RESEARCH ARTICLE

Hypoalbuminemia Increases Mortality after Two-Stage Revision Total Joint Arthroplasty

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Abstract

Objectives: This study aimed to evaluate the effect of hypoalbuminemia on failure rates and mortality after a two-stage revision for PJI.

Methods: 199 Patients (130 knees and 69 hips) with a mean age of 64.7 ± 10.7 years who underwent a two-stage exchange were retrospectively reviewed at a mean of 51.2 ± 39.7 months. Failure of treatment was defined as any revision within the follow-up period, failure to undergo reimplantation, or death within one year of initiating treatment.

Results: There were 71 failures (35.7%), including 38 septic failures (19.1%). We found no differences between successful revisions and failures regarding hypoalbuminemia (43% vs. 42% prior to stage 1, P=1 and 32% vs. 29% prior to stage 2, P=0.856). There were also no differences in hypoalbuminemia rates between septic failures and the rest of the cohort (42% vs. 43% prior to stage 1, P=1.0 and 34% vs. 30% prior to stage 2, P=0.674). Hypoalbuminemia prior to stage 2 was a significant predictor of mortality based on multivariate analysis (odds ratio 5.40, CI 1.19-24.54, P=0.029). Hypoalbuminemia was independently associated with a greater length of stay by 2.2 days after stage 1 (P=0.002) and by 1.0 days after the second stage reimplantation (P=0.004).

Conclusion: Preoperative hypoalbuminemia is a significant predictor of mortality and increased length of stay following two-stage revision but is not a predictor of failure of PJI treatment. Further study is required to understand if hypoalbuminemia is a modifiable risk factor or a marker for poor outcomes.

Level of evidence: III

Keywords: Albumin, Hypoalbuminemia, Periprosthetic joint infection, Two-stage

Introduction

Periprosthetic joint infection (PJI) is a devastating complication that occurs at a rate of approximately 2.2% after both primary total hip arthroplasty (THA) and total knee arthroplasty (TKA).[1] PJI is the most common indication for revision TKA and the third most common indication for revision THA.[2] As the demand for primary total joint arthroplasty (TJA) increases in the United States, the number of revision procedures for PJI is projected to increase to approximately 26,000 annual THA revisions and 40,000 annual TKA revisions by 2030. This represents a significant societal financial burden, costing an estimated $1.85 billion annually.[3]

Revision TJA for PJI not only represents a significant financial burden but is also fraught with extended and debilitating treatment courses. A two-stage exchange arthroplasty is currently considered the gold standard for treating chronic PJI in the United States.[4] However, failure rates after a two-stage revision are reported as high as 36% at a 3-year follow-up.[5-8] Furthermore, high attrition rates have been reported during the two-stage protocol, with one study reporting a one-year attrition rate of 18% that was primarily attributed to patient mortality.[9] Mortality rates as high as 24% after two-stage revision have been reported at a 4.5-year follow-up.[5] Therefore, preoperative identification and optimization of any modifiable risk factors before two-stage exchange is essential to reduce postoperative failure, attrition, and mortality.

Malnutrition is one of the most common modifiable risk

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factors in patients undergoing TJA, and previous studies have associated nutritional optimization with improved outcomes. [10-12] Malnutrition has been identified in up to 53% of patients undergoing revision surgery for PJI and also has been associated with an increased risk of PJI after aseptic revisions.[13-15] Hypoalbuminemia is one of the most commonly-used laboratory values for malnutrition in the orthopedic literature.[15,16] Preoperative hypoalbuminemia specifically has been associated with increased PJI rates, length of stay, delayed wound healing, and pneumonia after primary TJA.[17-21] Hypoalbuminemia has also been associated with nearly a six-fold increased risk of mortality within 30 days after primary THA.[22]

While several studies have evaluated hypalbuminemia in patients undergoing primary and aseptic revision arthroplasty, only one prior study has evaluated preoperative albumin levels in patients undergoing two-stage exchange for PJI.[15,17-22] In their retrospective study of 79 patients, Hong et al., found no significant differences in serum albumin levels between patients with successful and unsuccessful two-stage revisions.[23] However, a considerable limitation of this study was the use of laboratory data up to one year preoperatively, which may not accurately reflect the nutritional status at the time of surgery. Therefore, this study aimed to evaluate if preoperative hypoalbuminemia within 90 days of two-stage exchange for PJI is associated with rates of failure and mortality.

