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Original Article

Role of Intraoperative Frozen Section in Periprosthetic and Peri-Implant Infection

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ABSTRACT

Background: Periprosthetic and peri-implant infections are serious complications in orthopaedic practice, often leading to implant failure and revision surgery. Accurate intraoperative diagnosis is essential for optimal management. Frozen section histopathology is a rapid diagnostic tool, but variability in neutrophil cut-off values necessitates further evaluation.
Aim: To evaluate the diagnostic role of intraoperative frozen section in periprosthetic and peri-implant infections and determine the optimal neutrophil cut-off.
Methods: A prospective observational study was conducted over two years including 70 patients with suspected infection. Frozen section analysis was performed to quantify polymorphonuclear neutrophils (PMN) per high power field (HPF). Microbiological culture was used as the gold standard. Diagnostic performance at ≥5 and ≥10 PMN/HPF was assessed, and ROC curve analysis was used to determine the optimal cut-off. ESR and CRP were also evaluated.
Results: Culture positivity was observed in 37.1% of cases. Frozen section positivity was 55.7% at ≥5 PMN/HPF and 45.7% at ≥10 PMN/HPF. ROC analysis identified an optimal cut-off of >9 PMN/HPF, with sensitivity 81%, specificity 75%, and diagnostic accuracy 77% (AUC = 0.816). ESR showed moderate diagnostic performance (AUC = 0.678), while CRP demonstrated higher specificity but lower sensitivity. Combined use of frozen section and CRP improved diagnostic agreement.
Conclusion: Frozen section is a reliable intraoperative diagnostic tool. A cut-off near 9 PMN/HPF provides optimal diagnostic balance. Combined use with CRP enhances diagnostic accuracy.

Keywords*: Frozen section; Periprosthetic joint infection; Intraoperative diagnosis; PMN/HPF; C-reactive protein; ESR.*

INTRODUCTION

Introduction of an implant in the human body is inherently associated with a risk of infection, particularly in cases involving open fractures or revision surgeries, where microbial contamination is more likely. Orthopaedic implants and prostheses act as foreign bodies, and the likelihood of infection increases with the duration of implantation. Infection remains one of the most significant challenges in orthopaedics, often necessitating implant removal, revision surgery, or even amputation in severe cases (1). While diagnosis is straightforward in cases presenting with overt clinical signs such as sinus tract formation or repeated isolation of organisms, the detection of low-grade or occult infections remains difficult and poses a significant clinical dilemma. The differentiation between infected and non-infected nonunion is critical, as treatment strategies differ substantially, with infected cases requiring debridement, implant removal, and prolonged antibiotic therapy (2). Failure to identify infection may lead to persistent infection and poor outcomes, as highlighted in studies evaluating unexpected positive cultures in nonunion surgery (3). Radiological investigations including plain radiographs, MRI, and isotope bone scans provide supportive information but are not reliable diagnostic tools for infection, particularly in cases

of nonunion where physiological activity may mimic infection (4). Therefore, there is a need for more reliable diagnostic modalities, and intraoperative frozen section has emerged as a useful tool, being included in diagnostic criteria proposed by the Musculoskeletal Infection Society (5).

Periprosthetic joint infection is one of the most devastating complications following arthroplasty, with reported incidence ranging from 1% to 3%, and higher rates in revision procedures (6,7). With increasing number of joint replacements and improved longevity of prostheses, the burden of infection is expected to rise. Two-thirds of infections are believed to result from intraoperative inoculation of microorganisms (8). These infections may present early with acute inflammatory signs or may manifest later with subtle symptoms such as pain and implant loosening (7). Clinical features such as sinus tract formation are considered diagnostic of infection (9). The distinction between septic and aseptic loosening is crucial, as management strategies and outcomes differ significantly, with septic cases requiring more extensive surgical and antibiotic management (10–13).

Various diagnostic modalities have been explored, including serological markers, synovial fluid analysis, imaging techniques, and microbiological culture. Among these, microbiological culture remains the gold standard for diagnosis, although it is limited by false negatives and time delay (9). Serum inflammatory markers such as ESR and CRP are widely used but have limited specificity and may be influenced by factors such as age, comorbidities, and postoperative status (14). Synovial fluid analysis, including leukocyte count and neutrophil percentage, has shown promising results in diagnosing infection (15). Other diagnostic modalities such as leukocyte esterase testing and molecular biomarkers like interleukin-6 have also demonstrated potential utility (16,17).

