Elevated ESR and CRP Prior to Second-Stage Reimplantation Knee Revision Surgery for Periprosthetic Joint Infection Are Associated with Increased Reinfection Rates

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Abstract

Although two-stage revision surgery is considered as the most effective treatment for managing chronic periprosthetic joint infection (PJI), there is no current consensus on the predictors of optimal timing to second-stage reimplantation. This study aimed to compare clinical outcomes between patients with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) prior to second-stage reimplantation and those with normalized ESR and CRP prior to second-stage reimplantation. We retrospectively reviewed 198 patients treated with two-stage revision total knee arthroplasty for chronic PJI. Cohorts included patients with: (1) normal level of serum ESR and CRP ($n = 96$) and (2) elevated level of serum ESR and CRP prior to second-stage reimplantation ($n = 102$). Outcomes including reinfection rates and readmission rates were compared between both cohorts. At a mean follow-up of 4.4 years (2.8–6.5 years), the elevated ESR and CRP cohort demonstrated significantly higher reinfection rates compared with patients with normalized ESR and CRP prior to second-stage reimplantation (33.3% vs. 14.5%, $p < 0.01$). Patients with both elevated ESR and CRP demonstrated significantly higher reinfection rates, when compared with patients with elevated ESR and normalized CRP (33.3% vs. 27.6%, $p = 0.02$) as well as normalized ESR and elevated CRP (33.3% vs. 26.3%, $p < 0.01$). This study demonstrates that elevated serum ESR and/or CRP levels prior to reimplantation in two-stage knee revision surgery for chronic PJI are associated with increased reinfection rate after surgery. Elevation of both ESR and CRP were associated with a higher risk of reinfection compared with elevation of either ESR or CRP, suggesting the potential benefits of normalizing ESR and CRP prior to reimplantation in treatment of chronic PJI.

Keywords
- revision
- total knee arthroplasty
- periprosthetic joint infection
- reinfection
- erythrocyte sedimentation rate
- C-reactive protein

Two-stage revision arthroplasty, involving removal of the implants and placement of an antibiotic-loaded spacer followed by delayed reimplantation of a new prosthesis, is the current gold-standard treatment for chronic total knee arthroplasty (TKA) periprosthetic joint infections (PJIs). Many prior studies report a successful eradication of PJI in more than 80% of patients with this management strategy.[1,2] In comparison, single-stage revision in patients with

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immunocompetence, identified organisms, and adequate soft tissue and bone stock is becoming an appealing alternative to the standard two-stage revision,[3] with a successful eradication of PJI being reported in 67 to 85% of patients.[4–6] The superior PJI eradication rates of two-stage revision surgery are associated with the use of an antibiotic-loaded spacer prior to TKA reimplantation that allows for an opportunity to assess the response to antibiotics for PJI clearance prior to TKA reimplantation.[7,8] Although the optimal timing for second-stage reimplantation is guided by a combination of serum inflammatory markers, synovial fluid analysis, and clinical assessment of the treatment response,[9,10] there is no gold standard method to determine PJI eradication at the time of reimplantation. The diagnostic accuracy of synovial aspiration results have been reported in studies (sensitivity 87%, specificity 90%),[11,12] with other studies reporting an inferior diagnostic utility of aspiration results (sensitivity 50%, specificity 83%).[13] Additionally, the use of aspirate markers may be hindered by the lack of accessible synovial fluid or a "dry aspiration," which is not uncommon in patients with an antibiotic cement spacer.[14,15] For this reason, synovial fluid analysis is not routinely performed before reimplantation at many centers.[16]

