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ORIGINAL ARTICLE

Interleukin-33 as a Potential Diagnostic and Prognostic Factor in Human Brucellosis

Tielei Gao [1, *], Qingfeng Gao [2, *], Rui Wang [3], Zhe Chen [4]

[*] *These authors contributed equally to this work as first author*
[1] *Department of Forensic Medicine, Harbin Medical University, Harbin, China*
[2] *Department of Clinical Laboratory, Beidahuang Group General Hospital, Harbin, China*
[3] *Department of Prevention and Health Care, Heilongjiang Provincial Center for Disease Control and Prevention, Harbin, China*
[4] *Department of Infectious Diseases, Beidahuang Group General Hospital, Harbin, China*

SUMMARY

Background: **The balance between T-helper 1 (Th1) and T-helper 2 (Th2) cells plays an important role in the pathogenesis of brucellosis. Interleukin (IL)-33 induces the activation of Th2 cells while soluble suppression of tumorigenicity 2 (sST2) is a decoy receptor to antagonize the effect of IL-33. Herein, we aimed to identify whether plasma IL-33/sST2 levels could reflect the state of brucellosis and help to monitor the treatment.**
Methods: **A total of 78 patients were recruited and divided into acute, subacute, and chronic groups. The chronic group was further divided into chronic active brucellosis and chronic stable brucellosis according to the clinical manifestation. Twenty-six volunteers were assigned to the healthy control (HC) group. Plasma IL-33/sST2 levels were detected by enzyme linked immunosorbent assay (ELISA) and other routine laboratory parameters were obtained from the clinical central laboratory.**
Results: **The level of IL-33 in acute (49.48 ± 18.92), subacute (41.35 ± 17.12), chronic active (44.99 ± 16.80), and the chronic stable (28.92 ± 13.12) groups were higher than that in the HC group (11.66 ± 3.26) ($p < 0.001$). The IL-33 level in the acute group decreased significantly after treatment (49.48 ± 18.92 vs. 29.89 ± 12.92) ($p < 0.001$). Furthermore, the IL-33 level in the chronic active group (44.99 ± 16.80) was higher than that in the chronic stable group (28.92 ± 13.12) ($p < 0.01$). Interestingly, IL-33 correlated with white blood cells (WBC) ($r = 0.268$, $p < 0.05$) and C-reactive protein (CRP) ($r = 0.272$, $p < 0.05$). The level of sST2 increased in the acute (3,717.76 ± 2,036.25), subacute (3,130.41 ± 1,931.71), chronic active (3,381.43 ± 1,394.83), and the chronic stable group (2,707.03 ± 1,260.26) groups compared with the HC group (297.76 ± 290.93) ($p < 0.001$). However, the sST2 plasma level showed no differences among the groups and did not significantly change after treatment in the acute group.**
Conclusions: **IL-33 can reflect the state of brucellosis and may be a potential biomarker for diagnosis and monitoring treatment for brucellosis.**
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Correspondence:
Zhe Chen
Department of Infectious Diseases
Beidahuang Group General Hospital
235th Ha-shuang Road
Nan-gang District Harbin, 150088
People's Republic of China
Phone: + 86 451-55197654
Fax: + 86 451-55197854
Email: 459790641@qq.com

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KEY WORDS

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INTRODUCTION

Brucellosis is an important zoonosis caused by *Brucella* spp. and remains a major health problem globally [1]. It can affect cattle, sheep, goats, and other livestock. Brucellosis is generally transmitted from animals to humans through direct contact with infected animals and con-

sumption of raw dairy products that contain the bacteria or infected meat from domestic livestock [2]. Brucellosis is a systemic disease, involving multiple organs and systems, with various clinical manifestations [3]. Typical clinical manifestations of the acute stage include fever, fatigue, and hyperhidrosis [4]. Osteoarticular involvement is the most common complication in the chronic stage [5]. The treatment of brucellosis still faces significant challenges. Eradicating *Brucella* with antibiotics remains challenging as it is an intracellular parasite [6]. Besides, untimely and irregular treatment often leads to chronic brucellosis, which becomes refractory brucellosis [3]. Therefore, judging the disease status of patients with brucellosis and evaluating treatment outcomes is critical.

