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Original Article

Prevalence and risk factors associated with tuberculosis and HIV coinfection in Iran: A multivariate firth logistic regression for rare events

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Abstract

Introduction: Among the complications caused by HIV infection, tuberculosis (TB) is the most important challenge. The study aimed to determine the predictors of TB and HIV coinfection by using Firth logistic regression analysis.

Methodology: This cross-sectional study was conducted on 32,168 HIV-positive patients diagnosed in Iran. The required information was obtained from the national HIV/AIDS surveillance data.

Results: The prevalence of TB in HIV patients was 3.2%; the prevalence of TB in males and females was 944 (91.83%) and 84 (8.17%), respectively. Based on results of multivariate Firth logistic regression, male gender OR $_{male/female}$ = 1.91; injecting drug use (IDU) OR $_{YES/NO}$ = 1.46; illiterate or primary groups OR $_{illiterate\ or\ primary\ /university}$ = 2.23; high school group OR $_{high\ school/\ university}$ = 2.24 all increased the risk of TB and HIV coinfection ($p < 0.05$). Also, having CD4 > 500 [OR $_{CD4 > 500\ /\ < 200}$ = 0.39], CD4 351-500 [OR$_{351\ /\ < 200}$ = 0.65], and CD4 200-350 [OR$_{200\text{-}350\ /\ < 200}$ = 0.64] decreased the risk of TB and HIV coinfection ($p < 0.001$).

Conclusions: According to the results of this study, male gender, low education, injecting drug users, and low CD4 count at the time of diagnosis, were significant predictors of TB and HIV coinfection. Therefore, regular and periodic screening programs and linkage to the care and treatment of HIV patients need special attention.

Keywords: TB and HIV coinfection; Firth logistic regression; Iran.

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Introduction

The human immunodeficiency virus (HIV) remains a major global health challenge with 37.7 million infected people and approximately 1.5 million new infections in 2020 [1]. Despite the global decrease in the number of new HIV infections, in countries such as Iran, the rate of HIV infection is on the rise. According to the report of the National HIV Registration System in Iran, by the end of 2018, 38,966 people had been diagnosed with HIV [2]. Among the complications caused by HIV infection, tuberculosis (TB) is the most important challenge [1]. Tuberculosis is the leading cause of death among HIV-positive patients [3,4]. HIV/AIDS patients have a 3-15% annual risk of reactivation of latent tuberculosis infection, while the risk for the general population is only 0.1% [5]. In 2020, there were about 9.9 million cases of tuberculosis, with 13% coinfection of tuberculosis and HIV. Also, HIV is responsible for 215,000 cases out of the 1.5 million deaths caused by tuberculosis [6]. Therefore, the coinfection of HIV and tuberculosis each accelerates the progress of the other [6,7], and without proper treatment, almost all HIV-positive people with tuberculosis will die [6]. The results of studies indicate that some HIV-infected individuals get tuberculosis, while others do not. This idea suggests that being HIV positive is not the only cause of getting tuberculosis, and various determining factors play a role in its development [8,9]. Understanding the predictors of TB and HIV coinfection is critical to improve patient outcomes [10]. Few studies described the relationship between factors associated with TB and HIV coinfection although the results of the conducted studies showed that poverty, food insecurity,

malnutrition, cultural and religious issues, age, gender, and marital status are determinant factors of TB and HIV coinfection [11]. Therefore, this study aims to determine the prevalence and factors related to TB and HIV coinfection to improve the simultaneous management of infected patients.

Methodology

Study population

This cross-sectional study was conducted on 32,168 HIV-positive patients diagnosed in Iran from October 13, 1985, to June 23, 2016. The required information was obtained from the national system of management and care of HIV patients. In Iran, all patient care is done through harm reduction and counseling centers for behavioral diseases. In these centers, patient information includes demographic data; periodic tests and visits by the doctor, including CD4, viral load, examination for tuberculosis and viral hepatitis, and recording of high-risk behaviors, including sexual contact, injecting drugs, and prison history, are recorded by the center's experts.

This information is sent online to the Center for Prevention and Control of Infectious Diseases of Iran through Data Management Software for counseling centers for behavioral disorders. This information is extracted into Excel format.

The dependent variable is defined as having a positive sputum smear test or a positive PCR. Factors such as age group, gender, education level, years of diagnosis, and high-risk behaviors including Injection Drug Users (IDUS), Heterosexual contact, Homosexual contact, The coinfection was determined by being born with HIV, having a spouse with high-risk behaviors,

Table 1. Prevalence of TB in HIV patients by characteristics of study population.