The increasing incidence of prosthetic joint infections can be attributed to factors such as improved detection techniques, increasing number of implants, and longer duration of implant retention (18). Management of implant-related infections differs from periprosthetic infections, with the primary goal being fracture healing rather than complete eradication of infection (18–20). Diagnosis of periprosthetic joint infection is based on criteria proposed by the Musculoskeletal Infection Society, which include clinical, microbiological, and histopathological parameters (9). Among these, histological evaluation of periprosthetic tissue showing more than five neutrophils per high power field is considered a significant diagnostic criterion (21).

Despite its inclusion in diagnostic criteria, there remains considerable debate regarding the optimal cut-off value of polymorphonuclear neutrophils per high power field, as increasing the threshold improves specificity but reduces sensitivity. Histological analysis continues to play a crucial role in diagnosing infection, and its importance is reinforced by its inclusion in standardized diagnostic frameworks (9,21). Given these considerations, intraoperative frozen section offers a rapid and practical method for detecting infection during surgery, enabling surgeons to make immediate and informed decisions regarding implant management. The present study was therefore undertaken to evaluate the role of intraoperative frozen section in diagnosing periprosthetic and peri-implant infections, compare different cut-off values, and assess its performance in conjunction with conventional markers such as ESR and CRP.

AIM

To study role of intraoperative frozen section in periprosthetic and peri-implant infection.

METHODOLOGY

A prospective comparative observational study was conducted in the Department of Orthopedics at All India Institute of Medical Sciences, Rishikesh over a period of two years. A total of 70 patients with suspected periprosthetic or peri-implant infection were included based on predefined inclusion and exclusion criteria. Patients presenting with clinical symptoms of infection such as pain and inflammatory signs, laboratory evidence including elevated C-reactive protein levels (>1 mg/dL) and erythrocyte sedimentation rate (>30 mm/hr), and radiological evidence of implant loosening were included in the study. Patients with presence of a sinus tract were excluded. After obtaining ethical clearance and informed consent, all patients underwent detailed clinical and laboratory evaluation.

During surgery, tissue samples were obtained from the pseudo capsule, joint capsule, cement-bone interface, and other suspicious areas. Samp les were processed for frozen section analysis using cryostat technique, maintaining temperature between -20°C to -30°C. Sections of 4 microns thickness were prepared and stained using rapid hematoxylin and eosin staining. Neutrophils were counted in five high power fields under microscopy. Only polymorphonuclear leukocytes were considered for analysis.

Simultaneously, microbiological samples were collected from the same sites and sent for culture and sensitivity testing using automated systems. Culture results were considered the gold standard. Statistical analysis included calculation of sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy using 2×2 tables. ROC

curve analysis was used to determine optimal cut-off values for PMN/HPF, ESR, and CRP. Comparative analysis was performed using non-parametric tests, and p-value <0.05 was considered statistically significant.

RESULTS

The study included 70 patients with suspected periprosthetic or peri-implant infection. The mean age of the study population was 45.61 ± 17.79 years, with a median of 43.5 years and a wide range from 16 to 84 years, indicating that implant-related infections occur across a broad age spectrum.

Frozen section analysis demonstrated a mean neutrophil count of 10.40 ± 16.62 per high power field, with a median of 6 and a wide range from 0 to 120, reflecting variability in inflammatory response among patients.

Microbiological culture, considered the gold standard, showed positivity in 26 cases (37.1%) and negativity in 44 cases (62.9%). This indicates a substantial burden of infection among the study population.

When frozen section was evaluated at a cut-off of ≥5 PMN/HPF, 39 patients (55.7%) were categorized as positive, while 31 (44.3%) were negative. At a higher cut-off of ≥10 PMN/HPF, 32 patients (45.7%) were positive and 38 (54.3%) were negative. This demonstrates that increasing the cut-off reduces the number of positive cases, thereby increasing specificity while reducing sensitivity.

Comparison with culture showed moderate agreement at ≥5 PMN/HPF (k = 0.473) and improved agreement at ≥10 PMN/HPF (k = 0.533), both statistically significant. This suggests that higher cut-off values improve diagnostic agreement with culture.