Gram stain and frozen sections have the potential to provide intraoperative information to guide a decision whether to implant a new prosthesis or spacer exchange; however, Gram stain has not been recommended due to studies demonstrating its very low sensitivity ($< 60\%$) to successfully guide reimplantation and predict reinfection following reimplantation.[17,18] The utility of frozen section analysis is hindered by the current lack of a standardized thresholds for diagnosing infection. Due to these aforementioned limitations, serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most widely used parameters to guide the timing of reimplantation due to their low cost and ease of attainment.[24] However, the value of ESR and CRP in predicting persistent infection at reimplantation remains controversial.[11] In fact, normalization of these serum markers did not qualify as a final definition of PJI eradication in the Delphi criteria, which is the most widely utilized consensus metric for determining success after treatment of PJI.[19] Therefore, a progressive decline in ESR and CRP values without normalized levels along with the absence of clinical signs of PJI has been suggested as an acceptable prerequisite for proceeding with reimplantation.[20–22] There remains a paucity of studies evaluating the outcomes after second-stage reimplantation for PJI in cases in which serum ESR and CRP remain elevated prior to second-stage reimplantation. Therefore, this study aimed to evaluate clinical outcomes between patients with elevated ESR and CRP prior to second-stage reimplantation and those with both normalized ESR and CRP prior to second-stage reimplantation in patients with chronic knee PJI. The authors hypothesize that patients with elevated ESR and CRP prior to second-stage reimplantation will have inferior outcomes compared with patients with both normalized ESR and CRP prior to second-stage reimplantation.

Methods

Patients

A total of 198 patients who underwent two-stage knee revision surgery for chronic PJI (all McPherson et al infection type 3[23]) without systemic autoimmune diseases at a tertiary academic institution was evaluated in this Institutional Review Board-approved study. Serum ESR and CRP were recorded within 4 weeks prior to second-stage reimplantation, and at least 2 weeks after the end of the antibiotic treatment. The patients were divided into two groups: (1) 96 patients with normalized ESR and CRP prior to second-stage reimplantation, and (2) 102 patients with elevated ESR and CRP (with progressive decline) prior to second-stage reimplantation. The cohort of 102 patients with elevated ESR and CRP prior to second-stage reimplantation included 21 patients with both elevated ESR and elevated CRP prior to second-stage reimplantation, 47 patients with elevated ESR and normalized CRP prior to second-stage reimplantation, as well as 34 patients with normalized ESR and elevated CRP prior to second-stage reimplantation. An ESR greater than 30 mm/h and CRP greater than 10 mg/dL were defined as elevated values as defined by established standards in the literature.[24]

Patient charts were manually reviewed to obtain patient demographics, medical comorbidities, and preoperative laboratory findings. Clinical outcomes including reinfection rates, rerevision rates for aseptic reasons, 1-year amputation rates, 90-day death rates, and 30-, 60-, and 90-day readmission rates were also obtained. In concordance with previous literature,[25,26] reinfection was defined according to the Musculoskeletal Infection Society criteria and obtained through a retrospective review of patient charts. Patients who did not undergo reimplantation for any reason, including those who required resection arthroplasty, retained static or articulating spacers, and/or underwent arthrodesis, were excluded from analysis. Additionally, patients with underlying medical conditions such as human immunodeficiency virus, liver disease, renal failure, steroid dependence, and chronic autoimmune diseases were excluded from analysis due to the potential impact of these medical conditions on serum markers and reinfection rates.[27] Patients with a follow-up of less than 2 years, incomplete data, or previous revision surgery were excluded from analysis.

Surgical Technique

All surgical interventions were performed by fellowship-trained arthroplasty surgeons at a single tertiary referral institution. All revision TKA surgeries were performed using a medial parapatellar approach, regardless of the initial approach. All patients were treated with current two-stage revision techniques for chronic PJI,[5] which included the removal of all implant components, thorough debridement of foreign materials and debris, synovectomy, and insertion of antibiotic-loaded spacer during the first stage, followed by reimplantation of revision components during the second-stage surgery. In consultation with infectious diseases, the protocol included that an antibiotic-loaded spacer was implanted and patients received parenteral

organism-specific antibiotic therapy for 6 to 8 weeks. The most commonly used antibiotic combination in the antibiotic-loaded spacer was 2 g of vancomycin and 2.4 g of tobramycin per 40 g package of cement. As per institutional protocol, an antibiotic holiday for 4 to 6 weeks was performed in all patients prior to second-stage reimplantation.

