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# THE IMPORTANCE OF INFLAMMATION MARKERS IN ACUTE BRUCELLOSIS: DIAGNOSTIC, PROGNOSTIC, MONITORING, DIFFERENTIAL DIAGNOSIS, AND TREATMENT CONSIDERATIONS

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## Abstract

Acute brucellosis, a zoonotic bacterial infection caused by "Brucella" species, presents with systemic symptoms including fever, arthralgia, malaise, and potential focal complications, particularly osteoarticular involvement in 10–85% of cases (most commonly 20–40% in many series). Inflammation is central to its pathogenesis, with "Brucella" persisting intracellularly in macrophages and eliciting variable acute-phase responses. Traditional markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and neutrophils, alongside derived ratios like neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), provide accessible, cost-effective tools for preliminary diagnosis, severity assessment, complication prediction (e.g., osteoarticular in up to 30–70% of complicated cases), and treatment monitoring in endemic regions. These markers also aid in differential diagnosis from mimics like malaria, typhoid, tuberculosis, or viral fevers, where patterns differ (e.g., marked leukocytosis in pyogenic infections vs. normal/low WBC in brucellosis). Global incidence estimates range from 2.1 million annual cases, with high endemicity in Asia and Africa (e.g., rates >35/100,000 in some areas like Ningxia, China). Emerging biomarkers like irisin and cytokines further enhance utility. Treatment considerations involve prolonged dual-antibiotic regimens (e.g., doxycycline + rifampin for 6 weeks; relapse rates 4.8–10%), with markers guiding response and detecting relapses. These tools facilitate early intervention in resource-limited settings, reducing chronicity and morbidity.

This review integrates etiopathogenetic insights with statistical evidence from recent studies to underscore their multifaceted clinical value. Besides explains synthesizes etiopathogenetic mechanisms, clinical features, and systemic complications, incorporating updated insights from recent consensus guidelines and studies to enhance understanding and optimize patient outcomes.

## Keywords

Acute brucellosis; Inflammation markers; C-reactive protein (CRP); Erythrocyte sedimentation rate (ESR); Neutrophil-to-lymphocyte ratio (NLR); Systemic immune-inflammation index (SII); Osteoarticular involvement; Diagnostic biomarkers; Prognostic value; Differential diagnosis; Treatment monitoring; Endemic regions

## Introduction

Brucellosis remains a significant zoonotic disease, with global annual incidence conservatively estimated at 2.1 million cases, predominantly in Asia and Africa, though underreporting is common due to diagnostic challenges. In endemic areas (e.g., parts of Central Asia, China, Iran), incidence rates can exceed 35–84/100,000 in high-burden regions like Ningxia (average 35.08/100,000 from 2010–2024) or certain Iranian provinces (>200/100,000 historically). The acute phase features systemic inflammation from bacterial dissemination and host response,

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often complicated by osteoarticular involvement (10–85%, most frequently 20–40%; sacroiliitis in ~48–62%, peripheral arthritis in children). Inflammation markers offer rapid, inexpensive insights for diagnosis (complementing serology/culture), severity grading, complication prediction (e.g., focal forms in 30–40% of cases), differential diagnosis, and monitoring response to antibiotics (e.g., doxycycline + rifampin). Their importance is amplified in settings with delayed confirmation, where early marker assessment prevents progression to chronicity.

This review details the inflammatory basis of acute brucellosis and evaluates key markers' statistical performance in diagnosis, prognosis, differential diagnosis, and management.

**Etiopathogenesis of Inflammation in Acute Brucellosis**

Brucella species enter and survive within macrophages primarily through their Type IV secretion system and a structurally atypical, low-endotoxin LPS that blunts early TLR4 signaling. This strategy effectively dampens initial innate immune activation, limiting neutrophil recruitment while simultaneously favoring a robust Th1-polarized adaptive response characterized by elevated production of IFN-γ, TNF-α, IL-6, and IL-12.

Ongoing intracellular replication of the pathogen perpetuates a sustained cytokine storm, driving persistent inflammation, granuloma formation in affected tissues, and progressive tissue injury. These processes account for the marked elevation of classical acute-phase reactants—most notably CRP (induced mainly by IL-6) and fibrinogen (which accelerates ESR)—even though peripheral white blood cell counts are frequently normal or reduced (leukopenia) as a result of effective immune evasion and bone marrow suppression.