Although the pathophysiological process of brucellosis is still elusive, immune factors are believed to play an important role in the pathogenesis of brucellosis [7-9]. As the hallmark of different immune states, the balance between T-helper 1 (Th1) and T-helper 2 (Th2) cells has been confirmed to be involved in *Brucella* infection [7,10]. In a previous study, Th1 cells secreted more pro-inflammatory cytokines, which played a pivotal role in resistance to brucellosis infection in the acute stage while Th2 cell immunity predominated in the chronic stage.

Interleukin (IL)-33 is a tissue-derived nuclear cytokine belonging to the IL-1 family [11]. IL-33 functions as an alarm to alert the immune system during tissue damage or cell injury [12]. In addition, IL-33 has been implicated in Th2 immune responses [13,14]. IL-33 can induce the expression of Th2 cytokines, such as IL-4, IL-5, and IL-13, and mediates strong chemotaxis of Th2 cells [15]. Extracellular IL-33 exerts its biological effects by binding to its receptors. Suppression of tumorigenicity 2 (ST2) is one of the receptors of IL-33. ST2 has two major forms: transmembrane ST2 (with transmembrane sequence), which is mainly expressed on Th2 cells and is an important effector of Th2 cell function [16] and soluble ST2 (sST2, without transmembrane sequence), which can be secreted out of cells [17]. sST2 can bind to IL-33 without activating intracellular signal transduction, hence, it can be used as a decoy receptor to antagonize the effect of IL-33 [18]. Mounting evidence shows that IL-33/sST2 signaling plays a critical role in both infectious and non-infectious diseases, such as tuberculosis, hepatitis, acquired immunodeficiency syndrome (AIDS), asthma, cardiovascular disease, Alzheimer's disease, etc. [19-24]. However, whether IL-33/sST2 pathway is involved in the pathogenesis of brucellosis remains elusive. Besides, previous studies have mainly focused on the relationship between inflammatory factors and brucellosis state [25, 26]. Herein, we investigated the plasma levels of IL-33 and sST2 in brucellosis patients. We also evaluated the ability of IL-33/sST2 to distinguish between acute, subacute, and chronic types of brucellosis and whether plasma levels of IL-33/sST2 can monitor the treatment of brucellosis.

MATERIALS AND METHODS

Ethics statement

The study protocol was approved by the Ethics Committee of the General Hospital of Heilongjiang Land Reclamation Bureau, Heilongjiang (Number: NKZYY-2017-009-KT). Informed written consent was obtained from all participants.

Study design and participants

This study recruited 78 brucellosis patients who were admitted to the Department of Infectious Diseases of the General Hospital of Heilongjiang Land Reclamation Bureau between October 2017 and May 2018. All cases were confirmed according to the diagnosis standard for brucellosis (WS269-2007) of the National Health Commission of the People's Republic of China. The diagnostic criteria were as follows: (i) *Brucella* species were isolated from blood cultures. (ii) The titer of the standard tube agglutination (STA) test was more than 1:100 or the titer of patients with a course of more than one year was more than 1:50, which were associated with corresponding clinical manifestations and contact history. The exclusion criteria were immunosuppressant patients and patients with tuberculosis, AIDS, hepatitis, and other serious diseases.

Patients were divided into three groups based on the course of the disease: acute group (less than 3 months), subacute group (3 - 6 months), and chronic group (more than 6 months). The chronic group was further divided into two subgroups according to the clinical manifestation: chronic active brucellosis and chronic stable brucellosis. There were 34 patients in the acute group (24 males and 10 females; aged 46.24 ± 10.60 years), 13 in the subacute group (9 males and 4 females; aged 44.85 ± 16.09 years), 14 in the chronic active group (10 males and 4 females; aged 47.71 ± 10.56 years), and 17 in the chronic stable group (16 males and 1 female; aged 50.66 ± 11.19 years). Twenty-six healthy volunteers (16 males and 10 females; aged 42.13 ± 13.52 years) were assigned to the HC group. The Rose-Bengal plate agglutination test was negative in the HC group. The exclusion criteria were similar to those of brucellosis patients.

