical scoring model. The model indicated good discrimination, including AUC = 0.858 (95% CI: 0.782-0.943) in the derivation cohort, and AUC = 0.867 (95% CI: 0.832-0.902) in validation cohort, respectively. The predicted scores were categorized into two groups to predict the mortality: low-risk (0-2 points with mortality with 3.6-9.1%) and high-risk (4-16 points with mortality with 26.42-74.62%), in which 54.55% and 74.62% of patients with score of 5 to 11 and 12-16 were died among high-risk group. Kaplan-Meier curve indicated a significant difference in the cumulative mortality in the two groups by log-rank test (p < 0.001). A clinical scoring model to assess the prognosis in HIV/TB patients at end stage of AIDS was constructed based on simple laboratory and clinical features available at admission, which may be an easy-to-use tool for physicians to evaluate the prognosis and treatment outcome in HIV/TB co-infected patients. The model was also applicable for predicting the death of end-stage HIV/TB patients within a 12 months period after discharge.

Keywords: HIV, TB, mortality, risk score, China

1. Introduction

Mycobacterium Tuberculosis was the most important opportunistic pathogen in HIV/AIDS patients, and epidemiological data from World Health Organization (WHO) indicated that 12% of tuberculosis (TB) patients occurred in HIV/AIDS population (1). In sub-Sahara countries, the prevalence of HIV/TB co-infection was much higher and 80% of TB patients were found in
people living with HIV (/). Our previous study also indicated that TB infection was the most predominant opportunistic infection and prevalence was 32.5% in HIV-infected population in China (2).

It was reported that (3) synergic interaction was found in HIV/TB co-infection and TB infection promoted HIV-associated immunosuppression, which enhanced mortality in HIV/TB co-infected population. Although different guidelines were established to improve the principle for treatment outcome and prognosis in HIV/TB co-infected patients, TB was the most common cause of death in HIV-infected population. Epidemiological investigation indicated that overall mortality was 15.92% in HIV/TB co-infected patients in China (4).

Although previous studies (5) indicated that, in HIV/TB co-infected patients in China, some risk factors, including timely diagnosis of TB, optimization of timing of initiation of antiretroviral therapy, and tuberculous meningitis were associated with mortality, it was rarely reported that a standardized clinically scoring model was developed to assess the prognosis of HIV/TB co-infected patients at end stage of AIDS in China. Some literature reported (6) that at least a clinical scoring model was currently developed to predict mortality in HIV/TB co-infected patients, but complicated formula and calculation were required in this scoring model. Therefore, development of a clinically scoring model was badly in need for clinicians due to higher mortality, which helped to determine the prognosis and treatment outcome in HIV/TB co-infected patients at end stage of AIDS in China.

2. Patients and Methods

2.1. Ethical consideration

This observational study was carried out in Beijing Ditan Hospital based on principles of Declaration of Helsinki, and it was approved by ethical review committee of the hospital. Medical informed consent was waived due to anonymously using clinical information which was summarized from medical records.

2.2. Study population

We reviewed 1,070 HIV/TB co-infected patients at end stage of AIDS admitted to Beijing Ditan Hospital, the largest referral hospital for HIV/AIDS population in China, from August 2009 to January 2018. We excluded foreigners, those aged less than 18 years old, the ones who had baseline data missing, and those diagnosed as old tuberculosis (Figure 1). The patients received 12-month follow-up after discharge. Electronic medical records were reviewed and abstracted to develop a standardized clinically scoring model to determine the prognosis and treatment outcome in HIV/TB co-infected patients at end stage of AIDS.

2.3. Diagnosis and treatment

Diagnosis of active tuberculosis diseases in HIV-infected patients was based on Guidelines for Prevention and Treatment of Opportunistic Infections

Figure 1. Flow chart of study population and random assignment with ratio of 8:2.
in HIV-Infected Adults and Adolescents recommended by U.S. Center for Disease Control and Prevention (CDC) (7). Etiologic diagnosis in HIV-infected patients with suspected active tuberculosis was based on culture and isolation of Mycobacterium Tuberculosis in different samples, including sputum, bronchoalveolar lavage fluid (BALF), pleural effusion, ascites and cerebrospinal fluid (CSF). Gene-X-Pert and nucleic acid amplification were also applied in above samples to provide rapid diagnosis of tuberculosis infection. Interferon-γ releasing assay (IGRA) was also screened in blood samples in patients with suspected active tuberculosis with related clinical manifestations. Pathological examination of acid-fast bacilli (AFB) was conducted in BALF, pleural effusion, ascites, CSF and samples of lymph nodes or surgical resection.

