

# The microbiome of orthopedic implant-associated infections and its correlation with inflammatory markers



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## ABSTRACT

**Background:** Implant site and periprosthetic joint infections (PPJI) are of major concern with tremendous improvement in orthopedic operative procedures. Early diagnosis of infection is the cornerstone for success rate and prevention of implant failure. The need for inflammatory biomarkers followed by culture sensitivity remains inevitable in the diagnosis of infection.

**Aims and Objectives:** The aim is to study the prevalent biofilm-forming pathogens and to correlate with antimicrobial resistance and also to estimate inflammatory markers to predict the presence of PPJI. **Materials and Methods:** A descriptive cross-sectional study involving 57 patients showing signs of PPJI was evaluated. Clinical samples of these cases were processed, the bacterial pathogens were isolated and bio-film formation was tested. Inflammatory markers C-reactive protein by latex agglutination and interleukin-6 (IL6) by ELISA is determined. **Results:** A total of 36 bacterial pathogens are isolated, 17% are Gram-positive cocci (GPC) and 46% are Gram-negative bacilli (GNB). Among these, 54% are biofilm producers and pseudomonas species (33%) are predominant. Antibiotic susceptibility studies showed GPC to be highly sensitive to linezolid (100%) and vancomycin (100%). Among GNB, pseudomonas species showed susceptibility of 85%, 57%, and 47% to meropenem, amikacin, and piperacillin-tazobactam, respectively. Acinetobacter is the most resistant isolate. The IL value of 19.5 arrived by the receiver operating curve showed maximum sensitivity and minimal false positivity. **Conclusion:** Assessing the infection-specific biomarkers like IL6 levels is advantageous in earlier detection of implant site infection and aid in instituting specific antibiotics for the most common implant and PPJI before permanent implant failure and sepsis.

**Key words:** Microbiome; Periprosthetic joint infections; Implant site infection; C-reactive protein; Interleukin 6

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## INTRODUCTION

Implant site infection and peri-prosthetic joint infections (PPJI), remain as one of the major concerns for revision and re-revision surgeries. The prevalence of implant-associated infections requiring more complex surgical procedures is costing a huge burden both financially and mentally due to prolonged hospital stays and compromised treatment results.<sup>1</sup> The proposed theories behind the implant failure are septic detachment due to PPJI debris-induced release of interleukin 6 (IL6) by innate immune systems and aseptic implant failure.<sup>2</sup>

The cornerstone for any effective treatment strategy is early diagnosis. The immediate need for novel markers in diagnosing the PPJI and implant infections is because cases of chronic infection are often “silent” and culture negative to conventional tests and several patients with immunocompromised or immune deficiency state never present with classical clinical features of infection such as fever or elevated neutrophil counts, thus their pain is incorrectly attributable to the device instability, aseptic loosening, and malalignment causing increased morbidity.<sup>3</sup> Thereupon some infections remain undiagnosed until the

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time of surgery, which leads to deteriorated periprosthetic tissues and patient condition.

Although novel markers for diagnosing orthopedic implant-associated infections have not yet been established, the synovial IL-6 marker is found to have huge specificity and sensitivity to PPJI detection and classically differentiates aseptic loosening from PPJI than serum C reactive protein (CRP) and white cell counts (less specificity).<sup>4</sup> Aseptic loosening-associated IL-6 levels fall to normal levels 48 h post-arthroplasty, while infection-associated IL-6 levels remain to be high.<sup>5,6</sup>

Although several studies have explained the relationship between infection and inflammatory markers as well as microbiome prevalent at implant infections separately,<sup>7</sup> the effective correlation between the severity of graft failure caused by the specific microbial community and inflammatory marker variations (mainly IL-6) remains unknown.

This study compares the prevalence of severe antibiotic-resistant pathogens along with biofilm detection with the corresponding IL-6 and CRP variation for early detection of orthopedic implant infections with the help of these biomarkers in future.

