

## Original Article

# Clinical and Para-Clinical Comparison of Complicated and Uncomplicated Brucellosis in Patients Referred to Imam Hossein Hospital since 2001 to 2017

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## Abstract

**Background:** Brucellosis is one of the most prevalent zoonoses, with an annual incidence of half a million cases globally. Most parts of Iran are endemic for Brucellosis. Given the worse prognosis, knowledge and early diagnosis of the complicated forms is especially important. The present study aimed to identify the clinical and paraclinical predictive alarms for complications in Brucellosis.

**Materials and Methods:** This study was done as a retrospective study on records of inpatients suffering active Brucellosis in Imam Hussein Medical Center, SBMU, Tehran in 15 years (2001 April-2016 March) as the census. Epidemiological, clinical, and laboratory data were collected in the formerly prepared questionnaire. According to their clinical and paraclinical findings, cases were studied in two groups: Complicated and Uncomplicated. All data were analyzed and compared using SPSS version 19.0 ANOVA and K<sup>2</sup> tests (P values < 0.05).

**Results:** In 95 patients suffering Brucellosis, 56 (59%) were male, and 39 (41%) were female. 69 (73%) cases were evaluated as uncomplicated, and 26 (28%) cases were as complicated. 11 (28%) of females and 20 (35%) male cases were complicated without significant statistical difference. Arthritis was the most common form, followed by the nervous system. The mean patient age was 35.46 ± 22.2 years, (ranging 1- 86) with no difference in two groups and different complications. The frequency of the previous history of Brucellosis and unpasteurized dairy product use was more common in complicated cases but was not significant. Myalgia (92% vs. 50%) and fever (50% vs. 9%) were significantly more common in complicated Brucellosis. Lab test results had no significant mathematical difference.

**Conclusion:** Myalgia and fever were significantly more common in complicated Brucellosis. There was no significant difference in other classical symptoms of Brucellosis as sweating, malaise, fatigue, and chills between the two groups and no significant difference in serologic tests titer and lab tests.

**Keywords:** Brucellosis, Diagnosis, Complication, Prediction

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## Introduction

Human Brucellosis is the most common bacterial zoonotic infection globally, with more than half a million new cases annually<sup>1</sup>. The incidence of human Brucellosis is correlated to the frequency of disease in animals<sup>2</sup>. According to data from the National Commission on Communicable Diseases Control, the situation in Iran was improving. In 1989 the annual incidence exceeded 1000 cases per million; in 2003, the annual incidence had fallen to 238.6 cases per million<sup>1</sup>. Still, human Brucellosis remains a considerable burden for our country<sup>3</sup>. Brucellosis presents with clinical symptoms such as arthralgia, fever, sweating, chills, headache, myalgia, malaise, and laboratory evidence of *Brucella* infection diagnosed by bacterial culture or serology<sup>4</sup>. Based on the duration of the systemic disease, it is divided into three groups: acute Brucellosis (<2 months), subacute Brucellosis (2–12 months), and chronic Brucellosis (>12 months)<sup>5</sup>. A focal form of complication means the presence of symptoms or physical signs of infection at a particular anatomic site in a patient with active Brucellosis. *Brucella* infection may involve any organ or tissue in the body. The most common systems affected are osteoarticular as sacroiliitis, spondylodiskitis, peripheral arthritis, paravertebral, epidural, and psoas abscess, and lesser are gastrointestinal, genitourinary, hematologic, cardiovascular, respiratory, nervous systems, cutaneous and ophthalmic<sup>6</sup>. Focal involvement rates of between 27.7% and 43.2% have been reported<sup>7</sup>. Chronicity and recurring febrile conditions are common sequelae. Treatment regimens usually consist of antibiotics with prolonged duration 8-12 weeks<sup>6,8,9</sup>. Given the worse prognosis and long treatment, knowledge and early diagnosis of the focal forms of Brucellosis is important especially with *B.melitensis* infection, the dominant species in Iran<sup>9</sup>. There is only one study comparing complicated and uncomplicated Brucellosis in the world, showing fever significantly more common in the former and no comparison in our country<sup>9</sup>. Also, this is the first study aimed to find markers to predict complications in Brucellosis in Iran. Epidemiological, clinical, and laboratory findings were compared in patients with

and without complications. These markers might direct correct diagnosis, effective management and diminish the complication, mortality, and morbidity of human Brucellosis.