Anti-tuberculosis treatment was based on guideline recommended by U.S. CDC (7), including intensive phase with isoniazid, rifampin, ethambutol and pyrazinamide and continuation phase with isoniazid and rifampin. Adjunctive corticosteroid was also used in patients with HIV-related TB involving central nervous system or pericardium.

Beside active tuberculosis diseases, other opportunistic infections (OIs) in HIV/TB co-infected patients at end stage of AIDS were diagnosed and managed in accordance with Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommended by U.S. CDC (7). The malignant lymphoma and non-AIDS-defining malignancies were diagnosed based on pathological and imaging diagnosis, and managed according to HIVBOOK edited by Christian Hoffmann (8).

Antiretroviral therapy was recommended to HIV/TB co-infected patients at end stage of AIDS based on Chinese National free HIV antiretroviral treatment handbook and preferred regimen was tenofovir (TDF), lamivudine (3TC), plus efavirenz (EFV) (9).

2.4. Data collection and definitions

Demographic data included age and gender, and clinical data collected in this study included HIV transmission routes, ART initiation or not, duration of active ART initiation, documented opportunistic infections, malignant lymphoma, non-AIDS-defining malignancies. Laboratory tests were performed for baseline CD4, albumin as well as hemoglobin (HGB) levels after admission.

Primary treatment outcome was documented either survival or death when HIV/TB co-infected patients left hospital. Patients who survived when discharged received 12-month follow-up, and the date of last known alive was documented in electronical medical records base on records of last follow-up. The mortality in this study was a cumulative measure with a risk period of 12 months after discharge, i.e., dead cases within the 12 months after discharge were calculated.

In HIV/TB co-infected patients at end stage of AIDS, Unexplained infections was diagnosed based on compatible clinical symptoms and intensive pathogenic investigation of OIs without identifying pathogens, and unexplained space-occupying lesions was diagnosed on basis of clinical symptoms and results of Computerized tomography (CT) or magnetic resonance imaging(MRI) scan but lack of pathological diagnosis of biopsy.

Severe pneumonia was diagnosed based on the presence of severe acute respiratory failure and/or septic shock with organ system dysfunction due to different etiologies or pathogens (10).

2.5. Statistical analysis

Statistical analysis was conducted with SPSS 20.0 (SPSS Institute, Chicago IL, USA). Clinical data were evaluated with percentages for categorical variables and chi-square test or Fisher exact test was used for categorical variables.

Cox proportional hazard models were used to assess the predictors associated with mortality in HIV/TB co-infected patients at end stage of AIDS in the cohort. Univariate Cox proportional hazard models were firstly used to determine the association of the variables with mortality in HIV/TB co-infected patients, and multivariate Cox proportional hazard models were subsequently run and univariate factors with \( p < 0.1 \) were included into a forward stepwise multivariate Cox proportional hazard model. The integer scores were converted by rounding the hazard ratios (HRs) of the predictors. For example, the HR of 2.110 associated with tuberculous meningitis was equal to 2 points and the final score was the sum of these values. The clinical scoring model was validated in derivation and validation cohort, Receiver operating characteristics (ROC) curves were plotted and the area under curve (AUC) was evaluated in this study. The correlation between clinical scoring model and prognosis was plotted based on cumulative mortality according to scores. Log-rank testing was conducted to evaluate difference in cumulative mortality between the low-level and high-level scores.

Alpha was set to 0.05 with two-side, with 95% confidence intervals. \( P < 0.05 \) was considered significant.