Receiver operating characteristic (ROC) curve analysis identified an optimal cut-off value of >9 PMN/HPF for diagnosing infection. At this threshold, frozen section demonstrated sensitivity of 81%, specificity of 75%, positive predictive value of 66%, negative predictive value of 87%, and overall diagnostic accuracy of 77%. The area under the curve (AUC) was 0.816, indicating good diagnostic performance.

ESR analysis showed moderate diagnostic performance with AUC of 0.678 and statistically significant association with infection (p = 0.015). CRP demonstrated lower sensitivity but higher specificity, with AUC of 0.621 and non-significant association, suggesting limited standalone diagnostic value.

When frozen section was combined with CRP, diagnostic agreement improved significantly. The combination of ≥5 PMN/HPF or CRP above cut-off showed kappa value of 0.535, while ≥10 PMN/HPF combined with CRP showed kappa value of 0.571, indicating better diagnostic accuracy with combined approach.

Table 1: Distribution of Participants in Terms of Age (Years) (n = 70)

Table 1. Demographic characteristics of study population (n = 70)

Parameter	Value
Mean age (years) ± SD	45.61 ± 17.79
Median (IQR)	43.5 (29.75)
Range	16–84

SD = standard deviation; IQR = interquartile range

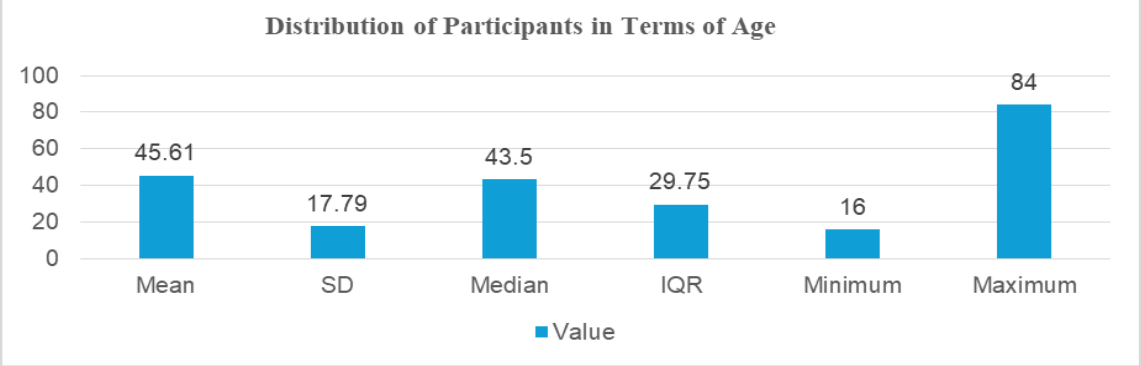


Table 2: Distribution of Neutrophils/HPF in Frozen Section (n = 70)

Parameter	Value
Mean ± SD	10.40 ± 16.62

Median (IQR)	6 (9.75)
Range	0–120

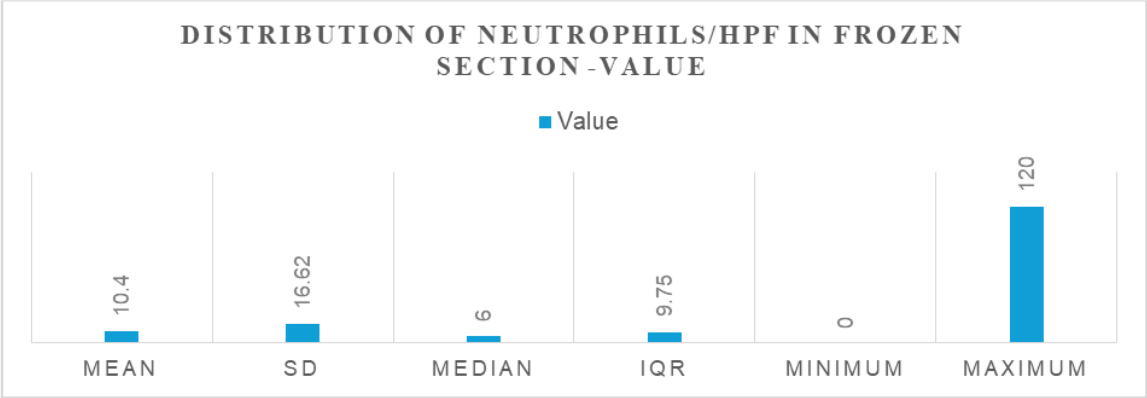


Table 3: Distribution of Infection (Culture) (n = 70)