Measurement of plasma levels of IL-33/sST2 and routine laboratory parameters

To detect the levels of IL-33/sST2 in plasma, 5 mL elbow vein blood was collected into a heparin sodium anticoagulant centrifuge tube after an overnight fast before any treatment. Furthermore, to compare the effect of antibacterial treatment on the level of IL-33/ sST2, 5 mL elbow vein blood samples were taken after treatment in the acute group. The blood sample was centrifuged at 3,000 rpm for 15 minutes after collection and immediately stored in liquid nitrogen until use. The human IL-33 ELISA kit and sST2 ELISA kit (BOSTER, China) were used to detect IL-33/sST2 level, according to the manufacturer's instructions. Other laboratory parameters were obtained from the blood samples at the same time points tested by the clinical central laboratory of the General Hospital of Heilongjiang

Table 1. Symptoms of the patients with brucellosis (n = 78).

Symptoms	Acute group	Subacute group	Chronic active group	Chronic stable group	Total
Fever, n (%)	30 (38.5)	11 (14.1)	10 (12.8)	2 (2.6)	53 (67.9)
Weakness, n (%)	26 (33.3)	12 (15.4)	14 (17.9)	12 (15.4)	64 (82.1)
Sweating, n (%)	19 (24.4)	4 (5.1)	11 (14.1)	2 (2.6)	36 (46.2)
Arthralgia, n (%)	24 (30.8)	12 (15.4)	14 (17.9)	16 (20.5)	66 (84.6)
Myalgia, n (%)	7 (9.0)	1 (1.3)	4 (5.1)	3 (3.8)	15 (19.2)
Chill, n (%)	3 (3.8)	1 (1.3)	-	-	4 (5.1)
Headache, n (%)	-	-	1 (1.3)	1 (1.3)	2 (2.6)
Back pain, n (%)	-	-	-	1 (1.3)	1 (1.3)
Testicular swelling and pain, n (%)	2 (2.6)	-	2 (2.6)	-	4 (5.1)

Table 2. Clinical findings and laboratory results in the patients with brucellosis (n = 78).

Clinical findings	Acute group	Subacute group	Chronic active group	Chronic stable group	Total
Fever (38ºC or higher), n (%)	21 (26.9)	7 (9.0)	9 (11.5)	1 (1.3)	38 (48.7)
Osteoarticular involvement, n (%)	5 (6.4)	5 (6.4)	4 (5.1)	6 (7.7)	20 (25.6)
Hepatomegaly, n (%)	3 (3.8)	-	2 (2.6)	-	5 (6.4)
Splenomegaly, n (%)	2 (2.6)	1 (1.3)	1 (1.3)	-	5 (6.4)
Lymphadenopathy, n (%)	4 (5.1)	-	2 (2.6)	-	6 (7.7)
Laboratory results					
WBC (x 1000/µL)	5.99 (2.35 - 18.35)	5.93 (1.72 - 9.66)	5.89 (3.48 - 12.06)	5.92 (3.74 - 9.62)	5.95 (1.72 - 18.35)
Platelet (cell × 10^9/mL)	234 (18 - 419)	239 (157 - 372)	195 (58 - 278)	246 (138 - 433)	230 (18 - 433)
AST (U/L)	39.8 (15.0 - 165.0)	28.2 (15.0 - 63.0)	25.2 (15.0 - 65.0)	22.1 (15.0 - 43.0)	31.4 (15.0 - 165.0)
ALT (U/L)	60.6 (12.0 - 278.0)	31.2 (9.0 - 89.0)	26.6 (12.0 - 52.0)	23.6 (10.0 - 70.0)	41.5 (9.0 - 278.0)
CRP (mg/L)	29.40 (3.03 - 126.0)	20.55 (3.03 - 113.0)	14.19 (3.03 - 81.12)	15.22 (3.03 - 111.79)	21.82 (3.03 - 126.0)
STA	1:800 (1:50 - 1600)	1:400 (1:50 - 800)	1:400 (1:50 - 1,600)	1:200 (1:50 - 1,600)	1:400 (1:50 - 1,600)
Blood culture positive, n (%)	17 (21.8)	4 (5.1)	2 (2.6)	-	23 (29.5)