Materials and Methods

Patient

Following institutional review board approval, we retrospectively identified a consecutive series of 225 patients who underwent a two-stage revision TKA or THA for PJI by a single fellowship-trained arthroplasty surgeon between January 1, 2002 and September 30, 2019. All patients met the 2011 Musculoskeletal Infection Society (MSIS) criteria for PJI preoperatively.[24] After PJI diagnosis, patients underwent implant removal with irrigation, debridement, and placement of an antibiotic spacer. Infectious disease consultants coordinated post-operative antibiotics, typically six weeks of organism-specific antibiotics. After a 2-week antibiotic holiday, patients were considered candidates for reimplantation if their inflammatory markers were trending down and there was no further clinical or laboratory evidence of PJI. Reimplantation consisted of removal of the antibiotic spacer, repeat irrigation and debridement, and placement of new implants.

Routine preoperative evaluation of these patients included serum laboratory testing and serum albumin level. Hypoalbuminemia was defined as serum albumin < 3.5 g/dL within 90 days preoperatively, which is the standard cutoff most commonly used in the orthopaedic literature for evaluating malnutrition.[16] Albumin levels were assessed within 90 days before both the first and second stage reimplantation. Patients without at least one preoperative albumin value before either the first or second stage were excluded from the analysis. Demographic variables reviewed include age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI), and smoking status.

Outcomes

Outcomes of PJI treatment were classified according to the MSIS outcome-reporting tool.[25] Using this system, failure of PJI treatment was defined as any revision within the follow-up period, failure to undergo reimplantation, or all-cause mortality within one year of initiating PJI treatment. Failure to undergo reimplantation included spacer retention in patients who were no longer surgical candidates or subsequent amputation, resection arthroplasty, or arthrodesis before completing the full two-stage revision in patients with persistent infection and/or unacceptably high risk of reimplantation failure. Septic failure was defined as any reoperation for recurrent, persistent, or new infection after initial PJI treatment.

Statistical Analysis:

Statistical analysis was performed using Stata® Version 15.1 (StataCorp, College Station, TX, USA). Univariate analysis was used to compare demographic variables and rates of hypoalbuminemia between patients with successful and failed PJI treatment and to assess the effect of hypoalbuminemia on septic failures, mortality, and length of stay. Continuous and categorical variables were evaluated using Student's t-test and Fisher's exact test, respectively. The septic failure group was compared to a cohort of aseptic failures and successes. Multivariate logistic regression modeling was further utilized to evaluate the independent effect of preoperative hypoalbuminemia on failure rates, septic failure rates, mortality, and length of stay. Covariates used for adjustment in the multivariate model included age, sex, BMI, ASA, CCI, smoking status, and procedure type (revision THA or revision TKA). Kaplan-Meier curves were generated for survival analysis with an endpoint of all-cause mortality.

Results

Of the 225 patients that underwent a two-stage revision for PJI, 199 (88.4%) patients with an average age of 64.7 ± 10.7 years were included for final analysis at an average follow-up of 51.2 months (interquartile range: 27.1 – 75.7 months) [Table 1]. Twenty-six patients were excluded due to missing albumin values within 90-days preoperatively. Sixty-nine patients (34.7%) underwent revision THA, and 130 (65.3%) underwent TKA revision. There were 71 failures (35.7%) which included 38 septic failures (19.1%), 14 aseptic revisions (7.0%), 14 cases (7.0%) of failure to undergo reimplantation, and five patients (21.7%) who died within one year of initiating PJI treatment.

