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LABORATORY SIGNIFICANCE OF SYSTEMIC INFLAMMATORY MARKERS IN VARIOUS FORMS OF BRUCELLOSIS AND OPTIMIZATION OF TREATMENT

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Abstract
Human brucellosis, an endemic zoonosis triggered by intracellular pathogens of the genus Brucella, continues to pose severe clinical challenges due to its extensive systemic polymorphism and a high propensity for chronic progression. Conventional serological and bacteriological assays confirm target exposure but fail to map real-time immunological stress or track localized tissue damage during therapeutic courses. Identifying precise biochemical indicators is therefore vital to improve clinical staging and avoid long-term disability.

Keywords: Brucellosis, systemic inflammation, biomarkers, cytokines, diagnosis.

Introduction

Human brucellosis remains an elusive and deep-rooted public health crisis across endemic agricultural regions worldwide, presenting an intricate clinical matrix that severely taxes modern healthcare frameworks. The primary survival strategy of *Brucella* species relies on their sophisticated ability to bypass initial host phagocytic clearance and create permanent replicative sanctuaries directly within host macrophages. By avoiding complete lysosomal destruction, the pathogen effectively embeds itself inside the reticuloendothelial system. This persistent host-pathogen interface drives a highly unpredictable clinical trajectory, triggering acute febrile episodes, subacute localized complications (such as osteoarticular and neurological involvement) and chronic systemic syndromes that systematically erode the patient's functional capacity and quality of life.

One of the most formidable obstacles in successful clinical infectology is the distinct lack of objective laboratory standards capable of reliably separating active, acute bacterial proliferation from persistent, low-grade intracellular infection, as well as detecting early warning signs of clinical relapse. While traditional screening protocols like the Wright and Huddleson serological agglutination reactions or standard blood cultures remain valuable for initial diagnostic confirmation, they are inherently static; they cannot map real-time tissue inflammation or objectively measure the clearance rate of the intracellular pathogen during antibiotic treatment.

To address this diagnostic gap, contemporary research focuses on evaluating circulating biochemical markers of the innate immune response. Biomarkers such as high-sensitivity C-reactive protein (hs-CRP), procalcitonin (PCT), and key pro-inflammatory cytokines specifically interleukin-6 (IL-6)

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serve as direct indicators of the cellular inflammatory cascade triggered by *Brucella* endotoxins and cell-wall antigens. Concurrently, calculating simple, cost-effective hematological ratios from complete blood counts, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), yields highly scannable, real-time insights into systemic homeostatic stress and immune equilibrium.

However, the precise quantitative boundaries, cut-off values, and diagnostic combinations of these markers across the different evolutionary stages of brucellosis remain insufficiently defined. Deciphering these specific laboratory patterns is crucial for understanding the exact immunological mechanisms that govern the transition from acute host defense to chronic pathogen survival. Furthermore, tracking these biomarker dynamics provides an objective, measurable foundation for implementing optimized, multi-component therapeutic protocols. By combining standard dual-antibiotic therapy with supportive immunometabolic agents, clinicians can actively protect tissues, accelerate cellular recovery, and fundamentally lower the rates of permanent chronic transition.

Material and methods

Study Design and Patient Selection

This prospective observational study was conducted from 2022 to 2024 at a specialized infectious diseases hospital and outpatient clinics. The research enrolled 120 adult patients aged 18 to 65 years with confirmed brucellosis. The diagnosis relied on clinical signs, epidemiological history, and standard laboratory tests. Patients were divided into four distinct clinical forms including acute, subacute, chronic, and focal trajectories. The reference control group included 30 healthy individuals who were matched by age and sex. None of the control subjects had any history of acute or chronic inflammatory diseases.

Laboratory Evaluation Protocols

All patients underwent comprehensive laboratory testing at admission and during the follow-up period. The laboratory evaluation included a complete blood count with a differential and the measurement of the erythrocyte sedimentation rate. Researchers also measured serum C-reactive protein and procalcitonin levels to assess acute inflammation. The cytokine profile assessment included tumor necrosis factor-alpha, interleukin-6, and interleukin-1β levels measured by enzyme-linked immunosorbent assay. Specific serological confirmation was achieved using the Rose Bengal and Wright agglutination tests, while blood cultures were performed in selected clinical cases.

