Predicting the Risk of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome in HIV-Infected Patients with Central Nervous System Tuberculosis

**Objective** — to identify risk factors associated with the development of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome (TB-IRIS) in HIV-infected patients with central nervous system tuberculosis. The analysis assessed the relationship between the risk of developing TB-IRIS with neurological manifestations and the following factors: 1) viral load before antiretroviral therapy (ART) initiation; 2) CD4⁺ lymphocyte of blood before ART initiation; 3) duration of antituberculosis therapy before starting ART; 4) presence of active tuberculosis at the time of ART initiation.

**Materials and methods.** 112 cases of neurological TB-IRIS were analyzed. These patients were treated and observed during the 1 year in anti-tuberculosis facilities in Kyiv and Kyiv region in 2017—2021. All patients received ART in accordance with the HIV treatment protocols adopted in Ukraine. Treatment according to the standard of tuberculosis treatment adopted in Ukraine. The logistic regression model construction method was used to analyze.

Statistical processing of the obtained data was carried out using free software — the EZR package (version 1.61; https://www.jichi.ac.jp/).

The study was carried out as part of the applied research work 0121U107800 «Predicting the development of the incidence of tuberculosis in Ukraine in connection with the COVID-19 pandemic», funded by the Ministry of Health of Ukraine.

**Results and discussion.** After calculations, two factor signs were identified, associated with the of developing TB-IRIS with neurological manifestations: the baseline level of CD4⁺ lymphocytes in 1 μl of blood at the beginning of treatment and the presence of active tuberculosis at the time of ART initiation.

**Conclusions.** It was found that the risk of developing TB-IRIS with neurological manifestations is significantly associated (p < 0.05) with the following factors: 1) the level of CD4⁺ lymphocytes in 1 μl at the beginning of treatment; 2) presence of active tuberculosis at the time of ART initiation.

**Keywords**
Tuberculosis, HIV, tuberculosis-associated immune reconstitution inflammatory syndrome, antiretroviral therapy.
TB-IRIS cases [2]. Mortality rates vary but range from 0—15 % for all forms of IRS [9], reaching 75 % in cases involving central nervous system (CNS) tuberculosis [7]. Additionally, TB-IRIS with neurological manifestations often leads to persistent disability [2].

Understanding key risk factors is crucial and greatly facilitates the diagnosis of TB-IRIS. The presence of infection in the body at the time of initial antiretroviral therapy administration in the setting of pronounced immunodeficiency increases the likelihood of TB-IRIS development. TB-IRIS is more frequently seen in young males. Different ART regimens have varying effects on the frequency of TB-IRIS occurrence. Genetic predisposition also plays a significant role [3].

Risk Factors for the Development of TB-IRIS in Order of Significance [3]:
- Active tuberculosis presence at the onset of ART.
- Severe immunosuppression.
- Simultaneous initiation (or a short time gap) of tuberculosis treatment and ART commencement.
- Social factors: drug addiction, alcoholism.
- Genetic predisposition.

Among the primary factors contributing to the development of TB-IRIS, the presence of localized or disseminated forms of active tuberculosis in patients starting ART is considered significant [1]. A substantially increased risk of TB-IRIS is associated with a low baseline CD4+ lymphocyte count (below 50 cells/μL) and a high baseline viral load (greater than 100,000 RNA copies/μL).

Objective — to identify risk factors associated with the development of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome (TB-IRIS) in HIV-infected patients with central nervous system (CNS) tuberculosis.

Materials and methods

The study was carried out as part of the applied research work 0121U107800 «Predicting the development of the incidence of tuberculosis in Ukraine in connection with the COVID-19 pandemic», funded by the Ministry of Health of Ukraine.

We conducted an analysis of 112 confirmed cases of central nervous system tuberculosis in HIV-infected patients who had recently (within 6 months) initiated ART.

All patients received treatment at tuberculosis facilities in Kyiv and the Kyiv region from 2017 to 2021.

All patients received ART according to established HIV treatment protocols.

Tuberculosis treatment was administered in accordance with the sensitivity of the pathogen to antituberculosis therapy, following tuberculosis treatment standards.

The outcome was considered negative if TB-IRIS with confirmed CNS tuberculosis developed in patients within 1 year from the start of ART.

Excluded from the study were cases where:
1) patients voluntarily discontinued ART or had ART discontinued for other reasons;
2) patients withdrew from the study (transferred);
3) patients died during the observation period from causes unrelated to HIV and TB (accidents, etc.).

For the analysis of risk factors associated with the development of CNS TB-IRIS, logistic regression models were constructed and analyzed. A multifactorial (four-factor) prediction model for assessing the risk of developing CNS TB-IRIS was developed.

Statistical data processing was performed using the free software package EZR [2] package (version 1.61; https://www.jichi.ac.jp/).