Table 1: Demographic and procedure characteristics of patients undergoing two-stage revisions for periprosthetic joint infection

	All patients	Success	Failure	P-value	Septic Failure	P-value
N (%)	199 (100%)	128 (64.3%)	71 (35.7%)		38 (19.1%)	
Age (years, mean ± std. dev)	64.7 ± 10.7	65.6 ± 10.8	63.0 ± 10.3	0.108	62.8 ± 10.7	0.235
Sex (n, (%))						
Female	93 (46.7%)	59 (45.7%)	34 (48.6%)	0.767	18 (47.4%)	1
Male	106 (53.3%)	70 (54.3%)	36 (51.4%)		20 (52.6%)	
BMI (kg/m², mean ± std. dev)	32.4 ± 7.7	31.4 ± 6.8	34.3 ± 8.9	**0.017**	35.1 ± 9.8	**0.021**
ASA score (n, (%))						
2	146 (73.4%)	101 (78.3%)	45 (64.3%)	**0.043**	21 (55.3%)	**0.008**
3	53 (26.6%)	28 (21.7%)	25 (35.7%)		17 (44.7%)	
CCI (mean ± std. dev)	3.1 ± 2.1	3.1 ± 1.9	3.3 ± 2.4	0.552	3.3 ± 2.6	0.561
Smoking Status (n, (%))						
Current	23 (11.6%)	13 (10.2%)	10 (14.3%)	0.307	5 (13.2%)	0.506
Former	75 (37.9%)	44 (34.4%)	31 (44.3%)		18 (47.4%)	
Never	82 (41.4%)	58 (45.3%)	24 (34.3%)		13 (34.2%)	
Not recorded	18 (9.1%)	13 (10.1%)	5 (7.1%)		2 (5.2%)	
Follow-up (months, mean ± std. dev)	51.2 ± 39.7	49.8 ± 42.3	53.7 ± 34.6	0.509	61.6 ± 34.8	0.073
Procedure (n, (%))						
Revision THA	69 (34.7%)	46 (35.7%)	23 (32.9%)	0.756	14 (36.8%)	0.850
Revision TKA	130 (65.3%)	83 (64.3%)	47 (67.1%)		24 (63.2%)	
Hypoalbuminemia (n, (%))						
Pre-explant (n = 160)	68 (42.5%)	43 (43.0%)	25 (41.7%)	1.000	13 (41.9%)	1.000
Pre-reimplant (n = 164)	51 (31.1%)	36 (31.9%)	15 (29.4%)	0.856	11 (34.4%)	0.674

BMI, body mass index; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; THA, total hip arthroplasty; TKA, total knee arthroplasty

The mean BMI was significantly higher among patients who failed treatment (34.3 vs. 31.4 kg/m2, P=0.017) and among septic failures (35.1 vs. 31.7 kg/m2, P=0.021). Similarly, the ASA score was significantly higher among failures (35.7% vs. 21.7% ASA of 3, P=0.043) and septic failures (44.7% vs. 22.4% ASA of 3, P=0.008). The average CCI and smoking use were similar between groups.

Of the 160 patients with albumin levels available before the first stage, 68 (42.5%) had hypoalbuminemia. Of the 164 patients with albumin levels available before the second stage reimplantation, 51 (31.1%) had hypoalbuminemia. On univariate analysis there were no significant differences in hypoalbuminemia rates (prior to stage 1: 43.0% vs. 41.7%, P=1; prior to the second stage reimplantation: 31.9% vs. 29.4%, P=0.856).

There were also no differences in hypoalbuminemia rates between the 38 septic failures and the rest of the cohort (prior to stage 1: 41.9% vs. 42.6%, P=1.0; prior to second stage reimplantation: 34.4% vs. 30.3%, P=0.674). Similarly, hypoalbuminemia was not associated with mortality on univariate analysis [Table 2].

After multivariate analysis, hypoalbuminemia before stage 1 or 2 was not associated with treatment or septic failure [Table 3]. Hypoalbuminemia before stage 1 was also not associated with mortality after PJI treatment but was associated with an increased length of stay by 2.2 days (95% confidence interval [CI] 0.81-3.56 days, P=0.002). Hypoalbuminemia before the second stage of reimplantation was a significant predictor of postoperative mortality with an odds ratio (OR) of 5.40 (CI 1.19-24.54, P=0.029). Hypoalbuminemia before the second stage was also associated with an increased length of stay by 1.0 days (CI 0.34-1.70, P=0.004).