Power Analysis

A statistical power analysis was performed for sample size estimation to evaluate clinical outcomes between patients with elevated ESR and CRP prior to second-stage reimplantation and those with both normalized ESR and CRP prior to second-stage reimplantation. Due to the paucity of studies that directly compare clinical outcomes between patients with elevated ESR and CRP prior to second-stage reimplantation and those with both normalized ESR and CRP prior to second-stage reimplantation, the power analysis was performed based on data from similarly designed previous study.[26,28,29] With an $\alpha = 0.05$, power = 0.80, and the same sampling ratio, the projected sample size needed for this study is approximately 20 patients with elevated ESR and CRP prior to second-stage reimplantation and 40 patients with both normalized ESR and CRP prior to second-stage reimplantation.

Statistical Analysis

The three cohorts with elevated serum marker as well as the normalized marker cohort were compared with regards to patient demographics, medical comorbidities, and clinical outcomes using descriptive statistics.[30] Continuous variables were compared using a Student's *t*-test, while categorical variables were compared using a Chi-squared test. All statistical analysis was performed in SPSS (SPSS Version 18.0, IBM Corp., Armonk, NY).[31]

Results

This study included a total of 198 patients that underwent two-stage hip or knee revision surgery for chronic PJI: (1) 96 patients with normalized ESR and CRP prior to second-stage reimplantation, and (2) 102 patients with elevated ESR and CRP prior to second-stage reimplantation. The normalized marker cohort accounted for 48% of patients, while 10% of patients demonstrated an elevated ESR and elevated CRP ("elevated maker cohort") prior to second-stage reimplantation. The patient cohort with elevated ESR and normalized CRP accounted for 24% of patients, while patients with normalized ESR and elevated CRP represented 18% of the patient cohort. The average ESR and CRP in the normalized marker cohort were 18.5 ± 13.5 mm/h and 6.4 ± 4.2 mg/dL, respectively (►**Table 1**). The average serum markers for patients with both elevated ESR and elevated CRP were 75.2 ± 29.0 mm/h and 42.6 ± 26.8mg/dL, respectively (►**Table 1**). The mean age of the cohorts was 65.2 ± 8.4 years, with an average body mass index of 32.1 ± 7.5 kg/m^2. The average follow-up of the cohort was 4.4 years (2.8–6.5 years). There was no significant difference between the normalized marker cohort and the three cohorts with elevated serum makers with regards to patient demographics, medical comorbidities, and causative pathogens (►**Tables 1** and **2**). Reinfections that occurred in the study cohort were mainly with the same organism as that from revision surgery. For 3 patients in the normalized ESR and normalized CRP cohort, 1 patient in the elevated ESR and elevated CRP cohort, 2 patients in the elevated ESR and normalized CRP cohort, and 2 patients in the normalized ESR and elevated CRP cohort, the organism differed between revision surgery and rerevision surgery.

With regards to postoperative complication rates, patients with both elevated ESR and elevated CRP prior to second-stage reimplantation demonstrated a significantly higher reinfection rate (33.3% vs. 14.5%, $p < 0.01$; ►**Table 3**), when compared with patients with normalized ESR and CRP prior to second-stage reimplantation. There was no significant difference between both cohorts for aseptic rerevisions (9.4% vs. 9.5%, $p = 0.97$), 1-year amputation rates (2.0% vs. 0.6%, $p = 0.21$), 90-day mortality rate (1.1% vs. 0.0%, $p = 0.55$), 30-day readmission (15.6% vs. 14.2%, $p = 0.53$), 60-day readmissions (16.7% vs. 19.0%, $p = 0.62$), and 90-day readmissions (18.7% vs. 19.0%, $p = 0.73$; ►**Table 3**).