### Aims and objectives

The study aims to isolate microbiome from PPJI and internal fixation device-associated infection, detect biofilm formation, and determine the pattern of antimicrobial resistance among pathogens to start early antimicrobial therapy. And also to estimate inflammatory markers to predict the presence of PPJI and implant failures and correlate with culture positivity.

## MATERIALS AND METHODS

This is a descriptive cross-sectional study conducted in a tertiary care hospital, Chennai, Tamil Nadu, for 4 months from June 2022 to September 2022. With institutional ethical committee approval and due informed consent, a total of 57 patients are included in the study by simple random sampling method.

### The inclusion criteria

All patients of both genders above 18 years of age and patients with suspected signs of infection after orthopedic implants showed joint pain, signs of joint inflammation, and the presence of sinus tract.

### The exclusion criteria

Patients with revision surgeries for metal allergy and traumatic causes are excluded from the study.

### Sample collection transport and processing<sup>8-10</sup>

Specimens obtained include synovial fluid, intraoperative samples including periprosthetic tissue, purulent discharges, implant devices changed by revision and re-revision surgeries, and patient blood. Clinical samples were analyzed by standard methods as follows:

The synovial fluid is centrifuged and deposited subjected to direct Gram stain and cultured on dried plates of blood agar, MacConkey agar, and chocolate agar and in enrichment broth and incubated the plates at 37°C aerobically for 24–48 h. The blood agar and chocolate agar were placed in a candle jar provided with 5–10% of CO<sub>2</sub> at 37°C for 24 h. Intraoperative samples were processed under a biosafety cabinet, and periprosthetic tissue specimens were homogenized in a tissue grinder, processed in standard media aerobically, and anaerobic culture in an anaerobic jar with the GasPak system.

### Implants and fixation devices

The screws and implants are placed in brain heart infusion broth and vortexed well to dislodge the pathogen from the biofilm and the fluid is cultured. The pathogens are phenotypically identified with standard microbiological techniques.

### Assessing inflammatory biomarkers<sup>11</sup>

The serum synovial fluid samples are assayed for CRP and IL-6.

CRP is tested by semi-quantitative latex agglutination method using Rhelax – CRP reagent. CRP concentration is estimated for the highest dilution at which visible agglutination occurred and calculated using the formula: CRP (mg/dL) = S × D (Where S is the sensitivity of test reagent, i.e., 0.6 mg/L) D is the highest serum dilution showing agglutination.

### IL6 estimation

By quantitative ELISA, the serum/synovial IL-6 levels were determined using the Diaclone Human IL-6 solid phase sandwich ELISA kit as per the manufacturer's assay procedure. Absorbance was read at 450 nm within 30 min of stopping the reaction.

### Antimicrobial susceptibility testing<sup>12</sup>

Antimicrobial susceptibility testing is performed by the Kirby–Bauer disc diffusion method. The test organisms grown on culture media are inoculated into peptone water and incubated at 37°C for 2–4 h. The turbidity is matched with 0.5 McFarland. Lawn culture is made over a Muller–Hinton plate and the antibiotic discs are placed according to the growth Gram-positive or Gram-negative organisms. The plates are incubated for 18–24 h at 37°C.

The zone diameter is recorded and interpreted as sensitive, intermediate, or resistant according to clinical laboratory standard institute (CLSI 2022).

### Biofilm detection by tube method<sup>13</sup>

A 10 mL of trypticase soya broth with 1% glucose is inoculated with loopful of test organisms and incubated for 24 h at 37°C. The tubes are decanted and washed with phosphate buffer saline of pH 7.5 to remove non-adherent cells and air dried. Then, the tubes are stained with 0.1% crystal violet and washed with deionized water to remove excess stain. The tubes were dried and placed in an inverted position and observed for biofilm formation. The lining of visible films at the sides and bottom of the tubes is considered positive for biofilm formation and it is scored as follows 0-absent, 1-weak, 2-moderate, and 3-strong biofilm producers.

### Statistical analysis

After methodology, all results were tabulated into MS Excel format. All statistical analysis was done with mean, proportion, and percentage. The Pearson correlation analysis validity testing was also made. Using all the data, the receiver operating curve (ROC) curve was made with the help of the SPSS software.