Characteristics of HIV Patients	TB		*p* value*
	No, N (%)	Yes, N (%)	
Gender			
female	4,954 (15.91)	84 (8.17)	**< 0.001**
male	26,186 (84.09)	944 (91.83)	
Age			
< 15	629 (2.36)	9 (0.88)	
16-30	8,938 (33.47)	301 (29.31)	
31-45	14,093 (52.77)	608 (59.20)	**< 0.001**
46-60	2,815 (10.54)	100 (9.74)	
> 60	230 (0.86)	9 (0.88)	
Years of diagnosis			
before 1995	250 (0.83)	0 (0)	
1996-1999	1,472 (4.90)	74 (7.2)	
2000-2003	4,724 (15.73)	196 (19.07)	**< 0.001**
2004-2007	9,003 (29.97)	276 (26.85)	
2008-2011	7,713 (25.68)	256 (24.90)	
2012-2016	6,875 (22.89)	226 (21.98)	
Education			
Illiterate or primary	8,064 (41.88)	390 (41.31)	
High school	10,347 (53.74)	538 (56.99)	**< 0.001**
University	842 (4.37)	16 (1.69)	
Injection Drugs users (IDU_S)			
No	9,746 (32.27)	192 (18.68)	**< 0.001**
Yes	20,455 (67.73)	836 (81.32)	
Heterosexual contact			
No	22,703 (75.17)	710 (69.07)	**< 0.001**
Yes	7,498 (24.83)	318 (30.93)	
Homosexual contact			
No	29,341 (97.15)	1,003 (97.57)	0.430
Yes	860 (2.85)	25 (2.43)	
Born with HIV			
No	29,708 (98.38)	1,019 (99.12)	0.061
Yes	489 (1.62)	9 (0.88)	
Having a spouse with high-risk behaviors			
No	27,450 (97.46)	1,007 (97.96)	0.319
Yes	715 (2.54)	21 (2.04)	
Having a HIV positive spouse			
No	27,667 (91.62)	977 (95.04)	**< 0.001**
Yes	2,531 (8.38)	51 (4.96)	
Baseline CD4			
< 200	3,837 (30.53)	366 (43.88)	
200-350	2,967 (23.61)	197 (23.62)	**< 0.001**
351-500	2,309 (18.37)	142 (17.03)	
> 500	3,456 (27.50)	129 (15.47)	

**p* value for chi-square test; *p* value less than 0.05 considered as significant.

having an HIV-positive spouse, and having a CD4 count at baseline.

Statistical analysis

In many clinical and medical studies, to model the factors affecting the binary dependent variable, logistic regression is usually used by maximum likelihood to estimate the regression coefficients. When applying logistic regression models to binary data in situations where the outcome is rare or sparse, conventional logistic regression based on standardized maximum likelihood estimation (MLE) faces several problems, including biased or infinite estimation of the regression coefficient and repeated failure of likelihood convergence due to isolation. Also, the Wald test and confidence intervals are usually incorrect. To overcome this problem, one of the suggested methods is the use of Firth logistic regression or penalized logistic regression. The penalized logistic regression allows for convergence to finite estimates in conditions of separation [12-14]. In the present study, the total prevalence of TB and HIV co-infection was 3.2%; therefore, it is considered a rare event, and Firth logistic regression was used to assess the relationships of factors that predict the prevalence of TB and HIV co-infection. To report the relationship, a multivariate Firth logistic regression odds ratio (OR) and 95% confidence interval (CI) were used. The patients' characteristics were described as frequency and percentage for qualitative variables. The chi-square test was used for the assessment of the relationships. Variables with a significant level of less than 0.20 enter into the multiple Firth logistic regression model. The significance level was set at $\alpha = 0.05$ for all tests.

Results

A total of 32,168 HIV patients were included in the study; of them, 1027 had TB. The total prevalence of TB in HIV patients was 3.2% [95% confidence interval (3-3.39)], and the prevalence of TB in males and females was 944 (91.83%) and 84 (8.17%), respectively. The highest prevalence of TB in HIV patients was 608 (59.20%) in the 31-45 age group, and the lowest was 9 (0.88%) in the < 15 years and > 60 years age groups. Based on the year of diagnosis, the highest prevalence of co-infection was 276 (26.85%) during the years 2007-2004, and the lowest was (0%) before 1995. Based on education levels, in illiterate or primary, high school, and university groups, this prevalence was 390 (41.31%), 538 (56.99%), and 16 (1.69%), respectively. The prevalence of co-infection in IDU_S, heterosexual contact, homosexual contact groups, and patients that were born with HIV was 836 (81.32%), 318 (30.93%), 25 (2.43%), and 9 (0.88%), respectively. In terms of CD4 count at the baseline, the prevalence of TB and HIV co-infection in patients with CD4 was less than 200 cells/μL, 366 (43.88%), in patients with CD4 between 200-350 cells/μL, 197 (23.62%), in patients with CD4 between 351-500 cells/μL, 142 (17.03%), and in patients with CD4 > 500 cells/μL was 129 (15.47%). Other descriptive information is reported in Table 1.