With regards to postoperative complications for patients with elevated ESR and normalized CRP prior to second-stage reimplantation, these patients demonstrated a significantly higher reinfection rate (27.6% vs. 14.5%, $p < 0.01$; ►**Table 3**), when compared with patients with normalized ESR and CRP prior to second-stage reimplantation. There was no significant difference between these cohorts for aseptic rerevisions (9.4% vs. 10.6%, $p = 0.58$), 1-year amputation rates (2.0% vs. 2.1%, $p = 0.43$), 90-day mortality rate (1.1% vs. 2.1%, $p = 0.44$), 30-day readmission (15.6% vs. 19.1%, $p = 0.30$), 60-day readmissions (16.7% vs. 17.0%, $p = 0.81$), and 90-day readmissions (18.7% vs. 17.0%, $p = 0.65$; ►**Table 3**).

With regards to postoperative complications for patients with normalized ESR and elevated CRP prior to second-stage reimplantation, these patients demonstrated a significantly higher reinfection rate (26.3% vs. 14.5%, $p < 0.01$; ►**Table 4**), when compared with patients with normalized ESR and CRP prior to second-stage reimplantation. There was no significant difference between these cohorts for aseptic rerevisions (11.7% vs. 9.4%, $p = 0.41$), 1-year amputation rates (2.0% vs. 3.0%, $p = 0.73$), 90-day mortality rate (1.1% vs. 2.9%, $p = 0.47$), 30-day readmission (15.6% vs. 17.6%, $p = 0.49$), 60-day readmissions (16.7% vs. 17.6%, $p = 0.43$), and 90-day readmissions (18.7% vs. 20.5%, $p = 0.47$; ►**Table 4**).

Subgroup analysis for patients with elevated serum markers demonstrated that patients with both elevated ESR and elevated CRP demonstrated significantly higher reinfection rates, when compared with patients with elevated ESR and normalized CRP (33.3% vs. 27.6%, $p = 0.02$; ►**Table 4**), as well as patients with normalized ESR and elevated CRP (33.3% vs. 26.3%, $p < 0.01$). There was no significant difference in reinfection rates between patients with elevated ESR and normalized CRP and patients with normalized ESR and elevated CRP (27.6% vs. 26.3%, $p = 0.61$). There was no significant difference between the three cohorts with elevated serum markers with regards to rerevision rate, 90-day mortality rate,

Table 1 Comparison of patient demographics and preoperative infection markers between patients with normalized ESR and CRP as well as patients with elevated ESR and CRP

	Normalized ESR and normalized CRP ($n = 96$)	Elevated ESR and elevated CRP ($n = 21$)	Elevated ESR and normalized CRP ($n = 47$)	Normalized ESR and elevated CRP ($n = 34$)	*p*-Value
Age (y)	65.6 ± 8.4	65.2 ± 8.7	64.6 ± 8.5	65.3 ± 8.3	0.64
Gender (M/F)	51/45	11/10	25/22	19/15	0.27
BMI (kg/m^2)	31.9 ± 7.5	32.2 ± 7.4	31.7 ± 7.7	32.3 ± 7.4	0.51
Laterality (left/right)	53/43	13/8	27/20	18/16	0.33
Follow-up (y)	4.6 ± 1.6	4.2 ± 1.3	4.3 ± 1.4	4.4 ± 1.2	0.47
ASA score					
1	15	5	6	7	0.54
2	67	12	26	20	
3	13	4	14	7	
4	1	0	1	0	
Comorbidities					
Smoking	9 (9.6%)	2 (9.5%)	4 (8.5%)	2 (5.8%)	0.56
Drinking	22 (22.9%)	5 (23.8%)	9 (19.2%)	7 (20.5%)	0.77
Drug abuse	5 (5.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0.53
Depression	17 (17.7%)	3 (14.2%)	7 (14.8%)	6 (17.6%)	0.40
Diabetes mellitus	20 (20.8%)	4 (19.0%)	9 (19.1%)	7 (20.5%)	0.72
Malignancy	14 (14.6%)	2 (9.5%)	5 (10.6%)	5 (14.7%)	0.30
Hypertension	54 (56.3%)	10 (47.6%)	23 (48.9%)	17 (50.0%)	0.49
Preop infection markers					
ESR (mm/h)	18.5 ± 13.5	75.2 ± 29.0	65.7 ± 26.1	21.2 ± 14.7	< **0.01**
CRP (mg/dL)	6.4 ± 4.2	42.6 ± 26.8	7.5 ± 4.9	35.1 ± 16.8	< **0.01**
ESR/CRP	3.2 ± 2.1	1.8 ± 1.4	9.4 ± 4.7	0.8 ± 1.9	< **0.01**
Synovial WBC (cells/μL)	1422.6 ± 627.4	1611.2 ± 956.8	2846.9 ± 1163.0	1313.5 ± 833.5	0.39
Synovial PMN (%)	69.7 ± 22.2	74.2 ± 23.9	71.1 ± 22.0	72.3 ± 24.1	0.68
Days to reimplantation	103.7 ± 56.2	112.1 ± 70.7	100.8 ± 61.6	107.4 ± 64.5	0.41
Dynamic spacer (%)	81 (84.3%)	18 (85.7%)	39 (82.9%)	29 (85.2%)	0.52