## RESULTS

A total of 57 patients showing signs of orthopedic implant-associated infections are studied. Of 57 cases, 31.6% of cases were in the age group of 19–30 years followed by 26.3% in the age group of 31–40 years. Among the cases, 48 (84.2%) are male and 9 (15.7%) are female (Table 1).

Among the 57 samples obtained from patients showing signs of infection, 36 (63%) patients showed positive culture reports and 21 (37%) showed negative culture of the total 36 isolates, 10 (17%) were Gram-positive cocci (GPC) and 26 (46%) were Gram-negative bacilli (GNB). Among these Staphylococcus species accounts to (9 isolates) were the most common organisms followed by pseudomonas (7 isolates) (Table 2).

Among the isolates, 54% are biofilm producers and 46% are biofilms non-producers. Out of the biofilm producers 44% are GNB and 10% GPC. Out of all bacterial biofilms, 19% are strong, 27% are moderate, and 54% are weak biofilm producers (Figure 1).

*Pseudomonas aeruginosa* (33%) is the predominant biofilm producer among the total isolates obtained. Among the strong biofilm producers, *P. aeruginosa* contributes the most (42.8%) followed by *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Among the GNB *K. pneumoniae* showed 86%

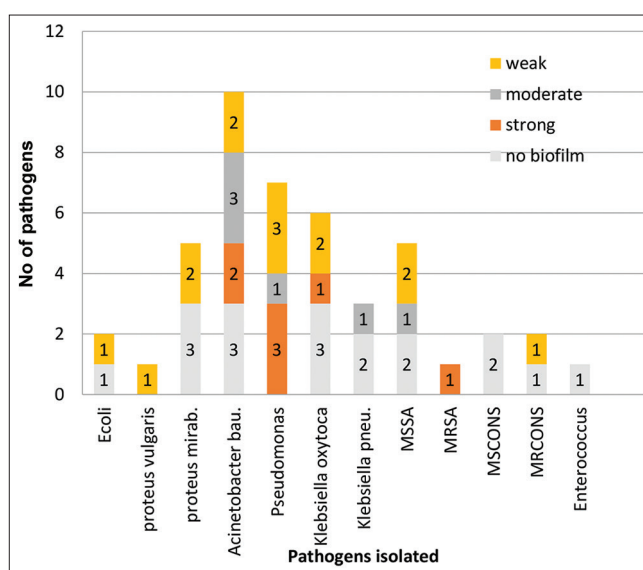
**Table 1: Age and gender-wise distribution of the cases (n=57)**

Age	Male, n (%)	Female, n (%)	Total (n=57)	Percentage
19–30	17 (29.8)	1 (1.8)	18	31.6
31–40	12 (21)	3 (5.3)	15	26.3
41–50	10 (17.5)	1 (1.8)	11	19.2
51–60	4 (7)	1 (1.8)	5	8.8
61–70	3 (5.2)	3 (5.3)	6	10.5
71–80	2 (3.5)	0	2	3.5

**Table 2: Distribution of pathogens in culture (n=36)**

Group	Isolates	n (%)
GPC (10 isolates) 17%	MSSA	5 (8.5)
	MRSA	1 (1.7)
	MSCONS	1 (1.7)
	MRCONS	2 (3.4)
	<i>Enterococcus faecalis</i>	1 (1.7)
GNB (26 isolates) 46%	<i>Pseudomonas aeruginosa</i>	7 (12.3)
	<i>Acinetobacter baumannii</i>	6 (10.61)
	<i>Klebsiella pneumoniae</i>	4 (7.07)
	<i>Klebsiella oxytoca</i>	2 (3.53)
	<i>Escherichia coli</i>	1 (1.76)
	<i>Proteus vulgaris</i>	5 (8.84)
	<i>Proteus mirabilis</i>	1 (1.76)

GPC: Gram-positive cocci, GNB: Gram-negative bacilli



**Figure 1:** Distribution of pathogens in culture (n=36) and its biofilm production among the cases

susceptibility for meropenem. *Pseudomonas* species showed susceptibility of 85%, 57%, and 47% to meropenem, amikacin, and piperacillin–tazobactam, respectively.