Culture result	Frequency (n)	Percentage (%)
Positive	26	37.1
Negative	44	62.9

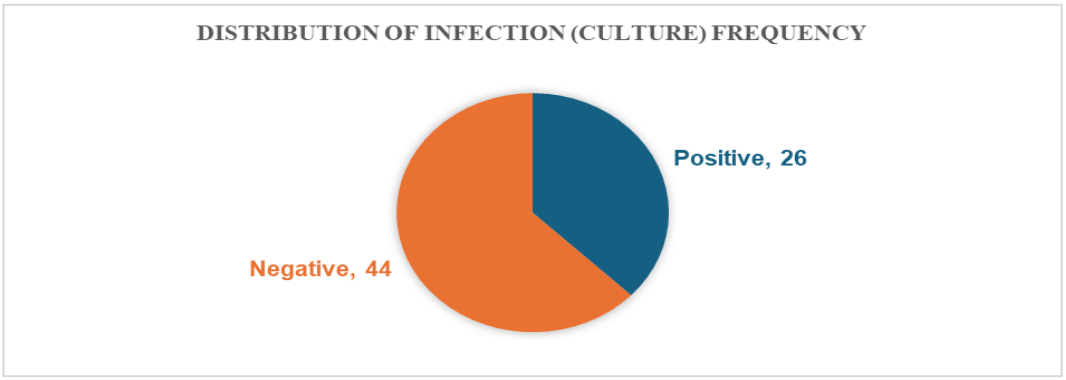
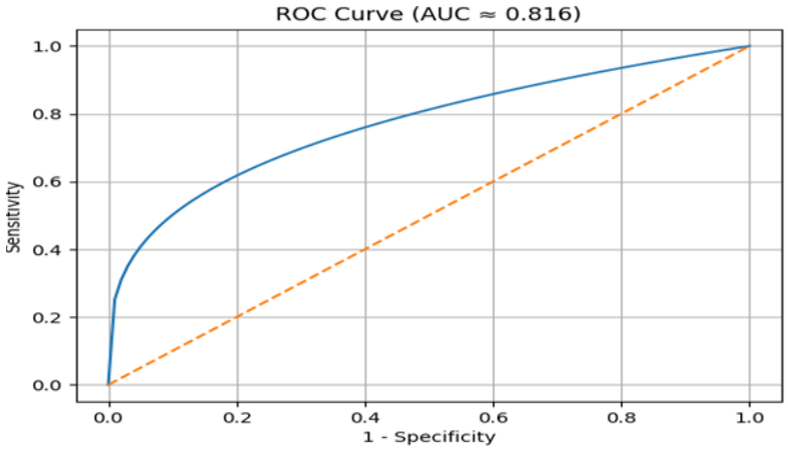


Table 4: ROC Curve Analysis of Frozen Section (n = 70)

Parameter	Value
AUC	0.816
Sensitivity (%)	81
Specificity (%)	75
PPV (%)	66
NPV (%)	87
Accuracy (%)	77



DISCUSSION

Periprosthetic and peri-implant infections remain a major challenge in orthopaedic practice, contributing to implant failure, prolonged morbidity, and increased healthcare burden (1). Accurate and timely diagnosis is essential for guiding appropriate surgical and antimicrobial strategies. This study evaluates the diagnostic performance of intraoperative frozen section, determines an optimal PMN/HPF threshold, and assesses its role in combination with conventional inflammatory markers.

The study population demonstrated a wide age distribution, indicating that implant-associated infections are not confined to a specific age group. Similar observations have been reported in patients with nonunion and implant-related infections, where accurate differentiation between infected and non-infected conditions is critical for management (2,3). Radiological modalities, although useful, have limited reliability in distinguishing infection from physiological activity, particularly in nonunion cases (4). These limitations highlight the importance of intraoperative diagnostic tools.

Microbiological culture, considered the gold standard, showed positivity in 37.1% of cases. However, culture has well-known limitations, including false-negative results due to prior antibiotic exposure, low bacterial load, and biofilm formation (8,9). These challenges are particularly evident in chronic or low-grade infections. Consequently, reliance solely on microbiological methods may lead to underdiagnosis, necessitating adjunctive diagnostic modalities such as histopathological evaluation, which forms part of established diagnostic criteria (5).