Treatment and Monitoring

All patients received standard antibacterial therapy in accordance with national and international clinical guidelines, including combinations of doxycycline, rifampicin, and, when indicated, aminoglycosides. Treatment duration and regimen adjustments were individualized based on clinical form, severity of disease, and laboratory indicators of inflammatory activity.

Systemic inflammatory markers were assessed before treatment initiation and dynamically during therapy to evaluate treatment response and guide therapeutic optimization.

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Statistical Analysis. Statistical analysis was performed using standard statistical software packages. Quantitative variables were expressed as mean ± standard deviation (SD) or median with interquartile range, as appropriate. Comparisons between groups were conducted using Student's t-test or Mann–Whitney U test. Correlations between inflammatory markers and clinical severity were assessed using Pearson or Spearman correlation coefficients. A p-value <0.05 was considered statistically significant.

Results

The final analysis included a total of 120 patients with laboratory-confirmed brucellosis. Based on clinical features and disease duration, 38 patients (31.7%) had acute brucellosis and 34 patients (28.3%) had subacute brucellosis. Additionally, 32 patients (26.7%) were diagnosed with chronic brucellosis, while 16 patients (13.3%) presented with focal forms. Most patients suffered from classic symptoms like fever, sweating, fatigue, arthralgia, and myalgia. In contrast, patients with focal forms mainly showed localized osteoarticular, genitourinary, or neurological involvement.

Hematological and Biochemical Inflammatory Profiles

The initial laboratory evaluation showed major differences in systemic inflammatory markers between brucellosis patients and healthy controls. Patients with acute and subacute forms had strong inflammatory reactions. These responses included leukocytosis, or relative leukopenia with lymphomonocytosis, alongside elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

Specifically, mean ESR values were significantly higher in acute (38.6±9.4 mm/h) and subacute forms (31.2 ±7.8 mm/h) than in chronic brucellosis (18.5 ±6.1 mm/h) and the control group (8.4±2.6 mm/h; $p < 0.05$). Serum CRP concentrations were also heavily elevated in acute and subacute patients, but they showed a gradual decline in chronic and focal cases.

Cytokine Cascade Dynamics and Biomarker Correlations

Testing for pro-inflammatory cytokines showed a significant increase in serum TNF-α, IL-6 and IL-1 β levels in all brucellosis patients compared to healthy controls ($p<0.01$). The acute brucellosis cohort had the highest cytokine concentrations, followed by the subacute group. In chronic brucellosis, cytokine levels stayed moderately high, which shows the presence of persistent, low-grade inflammation.

Statistical analysis revealed a strong positive correlation between serum IL-6 and CRP values ($r = 0.68$, $p < 0.01$). Another positive correlation was found between TNF-α levels and clinical severity scores ($r = 0.61$, $p < 0.05$). Meanwhile, serum procalcitonin levels were moderately higher in acute cases but stayed near normal in chronic and focal forms. This pattern suggests that procalcitonin has limited value for diagnosing chronic cases, but it helps identify acute systemic bacterial involvement. Following the start of antibacterial therapy, patients with acute and subacute brucellosis showed a significant drop in CRP, ESR, and cytokine levels by the end of the second week ($p < 0.05$). In patients with chronic forms, the normalization of these inflammatory markers was much slower and remained incomplete in several cases. This delayed laboratory response directly correlated with the persistence of their clinical symptoms. Furthermore, patients with focal brucellosis showed long-lasting

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elevations of inflammatory markers, which indicates a clear clinical need for extended or modified treatment plans.

Conclusion

Systemic inflammatory markers play a crucial role in the clinical and laboratory assessment of brucellosis. Their evaluation provides valuable information on disease activity, severity, and response to therapy. Incorporation of inflammatory biomarker monitoring into clinical practice contributes to optimization of treatment strategies, reduction of complications, and prevention of chronic disease forms. Further studies are needed to establish standardized biomarker-based algorithms for the management of brucellosis patients.

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