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Association of Immune Factors with Drug-Resistant Tuberculosis: A Case-Control Study

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Statistical Analysis C
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Background: Presently, studies of factors associated with drug-resistant tuberculosis (TB) focus on patients' socio-demographic characteristics and living habits, to the exclusion of biochemical indicators, especially immune factors. This study was carried out to determine whether immune factors are associated with drug-resistant TB.

Material/Methods: A total of 227 drug-resistant pulmonary TB patients and 225 drug-susceptible pulmonary TB patients were enrolled in this study. Information on socio-demographic characteristics and biochemical indicators were obtained through their clinical records. Non-conditional logistic regression was used to analyze the association of these indicators with drug-resistant TB.

Results: There were significant differences in re-treatment, marital status, alanine aminotransferase (ALT), blood uric acid (BUA), carcino-embryonic antigen (CEA), T-spot, and CD3 and CD4 counts between the 2 groups. In multivariable analysis, re-treatment [Odds Ratio (OR)=5.290, 95% Confidence Interval [CI]=2.652–10.551); CD3 (OR=1.034, 95% CI=1.001–1.068); CD4 (OR=1.035, 95% CI =1.001–1.070) and IgM (OR=1.845, 95% CI=1.153–2.952) were associated with drug-resistant TB.

Conclusions: These results suggest the need for greater attention to re-treatment cases and immune function when treating drug-resistant TB.

MeSH Keywords: **Drug Resistance, Bacterial • Immunity, Cellular • Retreatment • Tuberculosis, Pulmonary**

Abbreviations: **TB** – tuberculosis; **MDR-TB** – multidrug-resistant tuberculosis; **XDR-TB** – extensively drug-resistant tuberculosis; **HIV** – Human Immunodeficiency Virus; **DST** – drug susceptibility test; **OR** – odds ratio; **CI** – confidence interval; **LJ** – Lowenstein-Jensen; **MTB** – *Mycobacterium tuberculosis*

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Background

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. Thus, the continued spread of multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR-TB) poses a major threat to global TB control. According to the Global Tuberculosis Control Report 2016 [1], an estimated 1.4 million people died of TB in 2015. Moreover, the number of people with new MDR-TB in 2015 was 480 000. China has the world's second largest TB epidemic. A recent meta-analysis [2] indicated that the prevalence of MDR-TB in new cases and in previously treated cases in mainland China were 4.8% and 26.3%, respectively. These data underscore the importance of TB prevention and control and the need to study factors involved in drug-resistant TB.

Previous studies reported that age and history of previous anti-TB treatment were significantly associated with drug-resistant TB [3,4]. Studies have also indicated that employment status, educational background, income level, presence of TB patient in the house, low socio-economic status, and alcohol abuse are risk factors associated with MDR-TB [5–7]. Other independent risk factors include Human Immunodeficiency Virus (HIV) infection, history of imprisonment, immigrant status, high load of positive acid-fast bacillus smear, disability sufficient to prevent work, and smoking [8–10]. In addition, compared to normal and overweight individuals, people in poor nutritional status have poor immune function [11] and higher susceptibility to MDR-TB [12]. However, these factors are socio-economic, demographic, and lifestyle determinants. It is possible that other factors, such as biochemical indicators, may be associated with drug-resistant TB.

A recent study showed that CD4+ T cells from MDR-TB patients infected with MDR Haarlem strains show higher IL-17+ IFN-γ- and lower IL-17+ IFN-γ+ levels than LAM-infected patients [13]. In addition, the high prevalence of drug-resistant TB among AIDS and diabetes patients suggest that there might be some correlation between poor immune function and drug-resistant TB [14,15]. It has been reported that decreased levels of CD4, CD3/HLA-DR+, and Fas + T cells, and increased levels of NKT and γδ T cells can be used to distinguish between MDR-TB patients and drug-sensitive TB patients [16]. However, the study did not evaluate the influence of the patients' socio-demographic characteristics, living habits, and other potential factors affecting drug-resistant TB. Thus, there is limited information on the relationship between immune function and other associated factors with drug-resistant TB.

