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Letter to the Editor

Serum IL-1β and IL-18 correlate with ESR and CRP in multidrug-resistant tuberculosis patients

Dear Editor:

The emergence of multidrug-resistant tuberculosis (MDR-TB) is bringing new challenges. MDR-TB is caused by *Mycobacterium tuberculosis (M. tuberculosis)* that is resistant to isoniazid and rifampicin, with or without resistance to other anti-tuberculosis drugs. Approximately 450,000 people developed MDR-TB worldwide in 2012 and an estimated 170,000 people died from the disease[1]. Bacterial burden is not strictly correlated with disease progression, and several hallmarks of severe tuberculosis suggest that insufficiently controlled inflammation plays an important role in pathogenesis[2]. It has been reported that nucleotide-binding and oligomerization domain (NOD) like receptor 3 (NLRP3) inflammasome and its cytokines IL-1β and IL-18 play a critical role in host defense and immunopathologic process in chronic *M. tuberculosis* infection *in vitro* and in animal models[3-5]. However, little is known about the role of NLRP3 inflammasome and IL-1β and IL-18 in MDR-TB patients. We determined serum IL-1β and IL-18 contents in drug-susceptible tuberculosis (DS-TB) and MDR-TB patients and investigated their relationships with disease severity in tuberculosis.

Written informed consent was obtained from all study participants, and the study was approved by the Research Ethics Committee of Nanjing Medical University (Nanjing, China). TB patients were recruited from Nanjing Thoracic Hospital from January to December 2014 as a subset of a multi-center study.

The baseline characteristics of 30 healthy control subjects, 35 DS-TB patients, and 30 MDR-TB patients are summarized in ***Table 1***. MDR-TB patients had more severe radiographic features than DS-TB patients ($P=0.01$). Serum ESR and CRP levels were significantly higher in TB patients than in healthy controls, and in MDR-TB patients than in DS-TB patients.

ELISA showed (***Fig. 1A***) that the levels of IL-1β in MDR-TB (7.48±3.58) were significantly higher than that in DS-TB patients (3.07±2.26). Meanwhile, serum IL-18 displayed the same trend, which was higher in MDR-TB patients (131.03±94.92) than DS-TB patients (94.28±57.10) and healthy controls (61.66±24.78) (***Fig. 1B***). To investigate whether serum IL-1β and IL-18 are related to radiographic severity, we stratified TB patients according to unilateral and bilateral lesions. In DS-TB patients, IL-1β (***Fig. 1C***) and IL-18 (***Fig. 1D***) were significantly higher in patients with bilateral lesion

Table 1 **Baseline characteristics of the study subjects**

Groups	HC ($n=30$)	DS-TB ($n=35$)	MDR-TB ($n=30$)	*P* value
Age (years), mean±SD	44.91±17.79	44.42±17.06	42.20±12.52	0.78
Gender, male/female	15/15	20/15	17/13	0.82
Radiographic severity				
Unilateral, *n* (%)	NA	13(37)	3(10)	
Bilateral, *n* (%)		22(63)	27(90)	0.01
ESR (mm/h), mean±SD	12.30±4.69	37.20±14.26	62.03±23.35	<0.01
CRP (mg/L), mean±SD	7.35±1.93	50.02±19.87	83.24±20.53	<0.01

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HC: healthy control; DS-TB: drug-susceptible tuberculosis; MDR-TB: multidrug-resistant tuberculosis. Differences between means were analyzed using Kruskal-Wallis Test for multiple comparisons. A Spearman's rank correlation analysis was performed to determine the relationship between cytokines and clinic indexes. Statistical significance was defined as $P<0.05$

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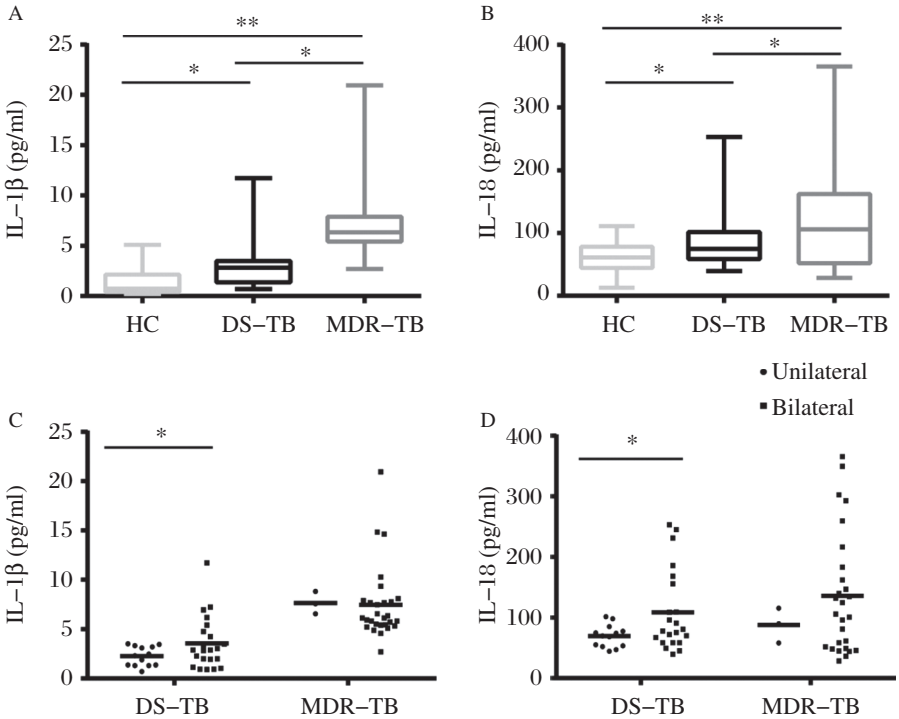