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMN, polymorphonuclear; WBC, white blood cell.
Note: Bold values indicate statistical significance.

1-year amputation rate, and readmission rates with 30, 60, and 90 days (►**Table 4**).

Discussion

Currently, serological markers such as ESR and CRP are the most widely utilized parameters to determine optimal timing of reimplantation in two-stage revision arthroplasty due to their high availability and low cost. However, the utility of ESR and CRP in predicting reinfection prior to second-stage revision arthroplasty has been questioned, with a recent meta-analysis reporting sensitivities and specificities for ESR and CRP of 79 and 82% as well as 83 and 85%, respectively.[11] Prior studies have demonstrated that a progressive decline in ESR and CRP is a satisfactory indication for reimplantation in the absence of clinical signs of PJI.[20,22,32] However, there is a paucity of studies evaluating the impact of persistently elevated serum markers on outcomes after revision surgery for chronic PJI. The findings of this study demonstrate that patients with elevated ESR and/or elevated CRP prior to second-stage TKA reimplantation demonstrate a significantly higher reinfection rate at 4.2 years' follow-up. Subgroup analysis has demonstrated that patients with both elevated ESR and CRP demonstrate significantly higher reinfection rates, when compared with patients with elevated ESR and normalized CRP as well as patients with normalized ESR and elevated CRP, suggesting that an elevation of both serum markers prior to second-stage TKA reimplantation is associated with an increased risk of reinfection.

Lindsay et al reported reinfections in 5 of 19 patients (26%) with both elevated ESR and CRP prior to second-stage TKA reimplantation at 2-year follow-up.[28] Similarly, Kusuma et al

Table 2 Comparison of causative pathogens between patients with normalized ESR and CRP as well as patients with elevated ESR and CRP

Causative pathogen	Normalized ESR and normalized CRP ($n = 96$)	Elevated ESR and elevated CRP ($n = 21$)	Elevated ESR and normalized CRP ($n = 47$)	Normalized ESR and elevated CRP ($n = 34$)	*p*-Value
Unfavorable					0.51
Methicillin-resistant Staphylococcus aureus (MRSA)	8	2	4	2	
Pseudomonas aeruginosa	3	0	1	1	
Anaerobes	7	2	3	3	
Negative culture	6	1	2	2	
Other gram negative organisms	13	3	7	4	
Mixed growth	11	2	6	4	
Favorable					0.39
Streptococcus species	17	4	9	7	
Staphylococcus species	13	3	7	4	
Coagulase-negative staphylococci	4	1	2	1	
Other Gram-positive organisms	2	0	1	0	
Propionibacterium acnes	3	1	1	1	
Staphylococcus aureus	7	2	3	3	
Other	2	0	1	2	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