The present investigation was conducted to evaluate the association of socio-demographic characteristics, immune factors, and some biochemical factors with drug-resistant TB.

Material and Methods

Study subjects

This study was designed as a case-control investigation. Based on the results of first-line anti-tuberculosis drug-sensitive test *in vitro* chemotherapy sensitivity test (isoniazid, rifampicin, streptomycin, and ethambutol) on pulmonary TB patients in Nanjing chest hospital from January 2013 to December 2013 in Nanjing, China, 227 drug-resistant TB patients were enrolled in the case group, while 225 drug-susceptible TB patients were randomly assigned to the control group. None of the participants had any of the following conditions: (1) history of liver dysfunction, (2) tumor history, and (3) HIV infection. The subjects were matched for age and sex with controls, so these factors were comparable between the 2 groups.

This study was strictly carried out in compliance with the Declaration of Helsinki of the World Medical Association, and the protocol was approved by the Medical Ethics Committee of Wannan Medical College (Permission No. 2014005). All participants were informed about the objectives of this study and provided verbal informed consent before the survey.

Data collection methods

Age, sex, marital status, smoking, drinking, and history of previous treatment for TB were obtained routinely for each patient by interview on admission to the hospital. The data were obtained before treatment from the clinical record after the patients were discharged. These data included clinical characteristics, biochemical indicators, DST, diabetes mellitus, and other associated indicators. Patients with HIV infection were excluded after HIV antibody screening.

Indicators of hepatic and renal dysfunctions were aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), albumin (Alb), total bilirubin (TBIL), blood urea nitrogen (BUN), creatinine (Cre), and blood uric acid (BUA). CA125, AFP, CA199, and carcino-embryonic antigen (CEA) were used as tumor biomarkers. All biochemical assays were performed with an automatic biochemical analyzer (DPP-800, Roche, Germany). Indicators of anti-TB antibody were TB, LAM, 16KD, 38KD, and T-spot and were measured by Dot Immunogold Filtration Assay (DIGFA). Immunological indicators contained CD3, CD4, CD8, IgG, IgA, IgM, C3, and C4, and were assayed by flow cytometry instrument testing technology of the United States BD Company and immune turbidimetric method.

Drug susceptibility test (DST)

DST was conducted for all participants before treatment and was done by proportion method. Sputum samples were cultured and

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Table 1. Demographic characteristic between cases and controls.

Characteristics		Cases (n=227)		Controls (n=225)		χ^2/z	P
Sex	Male	154	(67.84)	157	(69.78)	0.20	0.657
	Female	73	(32.16)	68	(30.22)		
Age-group*	<20	11	(4.85)	13	(5.78)	0.51	0.612
	20~30	42	(18.50)	55	(24.44)		
	30~40	31	(13.65)	15	(6.67)		
	40~50	49	(21.59)	31	(13.78)		
	≥50	94	(41.41)	111	(49.33)		
Marital status	Single	50	(22.03)	64	(28.44)	16.56	<0.001
	Married	168	(74.01)	132	(58.67)		
	Divorced or widowed	9	(3.96)	29	(12.89)		
Smoking	Yes	64	(28.19)	55	(24.44)	0.82	0.366
	No	163	(71.81)	170	(75.56)		
Drinking	Yes	33	(14.54)	25	(11.11)	1.19	0.276
	No	194	(85.46)	200	(88.89)		
Census register	Local	122	(53.74)	128	(56.89)	0.45	0.501
	Non-local	105	(46.26)	97	(43.11)		
Retreatment	Yes	85	(37.44)	31	(13.78)	33.18	<0.001
	No	142	(62.56)	194	(86.22)		
Diabetes mellitus	Yes	49	(21.59)	43	(19.11)	0.43	0.514
	No	178	(78.41)	182	(80.89)		

