# The Utility of an Elevated C-Reactive Protein Threshold in Two-Stage Revision Knee Arthroplasty Reimplantation

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**INTRODUCTION:** Two-stage knee reimplantation arthroplasty is a commonly used for treating and eradicating chronic periprosthetic joint infections (PJI) in the United States. The utility and interpretation of laboratory inflammatory threshold markers, including C-reactive protein (CRP) as a diagnostic tool for identifying periprosthetic joint infections requiring stage 1 hardware explant and antibiotic spacer placement has been well established. However, the value of these laboratory markers in determining the timing of stage 2 reimplantation and predictability of infection eradication remains ill-defined. Prior studies have investigated the percent change in CRP levels before and after two-stage reimplantation for PJI in addition to standard baseline CRP threshold cut-offs of <10mg/L to correlate pre-test probability of persistent infection prior to reimplantation without much success. Many patients do not meet the CRP threshold cut-off <10mg/L to proceed with stage 2 reimplantation revision arthroplasty but still have full eradication of infection when assessed intraoperatively. Previous studies have been limited by the low power and short-term follow-up in establishing the optimal CRP threshold level. This study aims to compare the utility of a higher CRP threshold level of <20 mg/L for stage 2 reimplantation revision total knee arthroplasty (rTKA) for persistent joint infection compared to rTKA for non-infectious etiology including aseptic loosening, instability, periprosthetic fracture, and arthrofibrosis. Comparing the value of a higher CRP level prior to revision arthroplasty in both infectious and non-infectious etiologies may aid with isolating elevated CRP levels and the predictability on outcomes beyond infection, including venous thrombosis, periprosthetic fracture, and surgical complications.

**METHODS:** The TriNetX US Collaborative Network database was queried for all who underwent rTKA from 2010 to 2023. 90-day postoperative complications following rTKA as well as patient demographics and comorbidities were collected. The study population was divided into 2 sub-groups: infectious and non-infectious revisions. Each sub-group was indexed into 2 cohorts based on their preoperative CRP: ≥20 and <20. Propensity score matching was performed for the 2 cohorts based on age, gender, race, ethnicity, diabetes, metabolic disorder, obesity, hypertension, heart disease, and chronic lower respiratory disease. Then, TriNetX's measures of association analysis was performed to determine differences in 90-day outcomes between cohorts including periprosthetic fracture, revision, instability or loosening, nerve injury, vascular injury, death, cardiac complication, respiratory complication, deep vein thrombosis, surgical site infection, and dehiscence.

**RESULTS:** A total of 10,345 (6,790 infectious and 3,693 non-infectious) patients were included in this study. Of infectious rTKAs, 4,841 were in the CRP ≥20 group and 1,949 were in the CRP <20 group. Of non-infectious rTKAs, 472 were in the CRP ≥20 group and 3,221 were in the CRP <20 group. Propensity score matching was performed to match 1,949 patients from each infectious cohort and 468 patients from each non-infectious cohort to form the final study population. After propensity score matching, there were no significant differences between infectious and non-infectious rTKA cohorts. For the infectious rTKA sub-group, compared to CRP ≥20, CRP <20 was significantly associated with a lower risk of periprosthetic infection (odds ratio [OR] 0.31, $P < 0.001$, 95% confidence interval [CI] 0.26-0.36), revision (OR 0.59, $P < 0.001$, 95% CI 0.49-0.71), vascular injury ($P = 0.002$), and deep vein thrombosis (OR 0.69, $P = 0.019$, 95% CI 0.50-0.94). For the non-infectious rTKA sub-group, compared to CRP <20, CRP ≥20 was significantly associated with a greater risk of periprosthetic fracture (OR 0.41, $P < 0.001$, 95% CI 0.25-0.67), periprosthetic infection ($P = 0.001$), and revision (OR 0.47, $P = 0.045$, 95% CI 0.22-1.00), as well as a significantly greater risk of instability or loosening (OR 1.67, $P = 0.029$, 95% CI 1.05-2.65).