Table 2: Univariate analysis of patients with and without preoperative hypoalbuminemia

	All Patients	Albumin ≥ 3.5 mg/dL	Albumin < 3.5 g/dL	P-value
Albumin Levels prior to Stage 1				
Total (N, %)	160 (100%)	92 (57.5%)	68 (42.5%)	
Failure (N, %)	60 (37.5%)	35 (38.0%)	25 (36.8%)	1.000
Septic Failure (N, %)	31 (19.4%)	18 (19.6%)	13 (19.1%)	1.000
Mortality (N, %)	22 (13.8%)	10 (10.9%)	12 (17.7%)	0.25
LOS (days, mean ± std. dev)	6.0 ± 4.4	4.7 ± 2.3	7.9 ± 5.7	**< 0.001**
Albumin Levels prior to Stage 2				
Total (N, %)	164 (100%)	113 (68.9%)	51 (31.1%)	
Failure (N, %)	51 (31.1%)	36 (31.9%)	14 (27.5%)	0.856
Septic Failure (N, %)	32 (19.5%)	21 (18.6%)	11 (21.6%)	0.674
Mortality (N, %)	17 (10.4%)	9 (8.0%)	8 (15.7%)	0.167
LOS (days, mean ± std. dev)	4.1 ± 2.3	3.6 ± 1.7	5.3 ± 3.0	**< 0.001**

Table 3: Multivariate analysis comparing outcomes in patients with and without preoperative hypoalbuminemia, controlling for age, sex, body mass index, American Society of Anesthesiologists score, Charlson Comorbidity Index, smoking status, and procedure type.

	OR/Coefficient	95% Confidence Interval	P-value
Hypoalbuminemia prior to Stage 1			
Failure	1.14	0.53-2.46	0.735
Septic Failure	0.86	0.33-2.22	0.760
Mortality	1.14	0.28-4.59	0.857
Length of Stay*	2.19	0.81-3.56	**0.002**
Hypoalbuminemia prior to Stage 2			
Failure	0.82	0.34-1.95	0.646
Septic Failure	1.34	0.52-3.50	0.547
Mortality	5.40	1.19-24.54	**0.029**
Length of Stay*	1.02	0.34-1.70	**0.004**

*Reported as a coefficient; all remaining variables reported as odds ratio. OR, odds ratio

Discussion

In the present study, the prevalence of hypoalbuminemia was 42.5% before the first stage and 31.1% before the second stage. These rates are similar to those observed in previous studies reporting preoperative hypoalbuminemia rates between 42.8-53.2% in patients undergoing revision surgery for PJI.[15,26] We also found that preoperative hypoalbuminemia was not associated with failure or septic failure rates after a two-stage exchange for PJI. Using a similar definition of failure, Hong et al. also reported no significant differences in albumin levels between successful and failed two-stage revisions for PJI.[23,27] However, our results differ from prior studies that found hypoalbuminemia to be associated with increased rates of septic failure after primary and aseptic revision TJA.[15,17] In a retrospective review of 375 patients undergoing aseptic revision TJA, Yi *et al.* found that patients with at least one laboratory value indicative of malnutrition was associated with an increased risk of acute postoperative PJI (OR 5.9, *P=0.02*) and chronic PJI (OR 2.1, *P=0.003*).[15,17-22]It is unclear why a similar

association was not seen in the present study. Our relatively small cohort may be underpowered to detect such differences. It is also possible that host factors such as hypoalbuminemia have a lesser influence on outcomes after two-stage revision for PJI than aseptic revision surgery. In contrast, infection severity and the causative organism may play a larger role.