*Acinetobacter* was the most resistant isolate among GNB with 10% sensitivity to meropenem and fluoroquinolones and 20% sensitivity for cefepime, ceftazidime, and cotrimoxazole. GPC was found highly sensitive to linezolid

(100%) and vancomycin (100%). All the MRSA isolates are vancomycin (100%) sensitive. *Enterococcus faecalis* is 100% susceptible to penicillin, ampicillin, linezolid, vancomycin, and high-level gentamicin.

The estimation of inflammatory biomarkers among the cases showed that there is a definitive correlation in patients presenting with signs and symptoms of implant-associated infection and IL-6 (Figure 2).

An analysis of IL-6 with culture positivity showed there correlation between them at  $P=0.01$  showing IL6 could be the best early predictive marker for infection suspicion (Figure 3).

Pearson's correlation analysis is negative between IL-6 and CRP (Figure 4).

The concentration of IL of 19.5 arrived by the ROC curve, showed maximum sensitivity and minimal false positivity in the ROC curve constructed with sensitivity in the Y-axis and 1-specificity in the X-axis.

After the construction of the ROC curve with various sensitivities under false-positive rate, at maximum sensitivity and minimal false positivity the point of IL6 is located. The value of IL of 19.5 is arrived by the ROC curve, showed maximum sensitivity and minimal false positivity. Thus from this study, the maximum sensitivity of IL-6 obtained was found to be 77.1% with a specificity as 89% and an overall accuracy of 91%.

## DISCUSSION

Orthopedic implant-associated infections emerge as an imperative patient safety problem, as it demands the huge financial and societal costs of patients.<sup>14</sup> This study was to determine the microbiome of orthopedic implant-associated infections, their antimicrobial resistance pattern and the usefulness of inflammatory markers (IL-6) to predict implant-associated infections with just signs of clinical suspicion and biomarkers assessment.

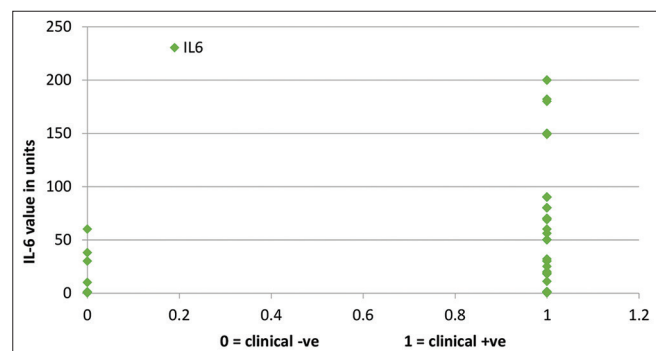


Figure 2: Chart showing correlation between the clinical diagnosis and IL6 level

In the present study, out of 57 cases, 31.6% of cases were in the age group of 19–30 years followed by 26.3% in the age group of 31–40 years. Among 57 patients, 48 (84.2%) are male and 9 (15.7%) are female. Predominantly, males are affected in our study, well correlating with studies of Jakribettu et al., who also have reported adult male predominance and the most common site affected was tibia. These findings can be

