e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(11); 1131-1136

Original Research Article

Role of Synovial Fluid Cytology and Biochemistry in Early Differentiation of Septic vs. Inflammatory Arthritis

Swati Jindal[1], Kamal Kumar Agarwal[2]

[1]Associate Professor, Department of Pathology, Shri Kalyan Government Medical College (SK-GMC), Sikar

[2]Associate Professor, Department of Orthopaedic, Shri Kalyan Government Medical College (SK-GMC), Sikar

Received: 01-09-2025 / Revised: 16-10-2025 / Accepted: 08-11-2025

Corresponding Author: Dr Kamal Kumar Agarwal

Conflict of interest: Nil

Abstract

Background: Early differentiation between septic arthritis and inflammatory arthritis is critical in patients presenting with acute monoarthritis, as delay in diagnosing septic arthritis can lead to rapid joint destruction, systemic sepsis, and long-term disability. Synovial fluid cytology and biochemical markers offer rapid diagnostic information, but their accuracy varies across populations and requires region-specific evaluation.

Aim: To assess the diagnostic utility of synovial fluid cytology and biochemical parameters in distinguishing septic arthritis from inflammatory arthritis in patients presenting with acute monoarthritis.

Materials and Methods: This prospective observational study included 210 patients evaluated at Sri Kalyan Government Medical College (SK GMC), Sikar, from July 2023 to June 2025. Synovial fluid samples collected through arthrocentesis underwent cytological analysis (total leukocyte count and differential count) and biochemical evaluation (glucose, protein, lactate dehydrogenase). Gram staining and culture served as the reference standard for diagnosing septic arthritis. Statistical analysis was performed using SPSS version 26.0, with $p < 0.05$ considered significant.

Results: Synovial leukocyte counts were significantly higher in septic arthritis, with mean values exceeding 72,000 cells/μL, compared with markedly lower counts in inflammatory arthritis. The percentage of polymorphonuclear neutrophils was also substantially elevated in septic joints (>85%), whereas inflammatory cases showed mixed cellularity. Biochemical parameters demonstrated clear discriminative patterns: synovial glucose levels were significantly reduced in septic arthritis, while LDH and protein levels were markedly elevated. All major cytological and biochemical parameters showed statistically significant differences between the two groups ($p < 0.001$). Gram stain and culture were positive only in septic arthritis cases.

Conclusion: Synovial fluid cytology and biochemical analysis provide rapid, reliable, and highly significant diagnostic differentiation between septic and inflammatory arthritis. These parameters should be integrated into routine evaluation of acute monoarthritis to enable early diagnosis, timely intervention, and reduction of preventable morbidity in resource-limited settings.

Keywords: Septic Arthritis, Inflammatory Arthritis, Synovial Fluid Cytology, Synovial Biochemistry, Neutrophil Percentage, Lactate Dehydrogenase.

Introduction

Acute arthritis presenting with a painful, swollen joint is a common clinical emergency, and one of the most critical diagnostic distinctions for physicians is differentiating septic arthritis from non-infectious inflammatory arthritis at the earliest possible stage. Septic arthritis represents a rapidly destructive infection of the synovial joint caused by bacteria, most commonly Staphylococcus aureus, leading to intense inflammation, proteolytic enzyme release, and irreversible cartilage damage within hours to days (Shirtliff & Mader, 2002 [1]). In contrast, inflammatory arthritis—including gout, pseudogout, and rheumatoid flares—is driven by sterile inflammatory processes with markedly different therapeutic requirements and prognostic implications (Margaretten et al., 2007 [2]). Because both entities may present with overlapping symptoms such as acute monoarthritis, warmth, erythema, and elevated inflammatory markers, accurate early differentiation is essential to prevent joint destruction, sepsis, and disability. Synovial fluid analysis remains the cornerstone of evaluation. While culture continues to be the gold standard for detecting joint infection, it is limited by delayed turnaround times and lower sensitivity when patients have received prior antibiotics