The result of multivariate Firth logistic regression for the association between prognostic factors and TB and HIV coinfection:

The adjusted Firth logistic regression model for the association between the prognostic factors and TB and HIV coinfection is presented in Table 2. According to the Chi-square test results presented in Table 1, age, sex, education level, years of diagnosis, IDUs, heterosexual contact, born with HIV, having an HIV-positive spouse, and baseline CD4 were significant prognostic factors for TB and HIV coinfection ($p < 0.05$). In addition, the multiple Firth logistic regression results showed male patients [$OR_{male/female} = 1.91$, 95% CI = 1.33–2.74, $p < 0.001$] were at a higher risk of TB and HIV coinfection than females.

In terms of education level, illiterate or primary groups ($OR_{illiterate\ or\ primary\ /university} = 2.23$, 95% CI = 1.29–3.84, $p = 0.004$) and high school group ($OR_{high\ school/university} = 2.24$, 95% CI = 1.31–3.84, $p = 0.003$) were at a higher risk of TB and HIV coinfection than those who have a university degree. The risk of TB and HIV coinfection for IDU_s was higher in patients who were not IDU ($OR_{YES/NO} = 1.46$, 95% CI = 1.15 - 1.86, $p = 0.001$).

In terms of the baseline CD4 count cells/μL, patients with CD4 > 500, [$OR_{CD4 > 500/ < 200} = 0.39$, 95% CI = 0.31 - 0.48, $p < 0.001$], patients with a CD4 between 351-500 [$OR_{351/<200} = 0.65$, 95% CI = 0.53 - 0.80, $p < 0.001$], and those with a CD4 between 200-350 [$OR_{200\text{-}350/<200} = 0.64$, 95% CI = 0.53 - 0.77, $p < 0.001$] had a lower risk of TB and HIV coinfection than those with a CD4 less than 200. In other words, by increasing the amount of CD4 at the time of diagnosis, the risk of TB and HIV coinfection decreases significantly.

Discussion

This study was conducted on national HIV/AIDS surveillance data between October 13, 1985, and June 23, 2016, to determine the prevalence of TB and HIV coinfection and its related factors by using Firth logistic regression.

In people with HIV infection, as the immune response to mycobacterium infection is weakened, the incidence of tuberculosis also increases [6]. According to the World Health Organization, about 45% of HIV-negative people with tuberculosis and almost all HIV-positive people with tuberculosis have a high risk of mortality without proper treatment [15]. Co-infection with HIV and TB has been described as a lethal combination [16]. These results obtained from the studies led to updating the HIV/TB treatment approach in 2012 by WHO; Placement of HIV-infected individuals on preventive TB treatment after confirmation of TB status regardless of CD4 cell count. This allows such cases to be quickly identified and treated appropriately [17].

In the present study, the prevalence of co-infection with HIV and TB was 3.2%. The findings of this study are slightly lower compared to studies conducted in Ethiopia (7.5%) [18], Nigeria (7.8%) [7], and Tanzania (8.5%) [19]. Also, the prevalence reported in the studies of India [20] and Nigeria [21] was 34.4% and 32.8%, respectively.

These changes may be partially due to reasons such as the coverage level of antiretroviral therapy with high activity, less reporting, differences in TB diagnosis, study method used, and the epidemiology of TB disease in different countries [22]. However, this difference could be explained by the fact that this study considered only pulmonary TB but no other forms of TB. Based on the results, there is a relationship between the male gender and the coinfection of HIV and tuberculosis. Social behavior and hormonal differences between men and women are potentially important reasons for the greater influence of men than women, which has been confirmed by several studies [23-26]. Also, some studies [27,28] contradict this finding. In this study, the age group of 31-45 years and then 16-30 years had the highest percentage of co-infection with HIV / TB although this finding was not statistically significant [1]. These age groups are very active both in terms of job and sex. Because they are more involved in human interactions, they are more likely to be more vulnerable to infections than other groups. It is worth mentioning because these age groups economically have the highest

Table 2. Multivariate Firth logistic regression for assessing factors associated with tuberculosis and HIV coinfection in Iran.