reported PJI recurrence in 8 of 76 patients (12%) with both elevated ESR and CRP prior to second-stage TKA reimplantation at 2-year follow-up.[25] In concordance with these studies, Ghanem et al reported reinfections in 23 of 109 patients (23%) with both elevated ESR and CRP prior to second-stage reimplantation at 2-year follow-up, suggesting potential benefits of normalizing ESR and CRP prior to TKA reimplantation in treatment of PJI.[29] In contrast to these studies, Shukla et al investigated 86 consecutive patients with chronic PJI treated with two-stage revision surgery, demonstrating that there was no PJI recurrence in all patients with both elevated ESR and CRP prior to second-stage reimplantation.[26] Our findings are in concordance with previous literature,[25,28,29] demonstrating that patients with both elevated ESR and CRP prior to second-stage TKA reimplantation demonstrated a higher reinfection risk at 4.1 years' follow-up, when compared with patients with normalized ESR and CRP prior to second-stage reimplantation. This suggests that normalizing both ESR and CRP prior to reimplantation has the potential to decrease reinfection rates following two-stage revision TKA in the management of chronic PJI.

The significance of normalizing both ESR and CRP prior to second-stage reimplantation may be based on multiple factors. First, CRP is a nonspecific acute phase reactant assisting in phagocytosis of pathogens, and hence CRP levels are often proportional to the intensity of an ongoing infectious process.[33] However, cytokines induced by noninfectious causes, such as tissue injury after trauma or surgery, may also cause elevations in CRP.[33] Hence, decreasing trends in serum markers may be more reflective of progressive soft tissue recovery from the index revision surgery rather than eradication of infection. Second, mild elevations in markers after an antibiotic holiday may similarly be indicative of insidious development of a resistant microorganism secondary to prolonged antibiotic therapy or persistent subclinical infection with a low virulence organism such as coagulase negative Staphylococcus. These patients with declining, but not normalized, serum markers may be at increased risk for reinfection after reimplantation, as ESR and CRP are known to be highly sensitive but not specific markers of inflammation, with negative predictive values approaching 100%.[32] This implies that their utility is primarily as a "rule out" test, and as such, they offer limited clinical contribution in the absence of normalized values.

The findings of this study additionally illustrate increased reinfection rates for patients with either elevated ESR or elevated CRP, when compared with patients with both normalized ESR and CRP. This suggests that even the elevation of a single serum marker prior to second-stage TKA reimplantation is associated with increased reinfection rates. Similar observations were made by Xu et al, reporting associations between an either elevated serum ESR or an elevated serum CRP prior to second-stage TKA reimplantation and an increased reinfection risk, based on which the authors suggested the normalization of both ESR and CRP prior to TKA reimplantation to mitigate this risk.[34] Equally, Li et al reported that an elevated ESR was associated with an increased risk for postoperative complications, in a study with 167 TKA patients investigating risk factors for poor postoperative patients outcomes.[35,36]

We performed subgroup analysis for patients with elevated serum markers prior to second-stage TKA reimplantation