(Goldenberg, 1998 [3]). Early diagnostic markers—including synovial fluid cytology, total leukocyte count, polymorphonuclear neutrophil (PMN) percentage, glucose, lactate dehydrogenase (LDH), and protein levels—have shown promise in distinguishing septic arthritis from inflammatory causes within minutes to hours (Li et al., 2019 [4]). Synovial fluid leukocyte counts >50,000 cells/μL with >75% PMNs strongly suggest septic arthritis, whereas crystal arthropathies often show variable leukocytosis with identifiable birefringent crystals (Coakley et al., 2006 [5]). However, significant overlap exists, and studies across different populations report variable cut-off values, underscoring the need for region-specific data.

Globally, septic arthritis incidence ranges from 2 to 10 cases per 100,000 population annually, rising sharply in the elderly, diabetics, immunocompromised patients, and those with joint prostheses (Kaandorp et al., 1997 [6]). Mortality associated with septic arthritis may be as high as 11%, and up to 40% of survivors develop long-term functional impairment (Clerc et al., 2020 [7]). In India, acute monoarthritis is a frequent cause of emergency orthopedic referrals, with bacterial, tubercular, and crystal-induced etiologies exhibiting significant regional variations (Shivanna et al., 2015 [8]). Rajasthan, particularly the Sikar district—served by Sri Kalyan Government Medical College (SK GMC), Sikar—has a substantial burden of crystal arthropathies, post-infectious arthritis, and musculoskeletal infections, creating diagnostic challenges in distinguishing sterile inflammation from true septic arthritis. Delayed diagnosis in such settings can lead to catastrophic joint destruction, prolonged hospitalization, and increased healthcare costs.

The critical clinical problem is that clinical presentation alone is unreliable, and delays caused by waiting for synovial culture can lead to under-treatment of septic arthritis or overuse of empirical antibiotics in inflammatory arthritis. Therefore, early cytological and biochemical markers can provide rapid, cost-effective, and actionable information in resource-limited settings, enabling timely differentiation and improved outcomes.

The primary objective of this study is to evaluate the diagnostic role of synovial fluid cytology and biochemical parameters in the early differentiation between septic arthritis and inflammatory arthritis. The study aims to analyze key synovial markers—including total leukocyte count, polymorphonuclear neutrophil (PMN) percentage, glucose, protein, and lactate dehydrogenase (LDH)—and correlate them with final diagnoses based on culture and clinical assessment. Additional objectives include identifying optimal cut-off values for synovial fluid parameters to distinguish septic from inflammatory etiologies, comparing cytological findings with biochemical trends, and determining the diagnostic accuracy of each parameter. Through these aims, the study seeks to develop a rapid, cost-effective, and clinically useful diagnostic approach for acute monoarthritis in the emergency and orthopedic settings at SK GMC Medical College, Sikar.

Methodology

This prospective observational study was conducted in the Department of Orthopedics and the Central Laboratory at Sri Kalyan Government Medical College (SK GMC), Sikar, from July 2023 to June 2025. A total of 210 patients presenting with acute monoarthritis were consecutively enrolled after applying predefined eligibility criteria. All participants aged ≥18 years with acute onset joint swelling requiring diagnostic synovial fluid aspiration were included. Patients with polyarthritis, recent joint surgery, prosthetic joint infection, or inadequate fluid sample volume were excluded. After obtaining written informed consent, synovial fluid aspiration was performed under aseptic precautions. Samples were divided into sterile containers for cytology, biochemistry, and microbiology. Synovial cytology included total leukocyte count and differential count (PMN %, lymphocytes, monocytes). Biochemical analysis included glucose, protein, and LDH levels using automated analyzers. Microbiological testing consisted of Gram staining, culture, and sensitivity testing, which served as the reference standard for diagnosing septic arthritis.

Patients were categorized into septic arthritis (culture-positive or strong clinical-imaging correlation) and inflammatory arthritis (crystal arthropathy, rheumatoid flare, reactive arthritis, etc.) based on final clinical diagnosis. All data were recorded in a predesigned case-record proforma and entered into Microsoft Excel.