## Methods

This is a retrospective study on records of inpatients suffering active Brucellosis in Imam Hussein Medical Center, SBMU, Tehran in 15 years (2001April-2016 March) as the census. All patients with positive Wright  $\geq 1/80$  or Coombs Wright  $\geq 1/80$  with 2ME  $\geq 1/80$ , or a positive culture for *Brucella* in classic biphasic Castaneda Media were included. Epidemiological (sex, age, history of unpasteurized dairy products, previous history of Brucellosis), clinical, and laboratory data were collected in the formerly prepared questionnaire. "Focal form of complication" was defined as the presence of symptoms or physical signs of infection at a particular anatomic site in a patient with active Brucellosis. "Hepatic involvement" was defined as a five-fold increase ( $>200\text{IU/l}$ ) in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels without any other etiologic explanation, and/or total bilirubin levels of over 2.5 g/dl. "Hematologic involvement" was defined as hematologic abnormalities in the laboratory and clinical findings (epistaxis, bleeding, petechiae, purpura, disseminated intravascular coagulation (DIC), and thrombophlebitis), excluding asymptomatic or poorly symptomatic cytopenia or coagulation disturbances. Complete blood count, CRP, ESR, and liver enzymes were examined. Results were interpreted as Elevated ESR ( $\geq 20\text{ mm/h}$ ), Elevated CRP ( $\geq 12$ ), Leukocytosis ( $\text{WBC} \geq 10000/\text{mm}^3$ ), Leukopenia ( $\text{WBC} \leq 4000/\text{mm}^3$ ), Anemia ( $\text{Hgb} \leq 12\text{g/dl}$ ), Lymphocytosis ( $\text{Lymphocyte} \geq 40\%$ ), Neutrophilia ( $\text{PMN} \geq 75\%$ ). Cases were divided into two groups: Complicated and Uncomplicated according to their symptoms and clinical presentation. All statistical analysis was performed using SPSS version 19.0 software. The one-way ANOVA and the chi-square tests were used to compare intergroup differences. P values less than 0.05 were considered to be statistically significant. The Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran approved this study (IR.SBMU.MSP.REC.1396.79).

## Results

Of the 95 patients suffering Brucellosis enrolled in the study, including complicated and uncomplicated, 56 (59%) were male, and 39(41%) were female. Regarding definitions, 69(73%) cases were evaluated as uncomplicated and 26 (28%) cases as complicated. 11 (28%) of female and 20 (35%) of male cases were complicated without significant statistical difference. Arthritis was the most common form, as shown below (Table1).

The mean patient age was  $35.46 \pm 22.2$  years, ranging from 1 to 86 years with no difference in the mean age of two groups and different complications (Table 2). 15 (16%) patients had a previous history of Brucellosis. The frequency of previous history of Brucellosis in complicated cases (7, 27%) was more than uncomplicated 8 (12%) with no significant

nonsignificant in uncomplicated (32, 46%) than complicated cases (10, 38%).

Symptoms and clinical findings are mentioned in order of frequency in two groups (Table3).

Myalgia and fever were significantly more common in complicated Brucellosis.

Patients' mean age and standard deviation based on clinical findings were similar except for headaches. The mean age of patients with headaches was significantly lower. Considering the low number of patients with a headache may have no importance (Table 4).

Coombs Wright test was not done in patients with positive Wright test, so the ratio interpretations are unreliable and not calculated. There was no significant difference in the two groups in serologic results (Table 5).