Previous studies have found that revision surgery for PJI is associated with increased mortality rates compared to aseptic revisions at medium and long-term follow-up.[28,29] After comparing matched cohorts of 88 patients undergoing septic and aseptic revision TKA, Choi *et al*. found that revision for PJI was an independent predictor of mortality (OR 7.7, CI 2.0-32.1, *P<0.001*).[28] The authors observed an 18% mortality rate among patients undergoing revision TKA for PJI at a median 4-year follow-up, compared to the 11.6% mortality rate seen in the present study at an average 4.2-year follow-up.

The principal finding of our investigation suggests that hypoalbuminemia before the second stage of reimplantation is an independent predictor of all-cause mortality with an OR of 5.40 (95% CI 1.19-24.54, *P=0.029*). Interestingly, this difference was not significant in univariate analysis, which could be explained by the presence of a confounding variable having a suppressive effect. Hypoalbuminemia is a considerable risk factor for short-term mortality among primary THA and TKA patients.[22,30] Fryhofer *et al*. reported that patients with hypoalbuminemia had significantly higher mortality rates after primary THA (OR 21.19, CI 2.85-157.66, *P=0.003*) and primary TKA (OR 2.81, CI 1.01-7.80, *P=0.048*) at 30-day follow up.[30] Similarly, Kamath *et al.* found that hypoalbuminemia was associated with an increased risk of mortality after revision TKA (OR 9.81, CI 3.38-28.49, *P<0.001*).[31] However, to our knowledge, the present study is the first to associate hypoalbuminemia before the second stage of reimplantation with increased mortality risk.

We also observed that preoperative hypoalbuminemia was associated with an increased length of stay by 2.2 days (CI 0.81-3.56 days, *P=0.002*) following the first stage and 1.0 days (CI 0.34-1.70 days, *P=0.004*) after the second stage reimplantation. Similar results have been reported in previous studies.[20,32,33] Rudasill *et al.* reported that patients with preoperative hypoalbuminemia had an increased length of stay by 1.3 days after primary TJA and 2.3 days after revision arthroplasty.[33]

For these reasons, surgeons might consider preoperative optimization of hypoalbuminemia to reduce mortality rates and length of stay after a two-stage exchange for PJI. However, the role of hypoalbuminemia in malnutrition remains unclear, and there is a paucity of literature regarding the effect of nutritional optimization before arthroplasty surgery. In a randomized controlled trial of 60 patients undergoing hip fracture surgery, a perioperative energy-protein supplement was associated with a significant increase in serum albumin levels and decreased postoperative complications.[34] He *et al.* also found that postoperative supplementation of enteral nutrition powder after primary THA decreased the risk of PJI and readmission among patients undergoing THA.[10] Other authors have also supported routine screening for malnutrition before TJA and the use of protein supplementation for patients with hypoalbuminemia or other markers of malnutrition.[35]

By contrast, after a retrospective review of 819 primary TJA cases, Rao et al. found minimal concordance between various laboratory markers for malnutrition. They argued that routine preoperative nutritional testing is of little value.[36] The authors suggested that hypoalbuminemia is a marker of an increased comorbidity burden rather than malnutrition. Similarly, the consensus statement by the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition states that albumin levels are poorly correlated with nutritional status and do not reliably improve with nutritional optimization but instead are indicative of systemic inflammation and chronic illness.[37]

As a retrospective review, this study has certain limitations. Our small cohort size of 199 patients limits the power of the study to detect differences between patients with and without hypoalbuminemia. This was especially true given the small number of patients who died, which limits our mortality analysis. Similarly, not all patients had albumin values available before both the first and second stages. Lastly, several patients had to be excluded from our multivariate analysis due to missing covariates such as BMI and smoking status. However, the number of patients missing data was a small proportion of the total cohort, and we believe excluding these patients did not significantly bias our results.

Conclusion

In conclusion, we found that hypoalbuminemia before the second stage of reimplantation increases mortality risk in patients undergoing a two-stage exchange for PJI. Surgeons may consider delaying reimplantation in patients with hypoalbuminemia until patient comorbidities and known modifiable risk factors can be appropriately addressed. However, further research is needed to determine if hypoalbuminemia is indicative of malnutrition and if preoperative nutritional optimization can improve outcomes.

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