Results and discussion

To determine the relationship between the risk of developing TB-IRIS with central nervous system (CNS) tuberculosis, a multifactorial mathematical model of linear logistic regression was assessed and analyzed.

This model was constructed based on four factorial features:
1) viral load before initiating ART treatment (RNK HIV);
2) CD4+ lymphocyte count per microliter of blood before initiating ART treatment (CD4+);
3) duration of antituberculosis therapy before commencing ART (durationART);
4) presence or absence of active tuberculosis at the time of ART initiation (ActiTB).

The analysis was conducted on the results of examining 112 patients. When constructing the four-factor model, a dependency of the development of TB-IRIS with CNS tuberculosis on the specified factorial features was identified. The area under the ROC curve was 0.96 (95 % CI 0.914—1.000), which is statistically significant (p < 0.05) exceeding 0.5, indicating the adequacy of the constructed model (Fig. 1).

Table 1 presents the coefficients evaluation results of the model.

To select the minimal set of predictor variables related to the outcome variable, we used the Stepwise variable selection method and the Bayesian Information Criterion (BIC). After calculations, two predictor variables associated with the risk of fatal outcomes were identified:
1) CD4+ (baseline CD4+ lymphocyte count per microliter of blood at the beginning of treatment);
2) ActiTB presence of active tuberculosis at the time of ART initiation.
A logistic prediction model was constructed based on the selected predictor variables (the area under the ROC curve was 0.96, 95% CI 0.912—1.000), which is statistically significant (p < 0.05), exceeding 0.5, indicating the adequacy of the constructed model. When comparing the predictive characteristics of the two-factor model with the quality of the model built on five variables, no deterioration was observed.

Table 2 presents the results of the coefficients evaluation of the two-factor model.

Fig. 2 shows the ROC curve of the two-factor logistic regression model for predicting the risk of developing TB-IRIS with CNS tuberculosis.

**Conclusions**

Thus, it has been established that the risk of developing TB-IRIS with central nervous system tuberculosis is associated (p < 0.05) with the initial level of CD4+ lymphocytes in 1 μl of blood and the presence of active tuberculosis at the time of ART initiation. It has been found that the risk of developing TB-IRIS with central nervous system tuberculosis higher in patients with active tuberculosis at the time of ART initiation and a low level of CD4+ lymphocytes in 1 μl of blood.

References


Прогнозування ризику розвитку туберкульоз-асоційованого синдрому відновлення імунної системи з туберкульозним ураженням центральної нервової системи у ВІЛ-інфікованих пацієнтів

Мета роботи — виявити фактори ризику розвитку туберкульоз-асоційованого синдрому відновлення імунної системи (ТБ-СВІС) з туберкульозом ураженням центральної нервової системи у ВІЛ-інфікованих пацієнтів. Аналізувався зв’язок ризику розвитку ТБ-СВІС з неврологічними виявами та такими факторами: 1) вірусне навантаження перед початком антиретровірусної терапії (АРТ); 2) кількість CD4+ лімфоцитів перед початком АРТ; 3) тривалість протитуберкульозної терапії до початку АРТ; 4) наявність або відсутність активного туберкульозу на момент початку АРТ.

Матеріали та методи. Проаналізовано 112 випадків неврологічного ТБ-СВІС. Хворі проходили лікування та спостерігалися протягом 1 року в протитуберкульозних закладах м. Києва та Київської області у 2017—2021 рр. Усі пацієнти отримували АРТ згідно з прийнятими в Україні протоколами лікування ВІЛ-інфекції. Лікування туберкульозу проводили відповідно до прийнятого в Україні стандарту лікування туберкульозу. Для аналізу використана метод побудови моделі логістичної регресії. Статистичну обробку отриманих даних проводили за допомогою безкоштовного програмного забезпечення — пакета EZR (версія 1.61; https://www.jichi.ac.jp/).

Дослідження виконано в рамках прикладної науково-дослідної роботи 0121U107800 «Прогнозування розвитку захворюваності на туберкульоз в Україні у зв’язку з пандемією COVID-19», що фінансується МОЗ України.

Результати та обговорення. Після розрахунків виявлено дві факторні ознаки, пов’язані з розвитком ТБ-СВІС з неврологічними виявами: вихідний рівень CD4+ лімфоцитів в 1 мкл крові на початку лікування та наявність активного туберкульозу на момент початку АРТ.

Висновки. Встановлено, що ризик розвитку ТБ-СВІС з неврологічними виявами вірогідно пов’язаний (p < 0,05) з такими факторами: 1) рівнем CD4+ лімфоцитів у 1 мкл на початку лікування; 2) наявністю активного туберкульозу на момент призначення АРТ.

Ключові слова: туберкульоз, ВІЛ, туберкульоз-асоційований синдром відновлення імунної системи, антиретровірусна терапія.