CBC, ESR, Serum level of CRP, Bilirubin, and Creatinine test results showed some differences in two

**Table 1:** Number and percent of uncomplicated and complicated brucellosis based on gender and localization.

Number (%)	Total	Female	Male
Uncomplicated	64(67%)	28(44%)	36(56%)
Complicated	31(33%)	11(35%)	20(65%)
Arthritis		6	10
Spondylitis		2	2
Epididymo-orchitis		--	2
Meningitis		1	2
Epidural abscess		1	1
Encephalitis		1	2
Meningitis + Orchitis		0	1
Total	95 (100%)	39 (41%)	56 (59%)

difference.

The history of unpasteurized dairy product use was

groups of Uncomplicated and Complicated but with no mathematical significance (Table 6).

**Table 2:** Mean age and standard deviation in Uncomplicated and Different Complicated Brucellosis.

Complication	Mean	Standard Deviation	P-value
Uncomplicated	35.39	$\pm 21.51$	
Complicated			
Arthritis	28.75	$\pm 23.43$	0.08
Spondylitis	59	$\pm 8.41$	
Epididymo-orchitis	23	$\pm 0$	
Meningitis	20.50	$\pm 3.54$	
Epidural abscess	66.5	$\pm 9.19$	
Encephalitis	45.5	$\pm 6$	
Meningitis + Orchitis	26	$\pm 0$	

**Table 3:** Number and percent of symptoms and signs in two groups of Complicated and Uncomplicated Brucellosis.

Clinical Finding	Total 95 (100%)	Complicated 26 (100%)	Uncomplicated 69 (100%)
Fever	70 74%	24 92%	46 67%
Arthralgia	56 59%	17 65%	29 42%
Sweating	44 46%	10 38%	34 49%
Myalgia	37 39%	13 50%	6 9%
Fatigue	37 39%	3 12%	34 49%
Chills	36 38%	7 27%	29 42%
Malaise	35 38%	5 19%	30 43%
Anorexia	32 32%	7 27%	25 36%
Weight Loss	32 32%	10 38%	22 32%
Back Pain	23 25%	4 15%	19 28%
Headache	7 7%	4 15%	3 4%
Nausea	6 6%	4 15%	2 3%
Vomiting	4 4%	4 15%	0 0%
Constipation	3 3%	2 8%	1 1%
Tremor	2 2%	1 4%	0 0%
Convulsion	1 1%	1 4%	0 0%
Cough	1 1%	0 0%	1 1%
Diarrhea	0 0%	0 0%	0 0%
Hepatomegaly	3 %	1 4%	2 3%
Splenomegaly	12 13%	3 12%	9 13%

Myalgia and fever were significantly more common in complicated Brucellosis.

**Table 4:** Mean age and standard deviation of patients based on clinical finding.

Clinical Finding	Positive	Negative	P-value
Fever	34.45 ± 23.52	38.38 ± 18.03	0.46
Arthralgia	38.84 ± 21.72	40.72 ± 22.13	0.06
Sweating	34.34 ± 20.31	38.38 ± 36.47	0.65
Myalgia	38.83 ± 22.49	33.33 ± 21.95	0.25
Fatigue	35.50 ± 19.10	35.45 ± 22.91	0.99
Chills	37.39 ± 22.54	34.25 ± 22.09	0.51
Malaise	39.79 ± 20.94	32.97 ± 22.70	0.15
Anorexia	34.68 ± 21.52	35.86 ± 22.70	0.81
Weight Loss	40.39 ± 23.06	33.01 ± 21.53	0.13
Backpain	42.70 ± 21.31	33.09 ± 22.13	0.08
Headache	19.29 ± 10.29	36.78 ± 22.41	0.04
Nausea	32.01 ± 13.06	35.70 ± 22.73	0.69
Vomiting	24.25 ± 2.50	35.97 ± 22.57	0.31
Constipation	53.67 ± 28.75	34.86 ± 22.90	0.15
Hepatomegaly	36.01 ± 16.37	36.11 ± 22.14	0.12
Splenomegaly	27.25 ± 19.99	36.68 ± 22.37	0.17

All patients with abnormal tests were older than patients with normal tests except for leukocyte count. Leukocytosis was more common but not significant in younger patients (Table 7).