Abbreviations: ALT - alanine aminotransaminase, AST - aspartate aminotransferase, CRP - C-reactive protein, STA - standard tube agglutination, WBC - white blood cell.

Land Reclamation Bureau. The parameters included blood cultures, STA levels, the white blood cell (WBC) count, platelet count, C-reactive protein (CRP), aspartate aminotransferase (AST), and alanine aminotransaminase (ALT).

Data analysis

SPSS version 19.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA) was used for all statistical analyses. Differences between the two groups were analyzed using Student's *t*-test. Differences between more than two groups were analyzed using the least significant difference (LSD) *t*-test. The association between IL-33 and sST2 and routine laboratory parameters was measured by Spearman's rank correlation. Continuous variables were described as the mean ± standard error. Categorical variables were expressed by counts and percentages. For all analyses, statistical significance was defined as $p < 0.05$.

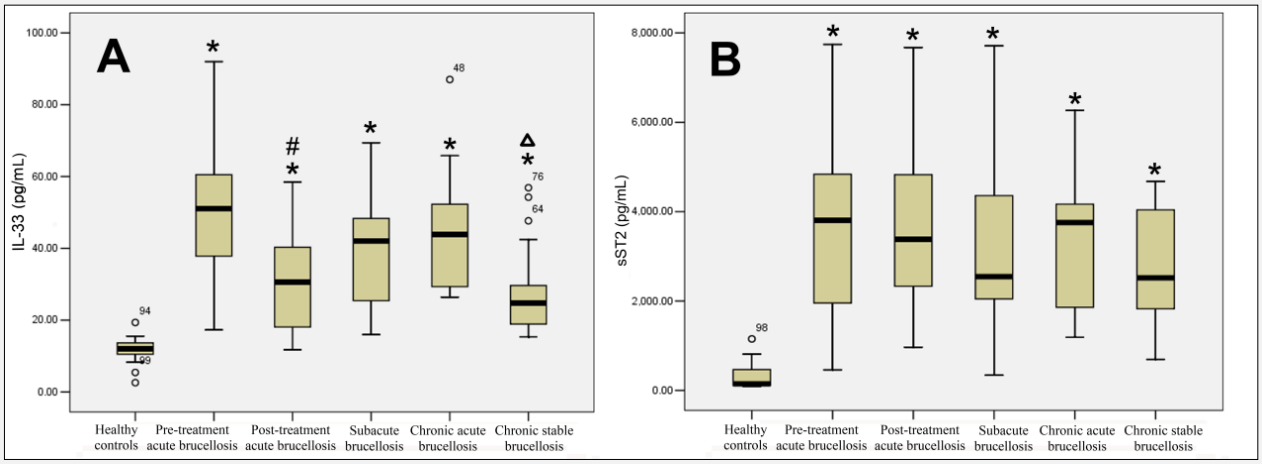

Figure 1. Box plot for IL-33 (pg/mL) and sST2 (pg/mL) levels in brucellosis patients and control subjects. * - p < 0.001, brucellosis cases versus healthy controls. # - p < 0.001, post-treatment group versus pre-treatment group. △ - p < 0.01, chronic stable group versus chronic active group.