Fig 1. **Serum IL-1β and IL-18 levels in tuberculosis patients and healthy controls.** A: The levels of serum IL-1β was significant higher in TB patients than in healthy controls, and serum IL-1β was higher in MDR-TB than in DS-TB. B: The levels of serum IL-18 was highest in MDR-TB patients, and serum IL-18 was higher in DS-TB patients than in healthy controls. C: In DS-TB patients, the levels of IL-1β and IL-18 were significant higher in patients with bilateral lesion than those in patients with unilateral lesion. D: In MDR-TB patients, the differences of IL-1β or IL-18 between patients with bilateral lesion and unilateral lesion are not statistically significant. * $P<0.05$, ** $P<0.01$. DS-TB: drug susceptible tuberculosis; MRD-TB: multidrug-resistant tuberculosis.

subgroup than patients with unilateral lesion. No differences were observed in IL-1β or IL-18 between MDR-TB patients with bilateral and unilateral lesion. Then, we analyzed the relationships between IL-1β/IL-18 and ESR/CRP. As shown in ***Table 2***, there was no obvious correlation between IL-1β/IL-18 and ESR/CRP in healthy controls. However, both in DS-TB and MDR-TB patients, IL-1β positively correlated with ESR and CRP, and IL-18 also positively correlated with ESR and CRP.

Mounting evidence shows that NLRP3 inflammasome can be activated by *M. tuberculosis* in host immune cells. Our results showed that the circulating levels of NLRP3 inflammasome-mediated IL-1β and IL-18 in sera of pulmonary tuberculosis patients, especially in MDR-TB patients, are higher than those in healthy controls and positively correlate with radiographic severity and ESR and CRP. We observed that serum IL-1β is higher in pulmonary tuberculosis patients, especially in MDR-TB patients, than that in healthy controls. The concept that exuberant IL-1β responses are causatively associated with TB progression immunopathology and poor treatment outcome in humans[7] has been receiving more attention. It is reported that higher IL-1β did not suppress the activity of IFN-γ-producing T cells, but correlated with neutrophil accumulation in the lung[7]. It is also documented that high-IL-1β expressing genotype was associated with the severity of pulmonary disease[7] which is in accordance with our results.

In our study, IL-18 is also higher in MDR-TB than in DS-TB patients and healthy controls, which corroborates with previously published literatures that IL-18 concentration is significantly increased in TB patients with severe disease[8].

Table 2 **Correlations between IL-1β, IL-18 and ESR, CRP**

		ESR		CRP	
		r	*P*	*r*	*P*
HCs	IL-1β	0.294	0.114	0.094	0.620
	IL-18	0.275	0.142	0.153	0.418
DS-TB	IL-1β	0.782	<0.001	0.809	<0.001
	IL-18	0.855	<0.001	0.897	<0.001
MDR-TB	IL-1β	0.535	0.002	0.529	0.003
	IL-18	0.836	<0.001	0.833	<0.001

Differences between means were analyzed using Kruskal-Wallis Test for multiple comparisons. A Spearman's rank correlation analysis was performed to determine the relationship between cytokines and clinic indexes. Statistical significance was defined as $P<0.05$

Our results showed that serum IL-1β and IL-18 levels positively correlated with radiographic severity in DS-TB patients. However, in MDR-TB patients, the differences of IL-1β or IL-18 between patients with bilateral lesion and unilateral lesion were not statistically significant. We considered that it was due to that there were only 3 patients with unilateral lesion in MDR-TB group.

Raised ESR and CRP are indicative of infection and have been shown to be increased in TB patients. The plasma levels of ESR and CRP reflect the intensity of the pathological process[6]. In our present study, serum IL-1β and IL-18 levels are positively correlated to ESR and CRP in both DS-TB and MDR-TB patients. It suggests that IL-1β and IL-18 are involved in the immunopathologic progression in tuberculosis.

To our knowledge, this is the first study to examine the relationship between inflammasome-associated cytokines and disease severity markers in pulmonary tuberculosis, especially in MDR-TB patients. Our results demonstrate that elevated levels of serum IL-1β and IL-18 are positively correlated to disease severity. IL-1β and IL-18 may be promising therapeutic targets for adjuvant treatment of MDR-TB.

Yours Sincerely,

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