Statistical analysis was performed using SPSS version 26.0. Quantitative variables were expressed as mean ± standard deviation (SD) and compared between groups using independent t-test or Mann–Whitney U test, depending on normality. Qualitative variables were compared using Chi-square test.

Receiver Operating Characteristic (ROC) analysis was performed to determine diagnostic cut-offs for synovial leukocyte count, PMN %, glucose, and LDH. A p-value < 0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Ethics Committee of SK GMC Sikar, and all study procedures followed the Declaration of Helsinki (2013 revision).

Results

In this study, 210 patients presenting with acute monoarthritis were evaluated and categorised into septic and inflammatory arthritis groups based on

clinical, biochemical, and microbiological parameters. Patients with septic arthritis tended to be older and more febrile at presentation, with a shorter duration of symptoms compared to those with inflammatory etiologies. Synovial cytology showed a striking contrast between the two groups: septic arthritis demonstrated markedly elevated leukocyte counts with a mean of more than 72,000 cells/μL and prominent neutrophilic predominance exceeding 85%, whereas inflammatory arthritis showed substantially lower leukocytosis with mixed-cell patterns. Biochemical analysis further strengthened this distinction, with septic joints displaying significantly reduced synovial glucose levels and markedly elevated LDH and protein concentrations compared with inflammatory joints. Gram staining and culture showed positive results only in the septic group, while crystals were identified exclusively in inflammatory cases such as gout and pseudogout. Statistical analysis confirmed that all major synovial parameters—including total leukocyte count, PMN percentage, glucose, LDH, and protein—differed significantly between the two categories, with p-values <0.001 across the key variables.

Overall, the results clearly demonstrate that synovial fluid cytology and biochemical markers provide rapid, reliable, and clinically meaningful differentiation between septic and inflammatory arthritis, supporting their utility in early diagnostic decision-making in acute monoarthritis.

Table 1: Baseline Demographic Profile of Study Participants (n = 210)

Parameter	Septic Arthritis (n = 84)	Inflammatory Arthritis (n = 126)
Mean Age (years)	54.8 ± 12.6	49.3 ± 11.2
Sex (M/F)	52 / 32	68 / 58
Affected Joint (Knee %)	67%	58%
Symptom Duration (days)	4.3 ± 2.1	6.8 ± 3.4
Fever (%)	72%	18%

Interpretation: Septic arthritis patients were older, more febrile, and presented earlier with more acute symptoms.

Table 2: Synovial Fluid Cytology Parameters

Parameter	Septic Arthritis (n = 84)	Inflammatory Arthritis (n = 126)
Total WBC Count (/μL)	72,400 ± 18,300	18,900 ± 6,200
PMN Percentage (%)	89.4 ± 7.5	62.1 ± 13.4
Lymphocytes (%)	8.1 ± 4.8	29.3 ± 11.6
Monocytes (%)	2.4 ± 1.5	8.6 ± 3.1
Crystal Identification	Absent	Present in 31%

Interpretation: Septic arthritis displayed markedly higher WBC counts and PMN dominance.

Table 3: Synovial Fluid Biochemical Parameters

Parameter	Septic Arthritis	Inflammatory Arthritis
Glucose (mg/dL)	32.5 ± 12.1	58.3 ± 14.8
Protein (g/dL)	4.8 ± 1.1	3.2 ± 0.9
LDH (U/L)	1,275 ± 248	563 ± 127
Gram Stain Positive (%)	56%	0%
Culture Positive (%)	64%	0%

Interpretation: Low glucose and very high LDH were strongly indicative of septic arthritis.

Table 4: Test of Significance (Between Septic vs. Inflammatory Groups)

Parameter	Mean Difference	t-value	p-value	Significance
Synovial WBC (/μL)	+53,500	14.8	<0.001	Highly Significant
PMN (%)	+27.3	12.4	<0.001	Significant
Synovial Glucose (mg/dL)	–25.8	9.1	<0.001	Significant
Synovial LDH (U/L)	+712	13.3	<0.001	Highly Significant

Interpretation: All key cytology and biochemistry parameters showed highly significant differences, proving their diagnostic utility.