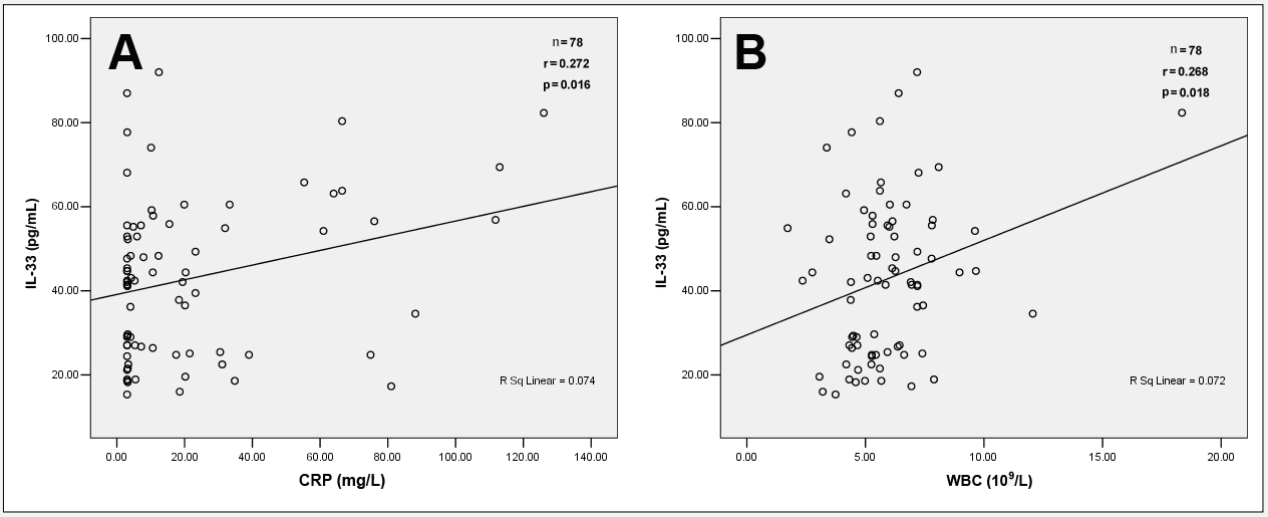

Figure 2. Correlation between plasma IL-33 and CRP levels or WBC in brucellosis patients (r = Pearson's correlation coefficient).

RESULTS

Clinical manifestations, clinical findings, and laboratory results are shown in Tables 1 and 2. The most common clinical manifestations were fever, weakness, sweating, and arthralgia. Most patients (48.7%) had a moderate and high fever (temperature > 38.0ºC). Among the 78 patients, 66 (84.6%) had joint pain and 20 (25.6%) had substantial lesions in the joints. A few patients had splenomegaly, hepatomegaly, and lymphadenopathy.

Occasionally, there were patients with myalgia, chills, headache, back pain, and testicular swelling and pain. The level of IL-33 was significantly higher in acute (49.48 ± 18.92), subacute (41.35 ± 17.12), chronic active (44.99 ± 16.80), and chronic stable (28.92 ± 13.12) groups than in the HC group (11.66 ± 3.26) ($p < 0.001$) (Figure 1A). In the acute group, the level of IL-33 in plasma significantly decreased after 60 days of standard antibacterial treatment (49.48 ± 18.92 vs. 29.89 ± 12.92) ($p < 0.001$), but it was still higher than that of the HC group (11.66 ± 3.26) ($p < 0.001$). The level of IL-33 was significantly higher in the chronic active group than in the chronic stable group (44.99 ± 16.80 vs 28.92 ± 13.12) ($p < 0.01$). Regarding plasma sST2 levels, the level of sST2 was significantly higher in the acute (3,717.76 ± 2,036.25), subacute (3,130.41 ± 1,931.71), chronic active (3,381.43 ± 1,394.83), and chronic stable (2,707.03 ± 1,260.26) groups compared with the HC group (297.76 ± 290.93) ($p < 0.001$) (Figure 1B). However, there was no significant difference between the chronic active group and the chronic stable group (3,381.43 ± 1,394.83 vs 2,707.03 ± 1,260.26) ($p > 0.05$). Furthermore, the standard antibacterial treatment did not significantly change the level of sST2 in the plasma in the acute group (3,717.76 ± 2,036.25 vs. 3,594.32 ± 1,679.81) ($p > 0.05$) (Figure 1B).