3. Results

3.1. Patients characteristics

From August 2009 to January 2018, 1,070 HIV-infected patients at end stage of AIDS were diagnosed as tuberculosis infection and 1,007 patients were enrolled in this study after excluding those not meeting inclusion criteria, in which 810 were alive and 197 were dead after 12-month follow-up. Random assignment in 8:2 ratio was conducted in alive group (650 and 160 cases)
Table 1. Baseline characteristics of HIV/TB patients at end-stage of AIDS in the study cohort

| Variables                        | Total n = 1007 | Derivation cohort n = 807 | Validation cohort n = 200 | p value |
|----------------------------------|----------------|---------------------------|---------------------------|---------|
| Age (years)                      |                |                           |                           |         |
| < 50                             | 820 (81.4%)    | 665 (82.4%)               | 155 (77.5%)               | 0.110   |
| ≥ 50                             | 187 (18.6%)    | 142 (17.6%)               | 45 (22.5%)                |         |
| Gender                           |                |                           |                           |         |
| Female                           | 902 (89.6%)    | 716 (88.7%)               | 186 (93%)                 | 0.076   |
| Male                             | 105 (10.4%)    | 91 (11.3%)                | 14 (7%)                   |         |
| Transmission route               |                |                           |                           |         |
| Homosexual                       | 752 (74.7%)    | 609 (75.5%)               | 143 (71.5%)               | 0.421   |
| Heterosexual                     | 147 (14.6%)    | 112 (13.9%)               | 35 (17.5%)                |         |
| Laboratory results               |                |                           |                           |         |
| Blood transfusion                | 108 (10.7%)    | 86 (10.6%)                | 22 (11%)                  |         |
| HGB > 90g/L                      | 722 (71.7%)    | 585 (72.5%)               | 137 (68.5%)               | 0.262   |
| HGB ≤ 90g/L                      | 285 (28.3%)    | 222 (27.5%)               | 63 (31.5%)                |         |
| ALB > 30g/L                      | 679 (67.4%)    | 552 (68.4%)               | 127 (63.5%)               | 0.185   |
| ALB ≤ 30g/L                      | 328 (32.6%)    | 255 (31.6%)               | 73 (36.5%)                |         |
| CD4 > 100 cells/uL               | 288 (28.6%)    | 231 (28.6%)               | 57 (28.5%)                | 0.972   |
| CD4 ≤ 100 cells/uL               | 719 (71.4%)    | 576 (71.4%)               | 143 (71.5%)               |         |
| ART prior to admission           |                |                           |                           |         |
| Yes                              | 411 (40.8%)    | 324 (40.1%)               | 87 (43.5%)                | 0.388   |
| NO                               | 596 (59.2%)    | 483 (59.9%)               | 113 (56.5%)               |         |
| Tuberculosis                     |                |                           |                           |         |
| Pulmonary tuberculosis           | Yes            | 754 (74.9%)               | 594 (73.6%)               | 0.062   |
| NO                               | 253 (25.1%)    | 213 (26.4%)               | 41 (20.5%)                |         |
| Tuberculous pleuritis            | Yes            | 213 (21.2%)               | 172 (21.3%)               | 0.801   |
| NO                               | 794 (78.8%)    | 635 (78.7%)               | 159 (79.5%)               |         |
| Tuberculous peritonitis          | Yes            | 69 (6.9%)                 | 54 (6.7%)                 | 0.685   |
| NO                               | 938 (93.1%)    | 753 (93.3%)               | 185 (92.5%)               |         |
| Tuberculous meningitis           | Yes            | 125 (12.4%)               | 100 (12.4%)               | 0.967   |
| NO                               | 882 (87.6%)    | 707 (87.6%)               | 175 (87.5%)               |         |
| Opportunistic Infections         |                |                           |                           |         |
| PCP                              | Yes            | 134 (13.3%)               | 117 (14.5%)               | 0.025   |
| NO                               | 873 (86.7%)    | 690 (85.5%)               | 183 (91.5%)               |         |
| CMV pneumonitis                  | Yes            | 52 (5.2%)                 | 42 (5.2%)                 | 0.907   |
| NO                               | 955 (94.8%)    | 765 (94.8%)               | 190 (95%)                 |         |
| Cryptococcal pneumonitis         | Yes            | 9 (0.9%)                  | 7 (0.9%)                  | 0.858   |
| NO                               | 998 (99.1%)    | 800 (99.1%)               | 198 (99%)                 |         |
| Fungal pneumonia                 | Yes            | 91 (9.1%)                 | 66 (8.2%)                 | 0.056   |
| NO                               | 916 (91%)      | 741 (91.8%)               | 175 (87.5%)               |         |
| Severe pneumonia                 | Yes            | 30 (3%)                   | 27 (3.3%)                 | 0.169   |
| NO                               | 977 (97%)      | 780 (96.7%)               | 197 (98.5%)               |         |
| MAC                              | Yes            | 63 (6.3%)                 | 51 (6.3%)                 | 0.867   |
| NO                               | 944 (93.7%)    | 756 (93.7%)               | 188 (94%)                 |         |
| CMV retinitis                    | Yes            | 54 (5.4%)                 | 46 (5.7%)                 | 0.339   |
| NO                               | 953 (94.6%)    | 761 (94.3%)               | 192 (96%)                 |         |
| Penicilliosis                     | Yes            | 21 (2.1%)                 | 19 (2.4%)                 | 0.230   |
| NO                               | 986 (97.9%)    | 788 (97.6%)               | 198 (99%)                 |         |
| Invasive fungal infections       | Yes            | 32 (3.2%)                 | 25 (3.1%)                 | 0.772   |
| NO                               | 975 (96.8%)    | 782 (96.9%)               | 193 (96.5%)               |         |
| CMV neurologic diseases          | Yes            | 13 (1.3%)                 | 7 (0.9%)                  | 0.017   |
| NO                               | 994 (98.7%)    | 800 (99.1%)               | 194 (97%)                 |         |
| Cryptococcal meningitis          | Yes            | 42 (4.2%)                 | 34 (4.2%)                 | 0.893   |
| NO                               | 965 (95.8%)    | 773 (95.8%)               | 192 (96%)                 |         |
| Cerebral Toxoplasmosis           | Yes            | 16 (1.6%)                 | 12 (1.5%)                 | 0.603   |
| NO                               | 991 (98.4%)    | 795 (98.5%)               | 196 (98%)                 |         |
| Unexplained infections or space-occupying lesions | Yes | 103 (10.2%) | 83 (10.3%) | 20 (10%) | 0.905 |
| NO                               | 904 (89.8%)    | 724 (99.7%)               | 180 (90%)                 |         |
| Malignancies                     | Yes            | 27 (2.7%)                 | 20 (2.5%)                 | 7 (3.5%) | 0.423 |
| NO                               | 980 (97.3)     | 787 (97.5%)               | 193 (96.5%)               |         |