Key intracellular signaling cascades, including NF-κB and MAPK pathways, become hyperactivated and amplify the inflammatory cascade, thereby contributing to the development of focal complications. Osteoarticular involvement is especially common (reported in 2–77% of cases depending on series and definition), while anemia occurs in 20–53% of pediatric acute brucellosis patients.

The observed heterogeneity in inflammatory biomarker profiles arises from the dual and opposing dynamics of the infection: strong suppression of certain innate immune arms contrasted with vigorous activation of adaptive (Th1) immunity.

**Clinical Importance of Traditional Inflammation Markers**

CRP and ESR serve as cornerstone acute-phase reactants in acute brucellosis. C-reactive protein (CRP) shows a rapid increase during active infection—commonly exceeding 10–50 mg/L—with reported diagnostic sensitivities of 65–80% and specificities around 72% (for example, one ROC analysis found 65% sensitivity and 72% specificity, while other studies report up to 77.8% sensitivity and 95% specificity at an optimal cut-off of 3.33 mg/L). CRP levels closely track disease severity and typically return to normal following successful treatment.

Erythrocyte sedimentation rate (ESR) is elevated in the majority of cases (70–76%), often ranging from >20–50 mm/h (e.g., mean 35.6 mm/h in patients vs. 12.2 mm/h in controls, $p<0.001$). While valuable for longitudinal monitoring, ESR lacks the specificity of CRP.

White blood cell count (WBC) shows considerable variability: it is frequently normal or even reduced (leukopenia secondary to bone marrow suppression), though neutrophilia may occur in some patients; overall diagnostic performance is modest (sensitivity ~54%, specificity ~66%).

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In complicated brucellosis (affecting 38–39% of cases overall), both ESR and CRP are markedly higher than in uncomplicated disease (e.g., ESR 48 vs. 38 mm/h, CRP 29 vs. 17 mg/L, $p<0.001$), underscoring their prognostic utility.

These traditional markers are particularly effective for treatment follow-up: failure of CRP and/or ESR to normalize, or their secondary rise, strongly suggests relapse, treatment failure, or the emergence of focal complications.

**Derived Hematological Ratios and Systemic Indices**

Derived hematological ratios and systemic inflammatory indices provide valuable insights into immune responses during brucellosis. For instance, the neutrophil-to-lymphocyte ratio (NLR) is frequently lower in affected patients (e.g., median 1.69 vs. 2.07 in controls, $p=0.013$; AUC 0.644), while the platelet-to-lymphocyte ratio (PLR) shows variable findings, the lymphocyte-to-monocyte ratio (LMR) tends to be elevated (median 5.28 vs. 4.12, $p=0.008$), and the systemic immune-inflammation index (SII) may be reduced in certain pediatric cohorts. These shifts mirror altered immune dynamics in the infection.

Multivariate or combined models, such as one integrating mean platelet volume (MPV) with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), demonstrate markedly improved diagnostic accuracy (AUC 0.891, with 84% sensitivity and 86% specificity) compared to single markers.

In pediatric and focal/complicated presentations, elevated neutrophil-to-monocyte ratio (NMR) and CRP levels serve as predictors of osteoarticular involvement (OI, occurring in ~23.7% of cases in some series; e.g., CRP 30.2 vs. 9.8 mg/L, $p=0.039$; accompanied by lower white blood cell counts, $p=0.015$). Additionally, reduced MPV is linked to the presence of complications ($p=0.038$), highlighting its potential prognostic significance.

**Emerging and Novel Biomarkers**

Irisin, a myokine released by skeletal muscle, shows reduced levels in brucellosis patients. These decreased concentrations correlate with markers of inflammation and bone marrow suppression, indicating a potential role in the disease's pathophysiology. Irisin levels are diminished and associate with inflammatory processes as well as bone marrow involvement. Acute-phase cytokines such as IFN-γ, TNF-α, and IL-6 are markedly elevated during active infection and generally decrease following successful treatment, while relationships between IL-2/IL-6 and CRP further highlight inflammatory dynamics. Emerging composite indices, including the CAR (CRP-to-albumin ratio), demonstrate promising utility as biomarkers in this context.

**Special Considerations: Pediatric and Complicated Acute Brucellosis**

Osteoarticular involvement (OI) occurs in 10–85% of brucellosis cases, with peripheral joint involvement being more frequent in children, while sacroiliitis is more commonly seen in adults. Pediatric studies report significantly higher CRP levels, lower white blood cell counts, and elevated NMR values in patients with osteoarticular disease ($p < 0.05$). These laboratory markers can help stratify risk, guiding decisions about the need for targeted imaging and extended treatment duration.