There was no difference in the plasma levels of IL-33/sST2 between patients of different ages or gender or between patients with positive blood culture and those with negative blood culture (data not shown). Moreover, there was no correlation between IL-33/sST2 and platelet count, AST, ALT, and STA levels. Similarly, there was no correlation between sST2 and WBC or CRP (data not shown). Interestingly, IL-33 correlated with CRP ($r = 0.272$, $p < 0.05$) and WBC ($r = 0.268$, $p < 0.05$), and the results were statistically significant (Figure 2).

DISCUSSION

To the best of our knowledge, this is the first study to detect the plasma IL-33/sST2 levels in patients with brucellosis, analyze the relationship between IL-33/sST2 levels and the disease status, and evaluate the value of IL-33/sST2 in monitoring the treatment of brucellosis.

The result showed that the level of IL-33 in the acute, subacute, and chronic groups was significantly higher than that in the HC group. To exclude the influence of drug treatment on the initial plasma level of IL-33, blood samples were taken before the treatment. Therefore, increased expression of IL-33 in plasma was due to brucellosis infection. IL-33 is highly expressed in endothelial cells and tissues [27]. In addition, some immune cells such as macrophages and dendritic cells can express high levels of IL-33 [28]. IL-33 is more strongly induced in activated macrophages, but not in resting macrophages [15]. After *Brucella* infects the human body, it is swiftly engulfed by macrophages, leading to the activation of macrophages; therefore, we speculated that activated macrophages might be an important source of IL-33 in the plasma of brucellosis patients. Increased plasma IL-33 concentration indicated that IL-33 was involved in the pathophysiological process of brucellosis. One of the main functions of IL-33 is to promote the transformation of Th2 cells and the secretion of related cytokines [14,29]. In addition, previous studies showed that Th1 cells were predominant in the acute stage of brucellosis whereas Th2 cells prevailed in the chronic stage [11]. Therefore, we speculate that IL-33 may be implicated in chronic brucellosis. It is noteworthy that the treatment of chronic brucellosis can be difficult.

Next, we evaluated whether effective antibacterial treatment would affect the level of IL-33. The results showed that the level of IL-33 in plasma decreased significantly in the acute stage group, after 60 days of standard antibacterial treatment. This was analogous to a previous study in which the levels of serum IL-33 significantly decreased after treatment in chronic hepatitis B (CHB) patients [30]. In the two subgroups of the chronic phase, the level of IL-33 in the chronic active phase group was significantly higher than that in the chronic stable phase group. Taken together, these results showed that IL-33 could not only reflect the therapeutic effect of drugs but also the state of disease. Therefore, IL-33 may be an important factor in determining the clinical course of the disease. Although the cause of IL-33 sensitivity to brucellosis remains vague, we speculate that IL-33 is related to the immune state of brucellosis in different stages. Further, our results showed that plasma IL-33 levels significantly correlated with WBC and CRP. WBC and CRP are classic indicators of the state of infection. Our results show that IL-33 may play a similar role to CRP in monitoring the immune state of the body.

The plasma level of ST2 in each brucellosis group was higher than that in the HC group. However, there was no statistically significant change in sST2 among brucellosis groups. In addition, no significant changes in sST2 levels were observed in the acute group before and after treatment. Therefore, sST2 is not a suitable biomarker for brucellosis.

Although our study is the first to evaluate changes in plasma levels of IL-33/sST2 in brucellosis patients, there are several shortcomings. First, although we infer that IL-33 may be related to the status of Th1 and Th2 cells, we have not further verified how IL-33 affects these cells. Second, the sample size included in this experiment is small and mainly from Northeast China. Therefore, these may lead to deviation of the results. Finally, the healthy volunteers are much younger than patients in this experiment; this may potentially influence the result.

In summary, IL-33 can reflect the state of brucellosis and may be a potential biomarker for diagnosis and monitoring treatment for brucellosis.

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Declaration of Interest:
The authors declare no conflict with respect to the financial interest.

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