## Discussion

Human Brucellosis is the most common bacterial zoonotic infection in the world. The situation in Iran was improving, according to data from the National Commission on Communicable Diseases Control<sup>1</sup>. Still, human Brucellosis remains a huge burden for our

country<sup>3</sup>. Focal or complicated form with symptoms or physical signs of infection at a particular anatomic site in a patient with active Brucellosis reported between 27.7% and 43.2%<sup>6,7</sup>. Treatment regimens usually consist of a combination of antibiotics with prolonged duration<sup>8</sup>. Given the worse prognosis and long treatment, knowledge and early diagnosis of the focal forms of Brucellosis is important. We may be directed to effective management and diminish the complication, mortality, and morbidity of human Brucellosis by complication predictive markers. In this study, epidemiological, clinical, and laboratory

**Table 5:** Frequency of different titer of Wright, Coombs Wright and 2ME Tests in two groups (GI: uncomplicated, GII: Complicated).

Test	Wright No (%)		Coombs Wright No (%)		2ME No (%)	
	GI	GII	GI	GII	GI	GII
Titer						
Negative	26 (38)	2 (8)	--	--	0 (0)	0 (0)
1/80	21 (30)	12 (46)	5	3	37 (54)	13 (50)
1/160	7 (10)	5 (20)	6	9	10 (14.4)	7 (27)
1/320	12 (17)	3 (12)	11	3	16 (23.2)	4 (15)
1/640	2 (3)	1 (4)	4	1	5 (7)	2 (8)
1/1280	0 (0)	2 (8)	0	0	1 (1.4)	0 (0)
1/2560	1 (1.4)	1 (4)	0	0	0 (0)	0 (0)
Total	69 (100)	26 (100)	26 (38)	16 (60)	69 (100)	26 (100)

**Table 6:** Test results of two groups of Complicated and Uncomplicated Brucellosis.

Test	Uncomplicated		Complicated	
High ESR	25	36%	17	55%
High CRP	7	14%	7	29%
Leukocytosis	8	12%	1	3%
Leukopenia	5	7%	1	3%
Anemia	4	6%	18	58%
Thrombocytopenia	50	70%	25	81%
High Bilirubin	3	4%	0	0%
High Creatinine	4	6%	0	0%

High ESR(If>20), High CRP (If ≥24), Leukocytosis (WBC >10000/mm<sup>3</sup>), Leukopenia (WBC<4000/mm<sup>3</sup>), Anemia (Hgb<12g/dl), Thrombocytopenia (Plat < 140,000, Lymphocytosis (Lymphocyte >40%), Neutrophilia (PMN>75%), High Bilirubin (Bill>2.5g/dl) High Creatinine (Cr>1.5)

**Table 7:** Mean age and standard deviation of patients based on lab data.

Test	Positive	Negative	P-value
High ESR	38.98 ± 23.93	32.62 ± 26.44	0.24
High CRP	39.07 ± 24.75	34.73 ± 22.12	0.49
Leukocytosis	28.63 ± 20.01	36.11 ± 22.39	0.37
Leukopenia	44.83 ± 27.39	35.11 ± 21.74	0.30
Anemia	36.07 ± 25.21	34.81 ± 21.04	0.82
Thrombocytopenia	35.91 ± 22.54	35.08 ± 22.40	0.91
High Bilirubin	35.89 ± 22.25	26.66 ± 11.72	0.48
High Creatinine	47.25 ± 23.57	36.33 ± 22.67	0.32

findings were compared in patients suffering Brucellosis with and without complications to find any predictive markers.

Ninety-five patients suffering Brucellosis enrolled in the study, including complicated and uncomplicated cases. 56 (59%) were male, and 39 (41%) were female, similar to another reports<sup>11-13</sup>. Concerning definitions, 69 (73%) cases were evaluated as uncomplicated and 26 (28%) cases as complicated. In previous studies, focal involvement rates have been

reported between 27.7% and 43.2%<sup>7</sup>. Our finding is similar in this range.