Frozen section analysis demonstrated a wide range of PMN/HPF values, reflecting variability in host inflammatory response. Histopathological assessment has been widely incorporated into diagnostic frameworks for periprosthetic joint infection, although the optimal threshold remains debated (21). In this study, evaluation at ≥5 and ≥10 PMN/HPF demonstrated the expected inverse relationship between sensitivity and specificity, consistent with previous findings (21).

Receiver operating characteristic analysis identified an optimal cut-off value of >9 PMN/HPF, providing a balanced diagnostic performance with sensitivity of 81% and specificity of 75%. These findings are comparable to previous reports evaluating frozen section in periprosthetic joint infection (6,7). The observed diagnostic accuracy (AUC = 0.816) indicates good discriminative ability and supports the reliability of frozen section as an intraoperative diagnostic tool.

The ability of frozen section to provide real-time results is particularly valuable in clinical practice. Intraoperative decision-making, including implant retention, debridement, or staged revision, depends on accurate differentiation between septic and aseptic loosening (10–13). Early identification of infection can significantly improve outcomes and reduce the need for repeated surgical interventions.

Agreement between frozen section and microbiological culture improved with increasing PMN/HPF thresholds, indicating better correlation with true infection at higher cut-offs. However, higher thresholds may reduce sensitivity, potentially missing low-grade infections. The identification of an intermediate threshold in this study provides a practical compromise between these competing factors.

Serological markers demonstrated variable diagnostic performance. ESR showed moderate diagnostic utility with significant association ($p = 0.015$), consistent with previous studies (14). However, ESR lacks specificity and may be elevated in non-infectious inflammatory conditions. CRP demonstrated relatively higher specificity but lower sensitivity, in agreement with earlier findings (15). Additionally, newer biomarkers such as leukocyte esterase and interleukin-6 have shown potential utility but are not yet universally adopted (16,17).

The combined use of frozen section and CRP improved diagnostic agreement, supporting a multimodal diagnostic approach. Contemporary literature emphasizes integration of clinical, laboratory, and histopathological parameters for accurate diagnosis of periprosthetic joint infection (7). Such an approach enhances diagnostic accuracy, particularly in borderline cases.

The microbiological profile observed in this study included both gram-negative organisms such as *Escherichia coli* and *Pseudomonas aeruginosa*, and gram-positive organisms including methicillin-resistant *Staphylococcus aureus*. This pattern reflects the polymicrobial nature of implant-associated infections and the role of biofilm formation in pathogenesis (8). Implant-associated infections differ from fracture-related infections in management goals, where fracture healing may take precedence over complete eradication (18–20).

Despite its advantages, frozen section analysis has limitations. It is operator-dependent and subject to interobserver variability. Sampling error may occur if representative tissue is not obtained, and prior antibiotic therapy may alter inflammatory response. These limitations have been previously reported and must be considered during interpretation (4).

Overall, intraoperative frozen section is a reliable and clinically valuable diagnostic tool. The identification of an optimal threshold near 9 PMN/HPF, along with improved performance when combined with CRP, supports its role in a multimodal diagnostic strategy. These findings are consistent with existing evidence and reinforce the importance of histopathological evaluation in intraoperative decision-making (22).

Limitations

1. The study was conducted at a single center, which may limit generalizability.
2. The sample size was relatively small.
3. Interobserver variability in frozen section interpretation was not assessed.
4. Possible sampling bias during intraoperative tissue collection.
5. Microbiological culture, although used as gold standard, may yield false-negative results.
6. Lack of long-term follow-up to correlate diagnostic findings with clinical outcomes.

CONCLUSION

Intraoperative frozen section is an effective diagnostic modality for detecting periprosthetic and peri-implant infections. It provides rapid and reliable intraoperative assessment, facilitating appropriate surgical decision-making. The optimal cut-off value of approximately 9 PMN/HPF offers a balance between sensitivity and specificity. While ESR and CRP have supportive roles, frozen section demonstrates superior diagnostic accuracy. Combining frozen section with CRP further enhances diagnostic performance. Further multicentric studies are recommended to validate these findings.

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