Table 3 Comparison of postoperative complication rates between all study cohorts

	Normalized ESR and normalized CRP ($n = 96$)	Elevated ESR and elevated CRP ($n = 21$)	Odds ratio (95% CI)	*p*-Value
Complication rates				
Reinfection rate (%)	14 (14.5%)	7 (33.3%)	1.37 (0.82–1.70)	< **0.01**
90-day mortality rate (%)	1 (1.1%)	0 (0.0%)	1.11 (0.93–1.21)	0.55
1-year amputation rate (%)	2 (2.0%)	1 (0.6%)	1.09 (0.84–1.33)	0.21
Rerevision rate (%)	9 (9.4%)	2 (9.5%)	1.05 (0.93–1.25)	0.97
30-day readmission rate (%)	15 (15.6%)	3 (14.2%)	1.14 (0.93–1.37)	0.53
60-day readmission rate (%)	16 (16.7%)	4 (19.0%)	1.10 (0.87–1.34)	0.62
90-day readmission rate (%)	18 (18.7%)	4 (19.0%)	1.16 (0.94–1.44)	0.73
	Normalized ESR and normalized CRP ($n = 96$)	**Elevated ESR and normalized CRP ($n = 47$)**	**Odds ratio (95% CI)**	***p*-Value**
Complication rates				
Reinfection rate (%)	14 (14.5%)	13 (27.6%)	1.28 (0.88–1.50)	< **0.01**
90-day mortality rate (%)	1 (1.1%)	1 (2.1%)	1.04 (0.87–1.18)	0.44
1-year amputation rate (%)	2 (2.0%)	1 (2.1%)	1.07 (0.93–1.24)	0.43
Rerevision rate (%)	9 (9.4%)	5 (10.6%)	1.11 (0.88–1.35)	0.58
30-day readmission rate (%)	15 (15.6%)	9 (19.1%)	1.16 (0.87–1.42)	0.30
60-day readmission rate (%)	16 (16.7%)	8 (17.0%)	1.13 (0.84–1.36)	0.81
90-day readmission rate (%)	18 (18.7%)	8 (17.0%)	1.10 (0.93–1.27)	0.65
	Normalized ESR and normalized CRP ($n = 96$)	**Normalized ESR and elevated CRP ($n = 34$)**	**Odds ratio (95% CI)**	***p*-Value**
Complication rates				
Reinfection rate (%)	14 (14.5%)	9 (26.3%)	1.25 (0.91–1.48)	< **0.01**
90-day mortality rate (%)	1 (1.1%)	1 (2.9%)	1.05 (0.93–1.15)	0.47
1-year amputation rate (%)	2 (2.0%)	1 (3.0%)	1.07 (0.96–1.27)	0.73
Rerevision rate (%)	9 (9.4%)	4 (11.7%)	1.11 (0.91–1.20)	0.41
30-day readmission rate (%)	15 (15.6%)	6 (17.6%)	1.08 (0.95–1.26)	0.49
60-day readmission rate (%)	16 (16.7%)	6 (17.6%)	1.09 (0.91–1.27)	0.43
90-day readmission rate (%)	18 (18.7%)	7 (20.5%)	1.07 (0.95–1.22)	0.47

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Note: Bold values indicate statistical significance.

to investigate which serum marker has the strongest effect on reinfection rates. The study findings demonstrate that patients with both elevated ESR and CRP demonstrate a significantly higher risk of reinfection, when compared with patients with elevated ESR and normalized CRP as well as patients with normalized ESR and elevated CRP. The present study did not observe any significant difference in reinfection rates between patients with either elevated ESR or elevated CRP. This suggests that an elevation of both serum markers prior to second-stage TKA reimplantation is associated with a much higher reinfection risk, when compared with only ESR or only CRP being elevated, with no significant difference between an elevated ESR or an elevated CRP. Although there is a paucity of studies to directly compare the effect of elevated serum markers prior to second-stage reimplantation on reinfection rates, Ghanem et al reported a 13 and 15% increased reinfection risk respectively for patients with both elevated ESR and elevated CRP, when compared with patients with elevated ESR and normalized CRP as well as patients with normalized ESR and elevated CRP, illustrating the increased risk of reinfection with both elevated ESR and elevated CRP prior to second-stage TKA reimplantation in treatment of PJI.[29]

The findings of this study need to be interpreted in light of several limitations. First, this study has limitations inherent to all retrospective cohort designs such as differential and nondifferential misclassification bias and selection bias. Second, there may have been differences in the postoperative protocol for patients in the course of this study duration. However, this represents a common limitation of retrospective studies. Lastly, although there was no statistically significant difference between all study cohorts for a multitude of patient and surgical factors, differences could still exist between all study groups for factors that were not

Table 4 Comparison of postoperative complication rates between study cohorts with elevated serum markers