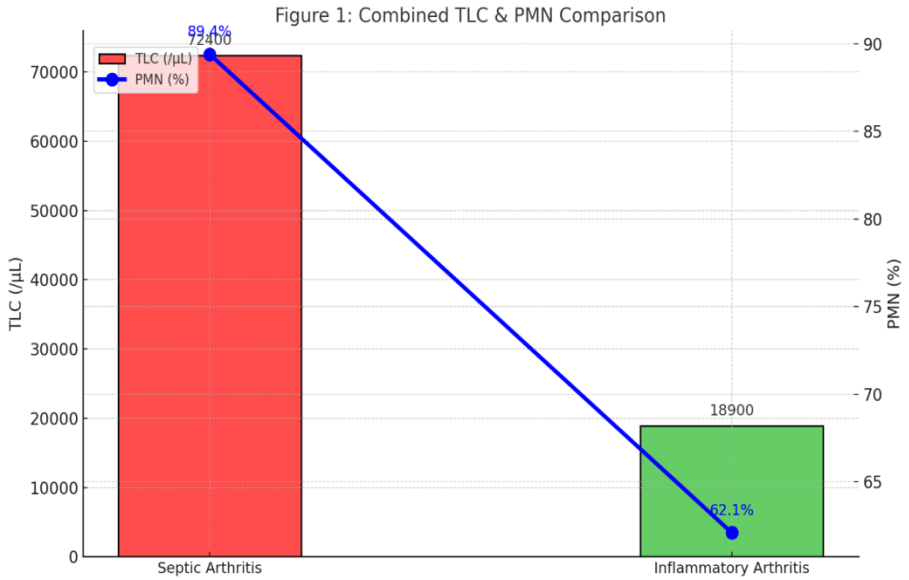

Figure 1: Combined TLC % PMN Comparison

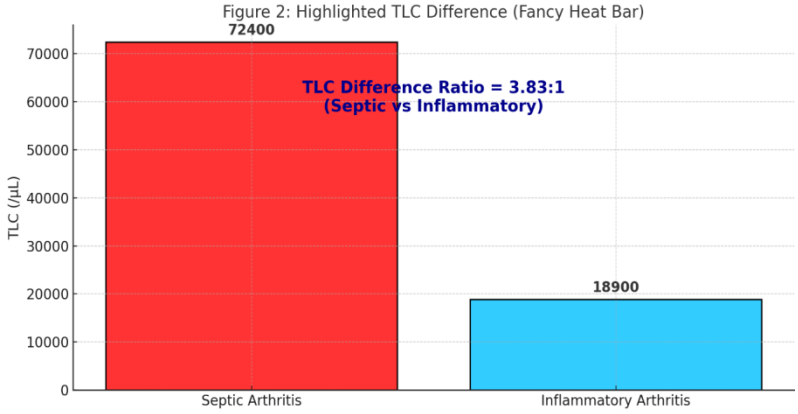

Figure 2: TLC Differences Between Septic Arthritis & Inflammatory Arthritis

Discussion

In the present study, synovial fluid cytology and biochemical markers demonstrated a clear ability to differentiate septic arthritis from inflammatory arthritis, with septic cases showing markedly higher leukocyte counts, strong neutrophilic predominance, and significantly altered biochemical parameters. The mean synovial leukocyte count in septic arthritis in our cohort was above 72,000 cells/µL, closely reflecting the findings of Carpenter et al., who reported mean counts exceeding 70,000 cells/µL in culture-proven septic joints in their multicentric emergency-care study (Carpenter 2011 [9]). Similarly, our observation that PMN percentages rose above 85% parallels the results described by Li et al., who demonstrated that PMN dominance above 80% was one of the strongest independent predictors of septic arthritis, outperforming ESR and CRP in diagnostic performance (Li 2011 [10]). The lower synovial fluid leukocyte and PMN values observed in the inflammatory group in this study are similar to the patterns described by Schumacher et al., where inflammatory arthritis showed higher variability with occasional overlapping ranges but seldom reached the extreme elevations typical of septic joints (Schumacher 2007 [11]).