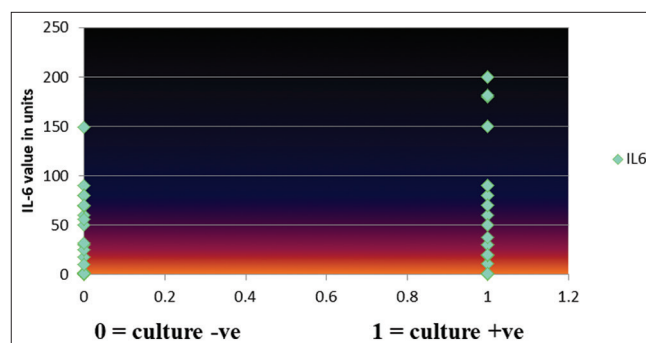


Figure 3: Chart showing correlation between IL6 and culture positivity

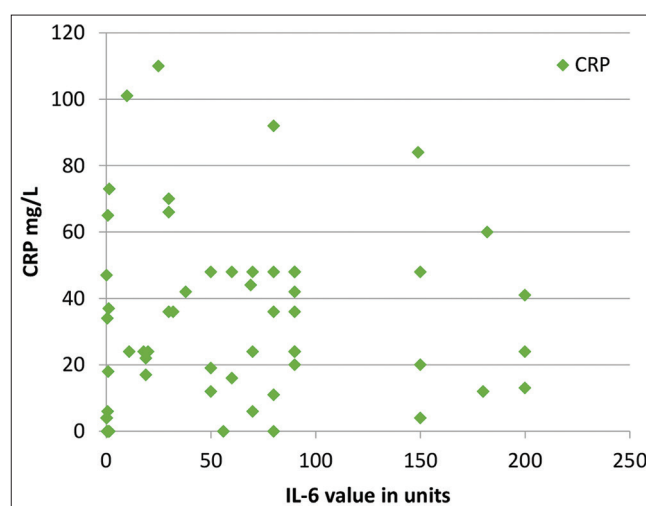


Figure 4: IL-6 versus CRP a correlation analysis

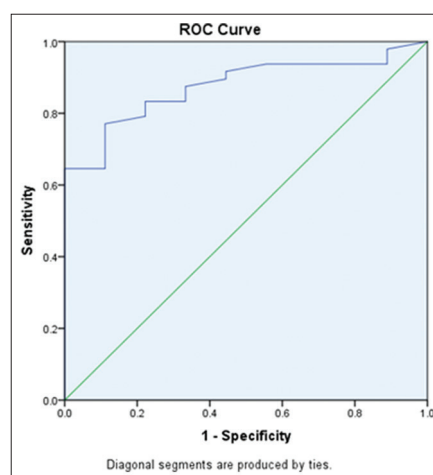


Figure 5: ROC curve diagonal segments are produced by ties

attributed to the fact that the majority of the cases included in this study were road traffic accidents.<sup>15</sup>

Among the 57 samples obtained from patients showing signs of infection 36 (63%) patients showed positive culture and 21 (37%) showed negative culture. In the present study, predominant pathogen associated with implant-associated infections are GNB accounting for 46 percent with pseudomonas (29%) and the GPC constituted about 17% with the predominant organism as staphylococcus. Anaerobic culture of the tissue samples showed no growth. This could be attributed to the prior antibiotic usage and difficulty in growing the anaerobes. In the study Philip et al.,<sup>15</sup> aerobic Gram-negative and Gram-positive isolates accounted for about 51.4% and 48.6%, respectively, and *Staphylococcus aureus* showed a predominance of about 38.5% well correlating with our studies. Similarly, Khosravi et al., and Fernandes et al.,<sup>16</sup> studies agree with the present study, where they reported that *S. aureus* as the most prevalent isolate followed by *P. aeruginosa* and *Klebsiella* species.<sup>16</sup> In contrast, the predominance of *S. aureus* was also reported by Finelli et al.,<sup>17</sup> and confirmed in the review study conducted by Li and Webster.<sup>18</sup>

In the present study, the antimicrobial susceptibility pattern of predominant GNB pseudomonas showed 71% susceptibility for meropenem (MRP) followed by 57% to piperacillin and tazobactam (Piptaz), 43% for ciprofloxacin and 43% for amikacin. While these Gram-negative organisms showed resistance to 3<sup>rd</sup> generation cephalosporins.