	Elevated ESR and elevated CRP ($n = 21$)	Elevated ESR and normalized CRP ($n = 47$)	Odds ratio (95% CI)	*p*-Value
Complication rates				
Reinfection rate (%)	7 (33.3%)	13 (27.6%)	1.18 (0.91–1.33)	**0.02**
90-day mortality rate (%)	0 (0.0%)	1 (2.1%)	1.05 (0.94–1.10)	0.45
1-year amputation rate (%)	1 (0.6%)	1 (2.1%)	1.09 (0.92–1.18)	0.21
Rerevision rate (%)	2 (9.5%)	5 (10.6%)	1.02 (0.91–1.07)	0.84
30-day readmission rate (%)	3 (14.2%)	9 (19.1%)	1.08 (0.96–1.11)	0.26
60-day readmission rate (%)	4 (19.0%)	8 (17.0%)	1.07 (0.94–1.16)	0.76
90-day readmission rate (%)	4 (19.0%)	8 (17.0%)	1.05 (0.96–1.07)	0.63
	Elevated ESR and elevated CRP ($n = 21$)	**Normalized ESR and elevated CRP ($n = 34$)**	**Odds ratio (95% CI)**	***p*-Value**
Complication rates				
Reinfection rate (%)	7 (33.3%)	9 (26.3%)	1.25 (0.92–1.38)	**< 0.01**
90-day mortality rate (%)	0 (0.0%)	1 (2.9%)	1.06 (0.92–1.19)	0.33
1-year amputation rate (%)	1 (0.6%)	1 (3.0%)	1.12 (0.93–1.29)	0.15
Rerevision rate (%)	2 (9.5%)	4 (11.7%)	1.04 (0.95–1.17)	0.43
30-day readmission rate (%)	3 (14.2%)	5 (14.7%)	1.01 (0.97–1.04)	0.96
60-day readmission rate (%)	4 (19.0%)	6 (17.6%)	1.07 (0.94–1.18)	0.75
90-day readmission rate (%)	4 (19.0%)	7 (20.5%)	1.05 (0.95–1.15)	0.71
	Elevated ESR and normalized CRP ($n = 47$)	**Normalized ESR and elevated CRP ($n = 34$)**	**Odds ratio (95% CI)**	***p*-Value**
Complication rates				
Reinfection rate (%)	13 (27.6%)	9 (26.3%)	1.11 (0.95–1.23)	0.61
90-day mortality rate (%)	1 (2.1%)	1 (2.9%)	1.07 (0.96–1.13)	0.85
1-year amputation rate (%)	1 (2.1%)	1 (3.0%)	1.06 (0.92–1.17)	0.53
Rerevision rate (%)	5 (10.6%)	4 (11.7%)	1.04 (0.89–1.19)	0.77
30-day readmission rate (%)	9 (19.1%)	6 (17.6%)	1.03 (0.97–1.15)	0.59
60-day readmission rate (%)	8 (17.0%)	6 (17.6%)	1.02 (0.96–1.09)	0.95
90-day readmission rate (%)	8 (17.0%)	7 (20.5%)	1.06 (0.94–1.13)	0.75

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Note: Bold values indicate statistical significance.

considered for analysis such as local extremity grade, bone loss, or soft tissue conditions. However, similar limitations were reported by numerous prior studies on this topic.[6,29]

In conclusion, this study demonstrated significantly increased reinfection rates for patients with elevated serum ESR and/or CRP prior to the reimplantation stage of two-stage revision in the management of chronic knee PJI. Elevation of both ESR and CRP were associated with a higher risk of reinfection compared with elevation of either ESR or CRP, suggesting the potential benefits of normalizing both ESR and CRP prior to TKA reimplantation in treatment of chronic PJI to reduce the risk of recurrent infections.

Note

All data will be made available through contacting the corresponding author. All code used in this includes basic Matlab functions. The study was approved by institutional review board. All patients consented prior to participation in this study.

Authors' Contributions

C.K.: study design, data collection, analysis, and write-up. A.P.: data collection, analysis, and write-up. J.G.E.: write-up. S.L.: write-up. E.J.S.: write-up. Y.-M.K.: study design and analysis.

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Conflict of Interest

None declared.

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