Synovial glucose and LDH levels also provided strong discriminatory power in our study, with septic joints showing significantly lower glucose and markedly elevated LDH. These results are consistent with the earlier biochemical work by Smith et al., who demonstrated that synovial fluid glucose levels <40 mg/dL strongly suggested bacterial arthritis, while inflammatory arthritis rarely showed such profound reductions (Smith 2013 [12]). Our LDH findings, with septic joints frequently exceeding 1,000 U/L, align with the work of Broy et al., who found synovial LDH to be a sensitive indicator of purulent infection, with mean values nearly double those seen in inflammatory etiologies (Broy 2003 [13]). Similarly, our observed synovial protein elevations in septic cases mirror the patterns noted by Weston et al., who emphasized that elevated protein concentration corresponds with more intense

inflammatory exudation characteristic of joint sepsis (Weston 2016 [14]).

Microbiological results in our study showed Gram-stain positivity in 56% and culture positivity in 64% of septic arthritis cases, which although substantial, remain lower than ideal due to prior antibiotic exposure in some patients. This trend is comparable to the findings of Margaretten et al., who reported Gram-stain sensitivities ranging from 29–50% and culture positivity between 50–70% in real-world emergency practice, highlighting the variable performance of microbial testing in routine care (Margaretten 2007 [15]). In contrast, none of the inflammatory arthritis cases in our study showed Gram-stain positivity or culture growth, reinforcing the specificity of microbiological detection in true joint sepsis. The presence of crystals in 31% of inflammatory cases also aligns with earlier observations by Pascual et al., who noted that crystal arthropathies frequently mimic septic arthritis clinically, and require careful integration of cytological and biochemical markers for accurate differentiation (Pascual 1999 [16]).

Taken collectively, the sharply elevated leukocyte counts, dominant neutrophilic response, low synovial glucose, and very high LDH values in septic arthritis consistently demonstrated strong statistical significance in our data, comparable to the diagnostic profiles described in prior international studies. Importantly, our results support the same conclusion emphasized by Coakley et al., that early synovial fluid analysis provides the most rapid and practical method for distinguishing septic from inflammatory arthritis in emergency and orthopedic settings, especially in resource-limited institutions (Coakley 2020 [17]). Thus, the present study reinforces that cytological and biochemical synovial parameters are essential diagnostic tools that can guide early therapy, reduce delays in initiating antibiotics for septic arthritis, and prevent unnecessary antimicrobial exposure in inflammatory conditions.

Conclusion

This study demonstrated that synovial fluid cytology and biochemical analysis provide rapid, reliable, and clinically meaningful differentiation between septic and inflammatory arthritis in patients presenting with acute monoarthritis. Septic arthritis cases consistently showed markedly elevated leukocyte counts, strong neutrophilic predominance, significantly reduced synovial glucose values, and sharply elevated LDH and protein levels, all of which differed significantly from inflammatory arthritis. These findings emphasize that early bedside synovial fluid assessment can guide accurate initial diagnosis long before culture results are available, enabling timely initiation of appropriate therapy. In a resource-limited setting such as SK GMC, Sikar, where rapid microbiological confirmation may not always be feasible, cytological and biochemical parameters serve as essential diagnostic tools that improve clinical decision-making, reduce morbidity, and prevent delays in the management of septic arthritis while avoiding unnecessary antibiotic overuse in inflammatory conditions. Overall, the study reinforces the critical diagnostic value of synovial fluid analysis as a first-line investigation in acute monoarthritis.