Note: ART: antiretroviral therapy; PCP: pneumocystis pneumonia; CMV: cytomegalovirus; MAC: Mycobacterium avium complex.

and dead group (157 and 40 cases) respectively to form derivation cohort (n = 807) and validation cohort (n = 200) in 8:2 ratio (Figure 1). The demographic, clinical and laboratory characteristics of these patients were detailed in Table 1, and there was no significant difference between characteristics in derivation and validation cohort.

3.2. Development of clinical scoring model of mortality in HIV/TB co-infected patients at end stage of AIDS

Univariate Cox proportional hazard models were used to identify the predictor associated with mortality in derivation cohort, revealing significant difference in anemia (HGB < 90g/L), tuberculous meningitis, severe
pneumonia, hypoalbuminemia, unexplained infections or space-occupying lesions, and malignancies (p < 0.05, Table 2 and Table S1, http://www.biosciencetrends.com/action/getSupplementalData.php?ID=41). These variables were entered into a forward stepwise multivariate Cox proportional hazard model, and results indicated that anemia (HGB < 90g/L) ((multivariate-adjusted hazard ratios (HRs) 1.726, 95% confidence intervals (CIs) 1.224, 2.435, p = 0.002), Tuberculous meningitis (HR: 2.110, 95% CI: 1.399, 3.181, p < 0.001), severe pneumonia (HR: 4.841, 95% CI: 3.002, 7.806, p < 0.001), hypoalbuminemia (HR: 2.062, 95% CI: 1.446-2.939, p < 0.001), unexplained infections or space-occupying lesions (HR: 7.485, 95% CI: 5.341-10.489, p < 0.001), and malignancies (HR: 4.866, 95% CI: 2.785-8.502, p < 0.001) remained independent risk factors of mortality in HIV/TB co-infected patients at end-stage of AIDS. The score was categorized into two groups of scores from each of the six predictors ranged from 0 to 16 (Table 2) in this study, and no one had score 1 or 3 according to predictive score of each predictor (Table 2) and the sum of scores from each of the six predictors.