* Age-group was analyzed by the Kruskal-Wallis method of nonparametric test.

isolated on Lowenstein-Jensen (LJ) culture media, which contained the anti-TB drugs isoniazide, rifampicin, streptomycin and ethambutol. The LJ culture media were incubated at 37°C for 4 weeks. Resistance was expressed as percentage of colonies that grew on the drug-containing media compared to those that were cultured on control media. Growth of colonies in the drug-containing plate was compared to that on the control plate and expressed as a proportion. If the bacterial growth on the media with the specific drug was ≥1% compared to the control, the strain was declared resistant to the specific drug. On the other hand, it was categorized as a sensitive strain if the growth rate was <1% relative to the control.

Definitions

MDR-TB refers to resistance to at least isoniazid and rifampicin [17].

Patients who had never taken anti-tuberculosis drugs or who had taken anti-TB drugs for less than 1 month were classified as initial treatment. Re-treatment refers to patients who had taken anti-TB drugs for 1 month or more, as well as relapsed and initial-treatment failure patients.

Statistical analysis

Statistical analyses were conducted with SPSS Version 18.0. Tumor markers CA125, AFP, CA199, and CEA were described by median, Q1 (the first quartile), and Q3 (the third quartile), due to their abnormal distribution. Differences in demographic characteristic between case and control groups were analyzed by chi-square test. Student's t-test was used to compare differences in hepatic function, renal function, and immunological indicators between the case and control groups. Differences in tumor and anti-TB antibody indicators between case and control groups were analyzed by Kruskal-Wallis method of nonparametric testing. Non-conditional logistic regression analysis was used for analysis of association with drug-resistant TB. *P* values <0.05 were considered as indicative of statistically significant differences.

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Table 2. The comparison of hepatic renal function between cases and controls.

Variables		Units	Cases	Controls	*t*	*P*
Hepatic function	AST	(U/L)	23.75±27.79	22.88±22.91	–0.36	0.716
	ALT	(U/L)	22.08±24.67	18.51±10.54	–2.01	0.046
	LDH	(U/L)	180.11±85.89	181.96±48.92	0.28	0.777
	Alb	(g/l)	38.56±5.50	38.38±6.01	–0.32	0.749
	TBIL	(μmol/L)	14.89±9.47	15.66±13.26	0.72	0.473
Renal function	BUN	(mmol/L)	5.13±2.36	5.30±2.15	0.79	0.432
	Cre	(μmol/L)	65.22±30.54	73.41±65.98	1.69	0.092
	BUA	(μmol/L)	312.10±138.40	277.76±124.77	–2.75	0.006

AST – aspartate transaminase; ALT – alanine aminotransferase; Alb – albumin; LDH – lactate dehydrogenase; TBIL – total bilirubin; BUN – blood urea nitrogen; Cre – creatinine; BUA – blood uric acid.

Table 3. The comparison of tumor biomarkers and anti-tuberculosis antibody between cases and controls.

Variables	Units	Cases		Controls		*z*	*P*
CA125*	U/ml	45.40	(22.98, 109.50)	45.40	(26.01, 101.20)	–0.19	0.848
AFP*	μg/l	1.29	(0.81, 1.90)	1.28	(0.73, 2.01)	0.15	0.885
CA199*	U/ml	9.34	(5.01, 15.33)	9.09	(5.86, 14.73)	0.21	0.832
CEA*	μg/l	2.10	(1.31, 3.40)	2.48	(1.55, 3.57)	–2.18	0.029
TB (+)#		173	(39.41)	168	(38.27)	0.17	0.868
LAM (+)#		160	(36.45)	162	(36.90)	–0.54	0.590
16KD (+)#		31	(7.06)	40	(9.11)	–1.44	0.150
38KD (+)#		157	(35.76)	160	(36.45)	–0.60	0.547
T-spot (+)#		62	(15.05)	82	(19.90)	–3.61	<0.001

* The indicators were described by M (Q1, Q3); # The indicators were described by constitution ratio (%).