MRP is found to be an effective antibiotic against them. Susceptibility patterns of other GNB are highly susceptible to amikacin, tetracycline (Piptaz), MRP, and the least sensitive to cotrimoxazole and ceftazidime. All the proteus species showed 100% resistance to cotrimoxazole and cefotaxime. The susceptibility pattern of GNB obtained showed similar findings in studies by Fernandes et al.<sup>16</sup> and Silva et al.<sup>19</sup>

GPC is highly sensitive to linezolid (100%) and vancomycin (100%). All the MRSA isolates are vancomycin (100%) sensitive. Among the GPC, all the isolates of *S. aureus* and coagulase negative *S. aureus* are sensitive to vancomycin with MIC <1. The pattern of susceptibility of *E. faecalis* is found to be 100% susceptibility for penicillin, ampicillin, linezolid vancomycin, and high-level gentamicin well correlating with studies of Alelign et al.,<sup>20</sup> where all 33% of enterococcus isolated showed 100% vancomycin susceptibility.<sup>3</sup>

In the present study, the total biofilm production tested by tube method is 54% biofilm producers and 46% non-biofilm producers. The strong, moderate, and weak producers of biofilm are 19%, 27%, and 54 %, respectively. Of the total biofilm formers, 44% are GNB and 10% are GPC. pseudomonas species contributed to the most biofilms

42.8%, in contrast to findings from study of Anisha et al., where MRSA was the predominant biofilm producer (33%).

The inflammatory biomarkers CRP and IL-6 are assayed for all patients with PPJI. The estimation of IL-6 is done by ELISA method. The concentration of IL 6 of 19.5 arrived by the ROC curve, showed maximum sensitivity and minimal false positivity (Figure 5). Thus, the maximum sensitivity of serum IL-6 obtained from this study is found to be 77.1% with specificity as 89%, and overall accuracy is found to be approximately 91%. These findings were very similar to the study by Xie et al.,<sup>4</sup> whose data showed the sensitivity and specificity of serum IL-6 to be 74% and 92%, respectively.<sup>24</sup>

IL-6 with its maximum cutoff value is plotted to find its degree of correlation between the culture positivity, clinically proven diagnosis, and CRP value for all 57 patients. The plot showed that there is no correlation between IL-6 value and CRP. This can be attributed to the fact that CRP values can be elevated not only in infective conditions but also in other inflammatory pathologies. It is studied to assess whether IL-6 is elevated specifically in relation to infective etiologies.

A plot is made simultaneously between IL-6 versus culture positivity and IL-6 versus clinically proven infective cases. It is found that there is a definitive correlation between IL-6 and clinically proven cases with P at 0.05 and hence IL-6 can be a specific novel marker for implant-associated infections in doubtful cases. There is also a correlation between IL-6 and culture with p at 0.01 stating that IL6 can definitely be an early marker for infective status even before the infection is well-established clinically. This shows that the high specificity and sensitivity of IL-6 can be used for immediate clinical suspects of implants and fixation device-associated infection and PJI to prevent the septic implant failure rates drastically.

#### Limitations of the study

The limited period, less sample size and difficulty to isolate anaerobes due to prior broad-spectrum antibiotics treatment are some of the limitations.

## CONCLUSION

Assessing the highly infection-specific biomarkers like IL-6 levels can have an advantage in earlier detection of implant site infection, and help in instituting specific antibiotics before permanent implant failure and sepsis.

Studying common microbiome associated with the orthopedic implants and antibiotic susceptibility tests can aid in controlling infection-related revision surgeries performed in a tertiary care hospital and instituting strict aseptic protocols during procedures. The anti-microbial susceptibility data

obtained from our hospital for implant-associated infection cases can be used effectively to modify drug therapeutic and prophylactic regimens in clinically uncertain cases. An attempt to study the prevalence of biofilm-forming pathogens and their severity can inculcate further future research possibilities to curb biofilm formation by bio-implant modification.

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### Authors' Contributions:

**K**- Data collection, implementation of the study protocol, literature survey, and prepared the first draft of the manuscript. **R**- Concept design, work protocol, preparation of manuscript, editing, and literature survey. **SN**- Study design, data compiling, interpretation statistical analysis, literature survey, manuscript revision, correction, and submission of the article.

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