3.3. Validation of the clinical scoring model

The potency of the clinical scoring model to predict mortality at 12-month follow-up in HIV/TB co-infected patients at end stage of AIDS was assessed using the area under the ROC curves with the validation cohort. The area under the ROC curves was 0.858 (95% CI: 0.782-0.943) in the derivation cohort, while the area under the ROC curves in validation cohort was 0.867 (95% CI: 0.832-0.902), which indicated that this clinical scoring model may be useful in predicting mortality at 12-month follow-up in HIV/TB co-infected patients (Figure S1, http://www.biosciencetrends.com/action/getSupplementalData.php?ID=41).

3.4. Correlation between the clinical scoring model and mortality in HIV/TB co-infected patients at end-stage of AIDS

All patients in this study were pooled to further assess the correlation between the clinical scoring model and mortality in HIV/TB co-infected patients at end-stage of AIDS. The score was categorized into two groups with low risk (scoring 0-2) and high risk (scoring 4-16) of mortality based on the maximum Youden index determined by receiver operating curve analysis. We found that patients with higher scores had higher mortality. Among patients with score of 0, 3.6% had died at 12-month follow-up, as compared to 9.1% of patients with score of 2, 26.42% of patients with score of 4, 54.55% and 74.62% of patients with score of 5 to 11 and 12-16, respectively (Figure 2). For the summed clinical scores of 0-2 and 4-16, the mortality at 12-month follow-up was 3.6-9.1% and 26.42-74.62%, respectively (Table 2). Furthermore, Kaplan-
Meier curve indicated a significant difference in the cumulative mortality between low-level scores and high-level scores groups (0-2 and 4-16) at 12-month follow-up by log-rank test ($p < 0.001$) (Figure 3), which demonstrated that the model may be useful in predicting mortality in HIV/TB co-infected patients at end-stage of AIDS.

4. Discussion

This predictive model was constructed based on the derivation and the validation cohorts, in which risk factors were found and their risk scores were evaluated based on multivariate Cox proportional hazard model, and a predictive model was developed in the derivation cohort, and the predictive model was further assessed using the area under the ROC curves in the validation cohort.

Routinely and preferably, a simple random sampling should have been applied to the whole sample of 1,007 patients, with 4:1 ratio for the derivation and validation cohorts, and it should meet a prerequisite: there was no significant difference in outcome status (alive vs. dead) between derivation and validation cohorts (12), which may experience multiple round random sampling to meet the prerequisite. In this study, we simplified the random sampling processes based on randomly stratifying sampling: random assignment in 8:2 ratio was conducted in alive group (650 and 160 cases) and dead group (157 and 40 cases) respectively to form derivation cohort ($n = 807$) and validation cohort ($n = 200$) in 8:2 ratio (Figure 1), which indicated that there was no significant difference in outcome status between two cohorts and selection bias were reduced to the utmost.

It was reported that several TB predictive scoring models were previously established (6,11), but some reason limited their application in specific context in China. HIV infection was reported to be the most important risk factor for mortality in several TB predictive scoring models, but they were not involved in end-stage AIDS patients, who were prone to be complicated by different opportunistic infection, malignancies and co-morbidities. Nguyen et al. (11) reported prognostic score model to predict mortality during TB treatment in HIV/TB co-infected patients in high-income countries, but this model had never been validated in China, which has completely different clinical features and healthcare conditions in HIV/TB co-infected population in China.