Complications of the disease are relatively widespread. 11 (28%) of females and 20 (35%) male cases were complicated without significant statistical difference. In another study also complications were more common in male<sup>14</sup>. It was found that the risk of recurrence of human Brucellosis is higher in females than males and also higher in people of advanced ages, but no comparison of localization in two sexes<sup>15</sup>. CNS and

musculoskeletal complications are the most localized form in the current study, totaling 97%. In the meta-analysis of thirty-three databases, CNS involvement was the second after epididymo-orchitis<sup>4</sup>; this difference may be due to studying out and inpatients, but our study is on inpatient cases only. In two other reports, musculoskeletal and epididymo-orchitis were the most common but no CNS involvement<sup>11-13</sup>. The mean patient age was  $35.46 \pm 22.2$  years with no significant age difference in the two groups and complications similar to other studies<sup>16</sup>. In Yujing Shi study, mean age was also our study but without differentiating complicated and uncomplicated patients<sup>5</sup>. However, in some reports, one of the risk factors to unfavorable prognosis was age more than 45 years as complication<sup>7,17-18</sup>. Increased age and a prolonged duration of disease until diagnosis were risk factors for developing nervous system damage in patients with brucellosis<sup>8</sup>. Misdiagnosis often leads to a delay in treatment and can result in long-term complications of disease<sup>19</sup>. Relapse rates are frequently around 5% to 15%, depending on the regimen used<sup>6</sup>. In our results, 15 (16%) patients had a previous history of Brucellosis. The frequency of previous history of Brucellosis in complicated cases (7, 27%) was more than uncomplicated 8 (12%) with no significant difference.

We found a significant correlation between myalgia, sweating, malaise, and chills with complicated Brucellosis. However, in Kassalan report, which was the only study similar to ours on comparison of complicated and uncomplicated Brucellosis, fever was the most significant predictive marker of complications. Other classical symptoms of Brucellosis like myalgia and malaise were absent in most complicated cases<sup>10</sup>. In another report, fever ( $>38.3^{\circ}\text{C}$ ), arthralgia, lumbar pain, and malaise were more common but insignificant in complicated patients<sup>14</sup>. There was no clinical risk factor for poor prognosis and relapse in other studies with no data about complications<sup>20,21</sup>. The mean age of patients with headache ( $19.29 \pm 10.29$ ) was significantly lower than the total ( $35.46 \pm 22.2$ ). Considering the low number of patients with a headache it may have no importance. We did not find any difference in physical findings as hepatomegaly, splenomegaly, and lymphadenopathy in two forms as to similar

report<sup>10,14</sup>. The frequency of different titer of Wright, Coombs Wright, and 2ME Tests in two groups had no significant difference. There is no comparison of serology and culture results in other surveys<sup>7,10,14</sup>. Anemia was significantly more common in the complicated group as 18% vs. 4%. On the contrary, thrombocytopenia was less common in complicated patients as 25% vs. 50%. WBC and cell differentiation, ESR, Serum level of CRP, Bilirubin, and Creatinine test results were different in two groups but had no mathematical significance. In one report, anemia with a mean hemoglobin level of  $10.8 \pm 1.6$  g/dl was present in 34% of patients and high ESR 73% with a mean rate of  $39 \pm 16$  mm/h in all cases without comparison<sup>14</sup>. Although abnormal hematologic findings have previously been shown to be a marker of poor prognosis, another study presented the opposite result but did not report any data about the complicated form of brucellosis<sup>5,22,23</sup>. It is proposed for further investigation in a prospective study of this view of Brucellosis with many more cases.

## Conclusion

The most frequent complication of Brucellosis was osteoarticular involvement followed by neurologic cases. Myalgia and fever were significantly more common in a complicated form. There was no significant difference in other classical symptoms of Brucellosis as sweating, malaise, fatigue, and chills between the two groups, and no significant difference in physical exam serologic tests titer and other studied lab tests.

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