Results

Demographic characteristics of study subjects

The demographic characteristics of the study population are depicted in Table 1. There were no significant differences in sex and age between the case and control groups. In terms of marital status, there were significant differences between the 2 groups (χ^2=16.52, p<0.001; χ^2=33.18, p<0.001, respectively). However, there were no significant differences in other characteristics between case and control groups.

Hepatic and renal functions in case and control groups

Table 2 shows that there were significant differences in ALT and BUA between the case and control groups (t=–2.01, p=0.046; t=–2.75, p=0.006, respectively). Other indicators of hepatic and renal functions did not differ significantly between the case and control groups.

Tumor biomarkers and anti-TB antibody indicators in the case and control groups

There were significant differences in CEA and T-spot between the case and control groups (z=–2.18, p=0.029; z=–3.61, p<0.001, respectively); but there were no significant differences in other tumor biomarkers and anti-TB antibody indicators between the 2 groups (Table 3).

Immunological indicators in the case and control groups

Table 4 shows that there were significant differences in CD3 and CD4 counts between the case and control groups (t=–2.34, p=0.020; t=–2.43, p=0.016, respectively). However, there were

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Table 4. The comparison of immunological indicators between case and control groups.

Variables	Units	Cases	Controls	*t*	*P*
CD3	%	67.96±9.39	65.25±10.47	–2.34	0.020
CD4	%	37.46±10.93	34.62±8.89	–2.43	0.016
CD8	%	28.04±10.19	27.73±9.53	–0.27	0.786
IgG	g/l	13.56±3.86	13.94±3.71	0.99	0.324
IgA	g/l	2.78±1.30	2.81±1.34	0.22	0.828
IgM	g/l	1.29±0.77	1.16±0.58	–1.94	0.054
C3	mg/dl	1.18±0.26	1.14±0.27	–1.46	0.146
C4	mg/dl	0.24±0.09	0.25±0.13	0.64	0.523

Table 5. Multivariate Logistic regression analysis on factors associated with drug resistant tuberculosis*.

Factors	B	S.E.	Wald χ^2	OR	95%CI	*P*
Retreatment	1.666	0.3523	22.362	5.290	2.652–10.551	<0.001
CD3	0.033	0.0167	3.997	1.034	1.001–1.068	0.046
CD4	0.034	0.0171	4.027	1.035	1.001–1.070	0.045
IgM	0.613	0.2398	6.522	1.845	1.153–2.952	0.011

* Drug resistance as dependent variable: drug resistance=1, drug susceptible=0.

no significant differences in other immunological indicators between the 2 groups.

Multivariate logistic regression analysis of association with drug-resistant TB

Multivariate logistic regression analysis showed that re-treatment (OR=5.290, 95% CI 2.652–10.551); CD3 (OR=1.034, 95% CI 1.001–1.068); CD4 (OR=1.035, 95% CI 1.001–1.070); and IgM (OR=1.845, 95% CI 1.153–2.952) were associated with drug-resistant TB (Table 5).

Discussion

In this study, multivariate logistic regression analysis showed that re-treatment was related to drug-resistant TB. This is consistent with the reports of Liang et al. [18] and Kliman et al. [19]. Re-treatment TB is easily resistant to first-line anti-TB drugs (e.g., isoniazid), and about one-third of re-treatment TB cases become MDR-TB at the initiation of re-treatment [20]. Moreover, previous treatment history is a major contributing factor to MDR-TB: patients with previous treatment history have a more than 5- to 7-fold increased risk of MDR-TB when compared to previously untreated TB patients [4,21]. Therefore, to establish feasible and safe re-treatment regimens, it is important to know the history of re-treatment patients, and to conduct drug susceptibility testing as early as possible.