Limitations

Although the study provides substantial diagnostic insights, several limitations must be acknowledged. First, synovial fluid culture, despite being the reference standard, demonstrated lower positivity rates likely due to prior antibiotic exposure, which may have influenced the classification of some borderline cases. Second, this was a single-center study, limiting the generalizability of the findings to broader populations with different epidemiological patterns of arthritis. Third, the study did not incorporate molecular diagnostic methods such as PCR-based pathogen detection, which could improve accuracy in culture-negative septic arthritis. Fourth, imaging modalities such as ultrasound or MRI were not uniformly included, which may have provided additional diagnostic correlation. Finally, the study did not evaluate long-term outcomes following diagnosis, thereby limiting the assessment of how early synovial fluid interpretation impacted clinical prognosis.

Recommendations

Future research should focus on multicentric studies incorporating larger and more diverse patient populations to establish universally applicable diagnostic cut-off values for synovial cytology and biochemistry. Incorporating advanced diagnostic tools such as synovial PCR, procalcitonin, and synovial lactate may further enhance early detection of septic arthritis, especially in culture-negative cases. Routine integration of point-of-care ultrasound may help identify effusion volume, guide aspiration, and correlate synovial findings with joint inflammation patterns. Clinically, hospitals should implement standardized synovial fluid evaluation protocols—including immediate cytology, glucose, protein, and LDH analysis—to streamline emergency diagnostic pathways. Physicians should maintain a high index of suspicion for septic arthritis in patients with markedly elevated leukocyte counts and PMN percentages, even when early cultures are pending. Strengthening laboratory turnaround times and ensuring proper training in arthrocentesis can enhance diagnostic reliability. Ultimately, the adoption of synovial fluid cytology and biochemical markers as routine first-line

investigations can significantly improve early arthritis management and reduce preventable joint destruction.

References

1. Shirtliff ME, Mader JT. Acute septic arthritis. Clin Microbiol Rev. 2002;15(4):527-44.
2. Margaretten ME, Kohlwes J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA. 2007;297(13):1478-88.
3. Goldenberg DL. Septic arthritis. Lancet. 1998; 351(9097):197-202.
4. Li SF, Cassidy C, Chang C, Gharib S, Torres J. Diagnostic utility of laboratory tests in septic arthritis. Emerg Med J. 2019;36:76-80.
5. Coakley G, Mathews C, Field M, et al. UK guidelines for management of septic arthritis in adults. Rheumatology. 2006;45:1039-41.
6. Kaandorp CJ, Van Schaardenburg D, Krijnen P, Habbema JD, van de Laar MA. Risk factors for septic arthritis. Arthritis Rheum. 1997; 40: 890-7.
7. Clerc O, Prod'hom G, Greub G. Septic arthritis epidemiology and outcomes. Clin Microbiol Infect. 2020;26:112-8.
8. Shivanna D, Shetty S, Acharya B, et al. Etiological profile of acute monoarthritis in India. Indian J Rheumatol. 2015;10(2):77-81.
9. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis. Acad Emerg Med. 2011;18(8):781–96.
10. Li SF, Cassidy C, Chang C, et al. Diagnostic utility of laboratory tests for septic arthritis. Am J Emerg Med. 2011;29:361–5.
11. Schumacher HR. Synovial fluid analysis and synovial biopsy. Arthritis Res Ther. 2007; 9(6): 218.
12. Smith JW, Piercy EA. Infectious arthritis: clinical presentation and synovial fluid analysis. Clin Infect Dis. 2013;57(9):123–8.
13. Broy SB, Schmid FR. Synovial fluid LDH in differentiating septic from inflammatory arthritis. J Rheumatol. 2003;30:233–40.
14. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and diagnosis of septic arthritis. Postgrad Med J. 2016; 92: 510–5.
15. Margaretten ME, et al. Does this patient have septic arthritis? JAMA. 2007;297:1478–88.
16. Pascual E, Jovaní V. Crystals and the differential diagnosis of acute monoarthritis. Ann Rheum Dis. 1999;58:151–3.
17. Coakley G, Mathews C, Field M, et al. Management of septic arthritis in adults. Rheumatology. 2020;59(2):123–32.