**DISCUSSION:** Traditional threshold levels of CRP <10mg/L as a marker of infection eradication may not be applicable in the stage 2 reimplantation revision arthroplasty setting. Many patients with chronic PJI who have undergone antibiotic stage 1 spacer placement and completion of systemic antibiotics may never reach subclinical CRP thresholds despite infection clearance. This study utilizes a large national database to suggest CRP <20 mg/L is a safe threshold limit with statistically significant lower risk for recurrent PJI, venous thrombosis, revision surgery, and vascular injury after stage 2 rTKA. In chronic PJI patients with clinical improvement and pre-reimplantation CRP levels between 10-20mg/L, stage 2 rTKA may be safe despite the elevated CRP level compared to traditional baseline limits. Delaying reimplantation until CRP levels are <10mg/L may significantly delay time to antibiotic spacer explant and increase risk for knee stiffness, instability, arthrofibrosis, and poor outcomes without improvement in re-infection rates. In patients undergoing rTKA for non-infectious etiology, elevated CRP levels ≥20 mg/L may also prove useful in counseling patients of greater risk for postoperative periprosthetic fracture, revision surgery, and subclinical PJI that may have been missed.

**SIGNIFICANCE/CLINICAL RELEVANCE:** The interpretation of CRP inflammatory values to determine the optimal timing of stage 2 reimplantation and predictability of infection eradication in rTKA remains unknown. The lower risk for recurrent PJI, revision, and complications despite an elevated CRP threshold level to 20mg/L may help providers when assessing timing of stage 2 reimplantation in patients with persistently elevated markers.

**IMAGES AND TABLES:**

**Table 1.** Comparison of 90-day postoperative complications following infectious and non-infectious revision total knee arthroplasty between propensity score-matched cohorts. Bold *P* values indicate statistical significance with $P < 0.050$.

| | Infectious | | | Non-infectious | | |
|---|---|---|---|---|---|---|
| Complication | CRP ≥20 Number (%) | CRP <20 Number (%) | OR, *P* value, (95% CI) | CRP ≥20 Number (%) | CRP <20 Number (%) | OR, *P* value, (95% CI) |
| Periprosthetic fracture | 87 (4.5%) | 71 (3.6%) | 1.24, 0.194, (0.90, 1.70) | 55 (11.7%) | 24 (5.1%) | 2.46, **<0.001**, (1.45, 4.05) |
| Instability or loosening | 50 (2.6%) | 61 (3.1%) | 0.82, 0.289, (0.56, 1.19) | 32 (6.8%) | 51 (10.8%) | 0.60, **0.029**, (0.38, 0.95) |
| Periprosthetic infection | 1715 (88.0%) | 1355 (69.5%) | 3.21, **<0.001**, (2.72, 3.80) | 10 (2.1%) | 0 (0.0%) | --, **0.001**, (--, --) |
| Revision | 328 (16.8%) | 207 (10.6%) | 1.70, **<0.001**, (1.41, 2.05) | 21 (4.4%) | 10 (2.1%) | 2.15, **0.045**, (1.00, 4.62) |
| Nerve injury | 10 (0.5%) | 10 (0.5%) | 1.00, 1.000, (0.42, 2.41) | 0 (0.0%) | 0 (0.0%) | --, --, (--, --) |
| Vascular injury | 10 (0.5%) | 0 (0.0%) | --, **0.002**, (--, --) | 0 (0.0%) | 0 (0.0%) | --, --, (--, --) |
| Cardiac complication | 21 (1.1%) | 34 (1.7%) | 0.61, 0.077, (0.36, 1.06) | 10 (2.1%) | 10 (2.1%) | 1.00, 1.000, (0.41, 2.43) |
| Respiratory complication | 21 (1.1%) | 33 (1.7%) | 0.63, 0.100, (0.37, 1.10) | 10 (2.1%) | 10 (2.1%) | 1.00, 1.000, (0.41, 2.43) |
| Deep vein thrombosis | 102 (5.2%) | 70 (3.6%) | 1.48, **0.013**, (1.09, 2.02) | 15 (3.2%) | 10 (2.1%) | 1.52, 0.311, (0.67, 3.41) |
| Surgical site infection | 21 (1.1%) | 18 (0.9%) | 1.17, 0.629, (0.62, 2.20) | 10 (2.1%) | 10 (2.1%) | 1.00, 1.000, (0.42, 2.38) |
| Dehiscence | 108 (5.5%) | 115 (5.9%) | 0.94, 0.629, (0.71, 1.23) | 18 (3.8%) | 10 (2.1%) | 1.83, 0.125, (0.84, 4.01) |