Characteristics of HIV Patients	Adjusted Odds Ratio (AOR)	%95 CI for AOR	*p* value
Gender			
female	1	-	**-**
male	1.91	1.33 to 2.74	**< 0.001**
Age			
< 15	1	-	-
16-30	2.35	0 .14 to 38.87	0.549
31-45	2.65	0 .16 to 43.67	0.495
46-60	2.48	0 .14 to 41.12	0.526
> 60	2.85	0.15 to 53.32	0.483
Years of diagnosis			
before 1995	1	-	-
1996-1999	2.32	0 .12 to 43.86	0.573
2000-2003	1.80	0 .09 to 33.62	0.691
2004-2007	0 .75	0.04 to 14.03	0.851
2008-2011	0 .70	0 .03 to 13.13	0.817
2012-2016	0 .68	0 .03 to 12.67	0.798
Education			
University	1	-	-
High school	2.24	1.31 to 3.84	**0.003**
Illiterate or primary	2.23	1.29 to 3.84	**0.004**
Injection Drugs users (IDUs)			
No	1	-	-
Yes	1.46	1.15 to 1.86	**0.001**
Heterosexual contact			
No	1	-	-
Yes	0 .89	0.76 to 1.05	0.185
Born with HIV			
No	1	-	-
Yes	2.87	0 .16 to 51.17	0.471
Having a HIV positive spouse			
No	1	-	-
Yes	0 .90	0 .59 to 1.39	0.659
Baseline CD4			
< 200	1	-	-
200-350	0.64	0 .53 to 0 .77	**< 0.001**
351-500	0.65	0 .53 to 0.80	**< 0.001**
> 500	0.39	0.31 to 0.48	**< 0.001**

socioeconomic production. As a result, if more effective action is not taken to deal with public health emergencies quickly, it will lead to significant economic losses [29].

The results showed that a lower percentage of people with higher education are infected with HIV and tuberculosis at the same time, which is consistent with the studies [10,30,31]. However, the results of studies [18,32] showed that there is no relationship between education and HIV and TB co-infection.

The results showed that HIV and TB coinfection were more prevalent in people with a CD4 count of fewer than 200 cells/μL. This finding is consistent with studies [7,10,18,33-35]. The lower the number of CD4 cells, the weaker the immune system, which is a good indicator for monitoring the health of the immune system in HIV patients. HIV patients with lower CD4 cell counts are at higher risk of opportunistic infections. Tuberculosis is the most important opportunistic infection during immune system suppression. [3] Similarly, abnormal radiographic manifestations of pulmonary tuberculosis are more common in AIDS patients with CD4 counts of less than 200 [36].

Studies have pointed to the fact that CD4 cell counts are lower among patients with co-infection compared to patients infected with HIV alone, resulting in more significant immunosuppression. Treatment of TB has a positive effect on CD4 counts [37]. Based on the results of the studies, the Directly Observed Therapy Short course (DOTS) program effectively prevents the emergence of multi-drug-resistant tuberculosis [38]. In this study, injecting drug addicts had a high risk of TB and HIV coinfection. For justification of this, it should be mentioned that in Iran, the common route of HIV transmission is needle-sharing, which is prevalent among injection drug users, and in this study, 21,291 (68.18%) of the HIV patients were in this group. Also, in a study conducted in Iran, about 50% of injecting drug users diagnosed with HIV were linked to HIV care services [39,40].

Limitations and Strength points

Due to the unavailability of information about extrapulmonary tuberculosis, we could not investigate this issue in this study. The use of national HIV/AIDS surveillance data with a sufficient sample size also requires the use of an appropriate model (Firth logistic regression for rare events) for data analysis.

Conclusions

According to the results of this study, male gender, low education, injecting drug users, and low CD4 count at the time of diagnosis were significant predictors of TB and HIV coinfection. Therefore, regular and periodic screening programs and their linkage to the care and treatment of HIV patients need special attention.

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Authors' contributions

MSh: final analysis, providing the main idea of the study, and methodology; AM: final analysis, developing the idea, and revising the final manuscript; JH: developing the idea and revising the final manuscript; MS: data analysis. All the authors approved the final version of the manuscript.

Availability of supporting data

The data that support the findings of this study are available from the Center for Infectious Disease Control and Prevention (CDC) in Iran but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding authors upon reasonable request and with permission of the CDC of Iran.

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1400.045). Informed consent was waived by the Research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1400.045). The study was done in accordance with the Declaration of Helsinki and the Strengthening of the Reporting of Observational Studies in Epidemiology (STORB) guidelines.

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