In China, although availability of potent free antiretroviral regimens has had the most profound influence on opportunistic infections or malignancies-related mortality (9), opportunistic infections and AIDS-related malignancies continued to cause morbidity and mortality due to unaware of their HIV status in Chinese HIV-infected population (2). These patients sought medical attention so late that their health condition had entered end-stage of AIDS due to severe immunosuppression when HIV infection was diagnosed. Our previous study indicated that (2), in HIV/AIDS patients with severe immunosuppression, the same pathogen can co-infected different organs or systems, such as Mycobacterium Tuberculosis which can infect nervous, respiratory, lymph, and digestive system, while different pathogens can infect same organ or system, such as respiratory system which can be co-infected with bacteria, virus and invasive fungi. Some pathogens and space-occupying lesions were also found to be difficult to be diagnosed etiologically in end-stage AIDS patients, which increased degree of difficulty of etiologic diagnosis in clinical practice. In HIV/ TB co-infected patients at end-stage of AIDS, we also highlighted different clinical complications, including AIDS-defining illnesses (including opportunistic infections and AIDS-related malignancies) and non-AIDS-defining malignancies, resulted in clinical
deterioration or even death in these patients.

TB disease is an important OI and AIDS-defining illness, it can occur at any CD4 cell counts, and its risk increases with progressive immunodeficiency. In this study, we found that TB disease was diagnosed in 28.6% of patients with CD4 > 100 cells/µL and 71.4% of patients with CD4 < 100cells/µL, respectively, which indicated that TB disease was diagnosed in HIV-infected patients with any CD4 cell counts in our cohort, and was more prone to occur in patients with lower CD4 levels. This clinical scoring model was constructed based on this cohort, which indicated that it can be used not only in patients with higher CD4 levels but also in patients with lower CD4 levels. In this study, the majority of TB disease occurred in HIV-infected patients with lower CD4 levels, who were prone to be complicated with different OIs or malignancies, which were common clinical features in HIV-infected patients with end-stage of AIDS in China (2). This clinical scoring model was used in HIV/TB co-infected patients at end stage of AIDS, which indicated its advantage in HIV/TB co-infected patients at end stage of AIDS in China.

The result in this study demonstrated that HIV/TB patients with hypoalbuminemia or anemia had significantly higher mortality. Hypoalbuminemia and anemia were commonly treated as marker of malnutrition, and it was associated with wasting and was considered as indicators of increased severity of OIs, which increased risk of mortality in HIV/TB patients (13,14).

Tuberculous meningitis was the most severe complication in individuals infected with Mycobacterium Tuberculosis, which killed or disabled half of these patients. TB meningitis was also found as a predictor of mortality in our clinical scoring model, which was consistent with some literature found in PubMed (11,15,16), and helped remind physicians of this severe complication in HIV/TB co-infected patients.

We found that unexplained infections or space-occupying lesions were another important risk factor of mortality in HIV/TB patients. Some studies demonstrated that some fatal infections or malignancies cannot be determined until at autopsy (17). Obscurely etiologic diagnosis increased risk of mortality and it was important to improve pathogenic and pathological diagnosis in HIV-infected patients with unexplained infections or space-occupying lesions.

Malignancies were another important risk factor of mortality in our clinical scoring model. Malignancies were caused based on immunosuppression, life-style and co-infections (HBV, HCV, or HPV) (18,19), which indicated that earlier initiation of HAART, healthy lifestyle, cancer screening and identification of co-infected pathogens would favorably improve prognosis of HIV-infected patients.

Severe pneumonia, which was caused by co-infections with pneumocystis pneumonia (PCP), cytomegalovirus, and invasive fungi, besides tuberculosis, in this study, was required invasive mechanical ventilation earlier admitting to Intensive Care Units (ICU). Several studies demonstrated that severe pneumonia was an important cause of death in patients later admitted to ICU (10,20) which was consistent with our result in this study, and helped remind physicians of earlier admitting to ICU to receive mechanical ventilation.

Several important variables having significance in univariate analyses such as CD4 cell count, pulmonary tuberculosis, PCP and fungal pneumonia were also included into a forward stepwise multivariate Cox proportional hazard model, but we cannot make conclusion that lower CD4 levels and some OIs, such as pulmonary tuberculosis, PCP and fungal pneumonia, were associated with mortality of HIV/TB co-infected patients at end stage of AIDS.