**Differential Diagnosis Using Inflammation Markers**

Acute brucellosis mimics numerous conditions due to nonspecific symptoms (fever, malaise, arthralgia), complicating diagnosis in endemic areas. Key differentials include infectious etiologies (malaria, typhoid fever, tuberculosis, leptospirosis, viral infections like influenza or

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dengue) and noninfectious ones (collagen-vascular diseases, lymphoma, histiocytosis, sarcoidosis). Inflammation markers aid differentiation: in brucellosis, CRP and ESR are often markedly elevated (CRP >20–50 mg/L in 70–90% of cases; ESR >50 mm/h in 70–76%), but WBC is normal or low (leukopenia in 20–40%, neutrophilia absent in most), contrasting with pyogenic bacterial infections (e.g., pneumonia, abscess) where leukocytosis (>10,000/μL) and neutrophilia predominate. For malaria or typhoid, similar low WBC may occur, but CRP is typically lower in viral fevers (e.g., <10 mg/L in uncomplicated influenza). Derived ratios like NLR are lower in brucellosis (median 1.69–2.5) vs. higher in acute bacterial infections (e.g., >5 in sepsis). In osteoarticular presentations, markers distinguish from rheumatoid arthritis (higher ESR/CRP with positive autoantibodies) or sacroiliitis from ankylosing spondylitis (normal WBC, variable CRP). Combined with serology (e.g., Rose Bengal test positive in 88–90%), markers achieve high diagnostic accuracy (e.g., ELISA + elevated CRP/ESR AUC >0.85 for sacroiliitis). Novel markers like endocan (elevated in brucellosis) may further refine differentials from healthy controls or subacute/chronic forms.

**Treatment Considerations and Role of Inflammation Markers in Monitoring**

Treatment of acute brucellosis requires prolonged combination antibiotics to prevent relapse (rates 4.8–10% with suboptimal regimens) and chronicity. World Health Organization guidelines recommend doxycycline (100 mg twice daily) + rifampin (600–900 mg/day) for 6 weeks (relapse risk ~8–10%), or doxycycline + streptomycin (1 g/day IM for 2–3 weeks; relapse ~4–5%, more effective for prevention). Recent meta-analyses favor doxycycline + gentamicin (1–2 weeks; SUCRA efficacy ranking 0.94, relapse <5%) or triple therapy (doxycycline + rifampin + aminoglycoside) for severe cases (e.g., endocarditis, meningitis; duration 4–6 months, case-fatality <1% with early intervention). For children <8 years, rifampin + trimethoprim-sulfamethoxazole (TMP-SMZ) for 6 weeks is preferred (avoid tetracyclines). In pregnancy, TMP-SMZ + rifampin is used (tetracyclines contraindicated). Inflammation markers guide therapy: baseline high CRP/ESR (>50 mg/L or >50 mm/h) predict need for prolonged courses; normalization (CRP <5 mg/L, ESR <20 mm/h) post-treatment indicates success (80–90% resolution in 2–3 weeks for uncomplicated cases). Persistent elevation (>2–4 weeks) signals relapse (10–15% risk) or complications, prompting extended therapy or adjunctive corticosteroids in severe inflammation. Cytokines (e.g., IL-6 decline) and ratios (NLR normalization) enhance monitoring, especially in resource-limited settings where culture (positive in 30–70%) is unavailable.

**Conclusion**

Inflammatory biomarkers play a central role in the management of acute brucellosis, offering robust statistical support across multiple clinical domains. They aid in diagnosis (with CRP and ESR frequently achieving AUC values of 0.7–0.8 or higher), prognostication (elevated levels strongly associated with complicated disease, affecting 30–40% of cases), differential diagnosis (characteristic patterns, such as relatively low white blood cell counts, help distinguish brucellosis from bacterial mimics), and treatment monitoring—particularly relevant given the ongoing global burden of approximately 2.1 million new cases annually.

Both conventional markers (CRP, ESR) and derived hematological ratios (NLR, SII, among others) facilitate timely intervention in endemic regions, thereby helping to decrease long-term morbidity. When used in conjunction with established treatment protocols—most commonly doxycycline-based combination regimens—these tools contribute to improved patient outcomes.

Future prospective studies validating combined biomarker models and establishing reliable diagnostic/prognostic cut-off values are expected to further refine and strengthen their clinical utility.

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