T cell-mediated immune responses directed against *Mycobacterium tuberculosis* (MTB) are important for effective pathogen containment. Most important T cell subsets, such as CD4+ and CD8+ T cells, play crucial roles in MTB containment by cytokine production or direct cytotoxicity [22,23]. The combination of CD4 and CD8 T cell responses accurately discriminates between active TB and latent infection [24]. Studies have shown that the absolute numbers and percentages of CD3 and CD4 in patients with pulmonary TB are lower than those in healthy controls [25]. In the present study, CD3 and CD4 were related to drug-resistant TB, and the MDR-TB patients had higher levels of CD3 and CD4. Geffner et al. demonstrated that CD4+ T cell levels were higher in MDR-TB patients than in drug-susceptible TB patients [26]. However, Yildiz et al. reported that the percentages of both CD3+ and CD3+CD4+ T lymphocytes were significantly lower in MDR-TB patients when compared with drug-susceptible TB patients [27]. The differences might be ascribed to severity of disease, association with diabetes mellitus, and different TB strains in different studies [26,28]. Moreover, during the advanced and/or chronic course of drug-resistant TB, the accumulated bacillary load probably induces continuous antigenic stimulation. Thus, dysregulation of homeostasis of T lymphocytes becomes persistent [29].

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Emerging evidence suggest a greater role for B cells and antibodies of humoral immune response against MTB [30,31]. This evidence, as well as the mechanisms of defense against MTB infection by B cells and antibodies, have been extensively discussed in several reviews [32,33]. The results of the present study indicate that IgM is associated with drug-resistant TB. Antibody production reflects the magnitude of infection. Indeed, it has been reported that antibody levels are higher and more frequent in multi-bacillary than in pauci-bacillary forms of the disease [34]. Studies have also shown that high bacillary count (3+) could be a marker of MDR-TB [35]. Therefore, drug-resistant TB patients are likely to have higher levels of antibody. However, further studies are needed to determine why only IgM is elevated in drug- resistant TB patients more than other antibodies. IgM is the first antibody to be synthesized and secreted in humoral immunity. It is possible that the patients in this study were at this stage of humoral immunity, hence the differences seen in antibodies. In addition, infection state (active TB versus LTBI), TB recurrence, and bacterial burden affect MTB antigen-specific IgG response, and probably also affect IgM response [36]. Factors such as individual genetic differences, nutritional status, and extent of disease may be responsible for the differences reflected in these results.

It is not clear whether alteration of immune factors is a cause or a consequence of drug resistance. Recently, a study suggested that the frequency of circulatory Treg, a subset of CD4+ T cells, was higher in active MDR-TB patients than in drug-susceptible TB patients, although the difference was not statistically significant [37]. However, after a 6-month anti-TB treatment, the frequency of Treg decreased to healthy control levels in both drug-susceptible TB and MDR TB patients [37]. Another study showed that isoniazid significantly reduced MTB antigen-specific immune responses by inducing apoptosis in activated CD4+ T cells [38]. This also demonstrates that drug resistance might lead to alteration in CD4+ T cells. Further studies are necessary to ascertain whether this conclusion is applicable to other immune indicators.

Study limitations

The present study had several limitations. In the first place, since it was carried out in a hospital, the validity of application of the results to populations in other settings may be limited. Secondly, it was a retrospective, case-control study based only on analyses of data on factors that were routinely recorded in the hospital. Thus, it was not possible to analyze other potential factors such as unemployment, income, education, treatment adherence, and imprisonment. Thirdly, data on CXR score was not included.

Conclusions

This study established an association between drug-resistant TB and IgM, CD3, and CD4. These findings strongly imply that successful control of drug-resistant TB requires greater attention to re-treatment pulmonary TB patients to ensure that they receive standard and regular treatment regimens. Moreover, greater emphasis should be placed on the immune function of TB patients when developing treatment regimens. For further studies, we should emphasize the pathways involved in the induction of Th cells and the relevance of improved diagnostic tools in MDR-TB patients.

Conflict of interests

None.

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