It was reported that lower CD4 levels was associated with mortality in HIV/AIDS patients (21), but we failed to demonstrate the conclusion in our cohort. Luo et al. (22) reported that lower CD4 level was not a predictor for predicting mortality in HIV/AIDS patients with OIs in Shanghai, China. The phenomenon may be due to following reasons: First, the majority of patients had lower CD4 levels on admission, and some patients maybe had died prior to arriving at hospital. Our model indicated that CD4 < 100cells/µL was found in 71.4% of HIV/TB co-infected patients at end-stage of AIDS. Second was associated with inherent biases in studies based on retrospective and observational data. Third, Revimohan et al. (23) reported that, in HIV/TB co-infected patients, early immunologic response, but not pre-ART CD4 counts was associated with early mortality.

Pulmonary tuberculosis was the most common OI in HIV-infected patients at end stage of AIDS, but we did not find that it was an independent predictor of mortality in HIV-infected patients with end-stage of AIDS, which was consistent with some reports about risk factors of mortality in HIV/AIDS patients with OIs (22,24,25). In this study, all of patients were diagnosed as tuberculosis, in which 74.9% of patients had pulmonary tuberculosis, which may explain why it was not significant difference among those who were dead in this study. Although pulmonary tuberculosis was not an independent risk factor of mortality in HIV/TB co-infected patients at end stage of AIDS, TB was still an important OI and active TB screening was necessary for HIV-infected patients.

This clinical scoring model indicated several advantages: First, the model was constructed based on HIV/TB infected patients at end-stage of AIDS in China, which was currently the most predominant clinical characteristics in Chinese HIV/AIDS patients. Second, the model used randomized assignment from
large cohort of HIV/TB co-infected patients and received accurate assessment of different predictors. Third, 6 predictors used in the model were common in clinical practice, and model was easy to use in routine clinical practice without complicated calculation. Fourth, the model could help physicians determine the prognosis of HIV/TB co-infected patients, especially for end-stage AIDS patients with tuberculosis.

The study also had some limitations: First, there were potential inherent biases in a retrospective study. Second, the conclusion was made in single center, which should be further validated prior to be generalizable to different hospitals in China.

In conclusion, a clinical scoring model to assess the prognosis in HIV/TB patients at end stage of AIDS was constructed based on simple laboratory and clinical features available at admission, which may be an easy-to-use tool for physicians to evaluate the prognosis and treatment outcome in HIV/TB co-infected patients. The model was also applicable for predicting the death of end-stage HIV/TB patients within a 12 months period after discharge.

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References

1. WHO 2010. Global Tuberculosis Control. WHO report 2010. whqlibdoc.who.int/publications/2010/9789241564069_eng.pdf. (accessed December 15, 2018)
2. Xiao J, Gao G, Li Y, Zhang W, Tian Y, Huang Y, Su W, Han N, Yang D, Zhao H. Spectrums of opportunistic infections and malignancies in HIV-infected patients in tertiary care hospital, China. PLoS One. 2013; 8:e75915.
3. Toossi Z. Virological and immunological impact of tuberculosis on human immunodeficiency virus type 1 disease. J Infect Dis. 2003; 188:1146-1155.
4. Xiao J, Du S, Tian Y, Su W, Yang D, Zhao H. Causes of death among patients infected with HIV at a tertiary care hospital in China: An observational cohort study. AIDS Res Hum Retroviruses. 2016; 32:782-790.
5. Ji YJ, Liang PP, Shen JY, Sun JJ, Yang JY, Chen J, Qi TK, Wang ZY, Song W, Tang Y, Liu L, Zhang RF, Shen YZ, Lu HZ. Risk factors affecting the mortality of HIV-infected patients with pulmonary tuberculosis in the cART era: A retrospective cohort study in China. Infect Dis Poverty. 2018; 7:25.
6. Pefura-Yone EW, Balkissou AD, Poka-Mayap V, Fatime-Abuicho HK, Enono-Edende PT, Kengne AP. Development and validation of a prognostic score during tuberculosis treatment. BMC Infect Dis. 2017; 17:251.
7. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the centers for disease control and prevention, the National Institutes of Health, and the HIV Medical Association of the Infectious Diseases Society of America. Available: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. (accessed December 15, 2018)
8. Hoffmann C, Jurgen K. Eds., HIVBOOK2010. Medizin Fokus Verlag. 2010.
9. Zhang F, editor. National free HIV antiretroviral treatment handbook. 3rd ed. Beijing, China: People’s Medical Publishing House (Chinese). 2012. (in Chinese)
10. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; PneumoniaGuidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: Update 2009. Thorax. 2009; 64 Suppl 3:i1-15.
11. Nguyen DT, Graviss EA. Development and validation of a prognostic score to predict tuberculosis mortality. J Infect. 2018; 77:283-290.
12. Geng M, Li Y, Gao F, Sun L, Yang X, Wang R, Chen J, Zhang Q, Wan G, Wang X. A scoring model predicts hepatitis B e antigen seroconversion in chronic hepatitis B patients treated with nucleos(t)ide analogs: Real-world clinical practice. Int J Infect Dis. 2017; 62:18-25.
13. Robson SC, White NW, Aronson I, Woolgar R, Goodman H, Jacobs P. Acute phase response and the hypercoagulable state in pulmonary tuberculosis. Br J Haematol. 1996; 93:943-949.
14. Sudfeld CR, Isanaka S, Aboud S, Mugusi FM, Wang M, Chalamilla GE, Fawzi WW. Association of serum albumin concentration with mortality, morbidity, CD4 T-cell reconstitution among Tanzanians initiating antiretroviral therapy. J Infect Dis. 2013; 207:1370-1378.
15. Thao LTP, Heemskerk AD, Geskus RB, et al. Prognostic Models for 9-Month Mortality in Tuberculous Meningitis. Clin Infect Dis. 2018; 66:523-532.
16. Nguyen DT, Jenkins HE, Graviss EA. Prognostic score to predict mortality during TB treatment in TB/HIV co-infected patients. PLoS One. 2018; 13:e0196022.
17. Cox JA, Lukande RL, Lucas S, Nelson AM, Van...
Marck E, Colebunders R. Autopsy causes of death in HIV-positive individuals in sub-Saharan Africa and correlation with clinical diagnoses. AIDS Rev. 2010; 12:183-194.

18. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): A multicohort collaboration. Lancet. 2014; 384:241-248.

19. Wormal SW, Bower M, Reiss P, et al. Non-AIDS defining cancers in the D:A:D Study – time trends and predictors of survival: A cohort study. BMC Infect Dis. 2013; 13:471.

20. Ferrer M, Travierso C, Cillonz C, Gabarrus A, Ranzani OT, Polverino E, Liapkou A, Blasi F, Torres A. Severe community-acquired pneumonia: Characteristics and prognostic factors in ventilated and non-ventilated patients. PLoS One. 2018; 13:e0191721.

21. Álvarez Barreneche MF, Restrepo Castro CA, Hidrón Botero A, Villa Franco JP, Trompa Romero IM, Restrepo Carvajal L, Eusse Garcia A, Ocampo Mesa A, Echeverri Toro LM, Porras Fernández de Castro GP, Ramírez Rivera JM, Agudelo Restrepo CA. Hospitalization causes and outcomes in HIV patients in the late antiretroviral era in Colombia. AIDS Res Ther. 2017; 14:60.

22. Luo B, Sun J, Cai R, Shen Y, Liu L, Wang J, Zhang R, Shen J, Lu H. Spectrum of opportunistic infections and risk factors for in-hospital mortality of admitted AIDS patients in Shanghai. Medicine (Baltimore). 2016; 95:e3802.

23. Ravimohan S, Tamuhla N, Steenhoff AP, et al. Early immunologic failure is associated with early mortality among advanced HIV-infected adults initiating antiretroviral therapy with active tuberculosis. J Infect Dis. 2013; 208:1784-1793.

24. Pang W, Shang P, Li Q, Xu J, Bi L, Zhong J, Pei X. Prevalence of Opportunistic Infections and Causes of Death among Hospitalized HIV-Infected Patients in Sichuan, China. Tohoku J Exp Med. 2018; 244:231-242.

25. Shahrin L, Leung DT, Matin N, Pervez MM, Azim T, Bardhan PK, Helfelfinger JD, Chisti MJ. Characteristics and predictors of death among hospitalized HIV-infected patients in a low HIV prevalence country: Bangladesh. PLoS One. 2014; 9:e113095.

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