CLINICAL ARTICLE

Hypoalbuminemia is Highly Prevalent in Patients with Periprosthetic Joint Infection and Strongly Associated with Treatment Failure

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Objective: The role of hypoalbuminemia throughout the course of chronic periprosthetic joint infection (PJI) remains poorly understood. This study aimed to determine the prevalence and risk factors of hypoalbuminemia in periprosthetic joint infection (PJI) patients and to explore the association between hypoalbuminemia and treatment outcomes.

Methods: This retrospective cohort study included 387 PJI cases who underwent two-stage exchange arthroplasty between January 2007 and August 2020, of which 342 were reimplanted. The mean follow-up period was 7.9 years. Multivariate logistic regression analyses were performed to identify risk factors for hypoalbuminemia and to assess the effect of hypoalbuminemia at 1st- and 2nd-stage exchange on the treatment outcome. Furthermore, the impact of dynamic changes in hypoalbuminemia was investigated.

Results: The prevalence of hypoalbuminemia at 1st- and 2nd-stage exchange was 22.2% and 4.7%, respectively. Patients with age ≥ 68 years and those with isolation of Staphylococcus aureus, Streptococcus, or Gram-negative bacteria exhibited a higher risk of hypoalbuminemia. Hypoalbuminemia at 1st-stage was significantly related to treatment failure (OR = 3.3), while hypoalbuminemia at 2nd-stage raised the OR to 10.0. Patients with persistent hypoalbuminemia at both the 1st- and 2nd-stage exchanges had a significantly higher rate of treatment failure than patients with hypoalbuminemia at the 1st-stage but normal albumin levels at the 2nd-stage exchange (55.6% *vs* 20.0%, $p = 0.036$).

Conclusion: One in five patients with chronic PJI exhibits hypoalbuminemia. Hypoalbuminemia is more likely to develop in patients of advanced age and those infected by specific highly virulent organisms. Also, our results highlight the close association between hypoalbuminemia and treatment outcomes.

Key words: Hypoalbuminemia; periprosthetic joint infection; risk factors; treatment outcomes

Introduction

Periprosthetic joint infection (PJI) occurs in 0.5%–2% of total joint arthroplasties (TJAs) and is one of the most devastating complications.[1] With an aging population and a rapid increase in TJAs, the number of PJIs is also predicted to grow exponentially.[2] Two-stage exchange arthroplasty

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remains the standard management protocol for chronic PJI; however, its failure rates, as reported in the literature, remain alarming, ranging from 14% to 45% according to different assessment criteria, and can result in substantial costs.[3–6] Of greater concern, the mortality rate after surgical treatment of PJI is more than five times higher than that following aseptic revision.[7]

As a modifiable risk factor, malnutrition has been documented as a potential cause of poor outcomes after orthopedic surgery.[8] Although there is no consensus on the best nutritional assessment tool, hypoalbuminemia remains one of the most recognized serum markers of malnutrition and has been extensively investigated.[9–11] Previous studies have reported that pathological conditions such as chronic infection and cancer can induce a high prevalence of hypoalbuminemia.[12,13] Meanwhile, hypoalbuminemia can reflect the pathological stress response caused by disease-related inflammation and may be associated with disease severity.[14,15] In a variety of chronic progressive diseases, hypoalbuminemia may worsen as inflammation progresses and the risk of death increases.[16] Moreover, its clinical significance as a prognostic marker has been extensively investigated in cardiovascular diseases,[17] renal diseases,[18] and hematologic diseases.[19]

Regarding infectious diseases, albumin plays a critical role in the host immune response to pathogens and systemic inflammation characterized by a cytokine storm.[20] Therefore, albumin contributes significantly to the antimicrobial defense and severe hypoalbuminemia may lead to multi-organ dysfunction.[21] Further studies have shown that antioxidant therapy after infection could facilitate the control of bacterial infection by inhibiting the secondary hit response.[22] Furthermore, coexisting hypoalbuminemia in patients is a potential predictor of adverse outcomes in several infectious diseases.[23–25] A recent prospective cohort study showed that hypoalbuminemia independently predicted a reduced effective response to infection.[26] The association of serum albumin levels with the progression of infectious diseases may be explained by the fact that inflammation alters albumin kinetics, allowing serum albumin levels to be a potential surrogate prognostic marker.[14]

It is recommended that the nutritional status of patients be routinely screened and promptly addressed to enhance patient safety and clinical outcomes.[27] Currently, there is also evidence that potential hypoalbuminemia may be associated with the development of PJI after TJA.[28–30] Green *et al.*[31] recently demonstrated in a small study that hypoalbuminemia can predict failure following first-stage resection in patients with PJI. However, the role of hypoalbuminemia throughout the course of chronic PJI remains poorly understood, suggesting that there is a significant opportunity to improve treatment decisions for PJI. Therefore, this study aimed to determine the prevalence and risk factors of hypoalbuminemia in chronic PJI patients and to explore the association between hypoalbuminemia and treatment failure.

Patients and Methods

Study Population

Ethical approval for this study was obtained from the Institutional Review Board (Number: S2021-015-01). Inclusion criteria were as follows: (i) patients with PJI of the hip or knee; and (ii) patients who underwent 1st-stage exchange arthroplasty at our institution between January 2007 and August 2020. A total of 416 patients (226 hips and 190 knees) were initially identified. Exclusion criteria were: (i) cases did not meet the International Consensus Meeting (ICM) 2018 criteria (n = 15);[32] (ii) patients were institutional transferred during the interstage period of two-stage exchange (n = 9); or (iii) missing laboratory test data (n = 5). It is noteworthy that patients with PJI prior to 2018 were not tested for alpha-defensin, yet they all met the remaining diagnostic criteria. The flow chart for the inclusion of PJI patients is shown in Figure 1.

A total of 387 patients who underwent the 1st-stage exchange were enrolled in the study. Their baseline characteristics are summarized in Table 1. The patients were (60.7 ± 13.5) years old, and 48.6% were men, with a mean BMI of (25.1 ± 4.0) kg/m^2. There were more infected hips (55.3%) than knees (44.7%). The most prevalent causative pathogen was coagulase-negative Staphylococcus (31.8%). Negative cultures were identified in 24.5% of patients. The microbiology of PJI varies across countries, and the present results were comparable to those of a large German PJI referral center, which reported that the most prevalent causative organism was coagulase-negative Staphylococci (39.3%).[33,34]

Two-stage Exchange Technique

Two-stage exchange arthroplasty is the standard regimen for the treatment of chronic PJI at our institution. All patients received institutional-based surgical and rehabilitation approaches. The 1st-stage resection involves the removal of the infected prosthesis, thorough debridement, and then placement of an antibiotic-loaded spacer. The spacer was manufactured by combining bone cement (pre-mixed with gentamicin) with additional antibiotic powder (broad-spectrum antibiotics such as vancomycin, or pathogen-sensitive antibiotics) during the surgical procedure. In our practice, dynamic spacers are more advocated. We only choose static spacers when knee stabilization is difficult to achieve, such as severe soft tissue deficiencies or substantial bone loss.[6] Multiple cultures were obtained intraoperatively for microbiological examination to guide the systematic administration of antibiotics further. In accordance with the recommendations of the infection specialist, sensitive antibiotics were administered to those with positive cultures, while broad-spectrum antibiotics were administered to those with negative cultures. Following a 6–12 week course of antibiotic therapy and a two-week antibiotic holiday, the timing of 2nd-stage reimplantation required a comprehensive assessment of clinical symptoms and laboratory tests. In the event that the infections were believed to have been eradicated,

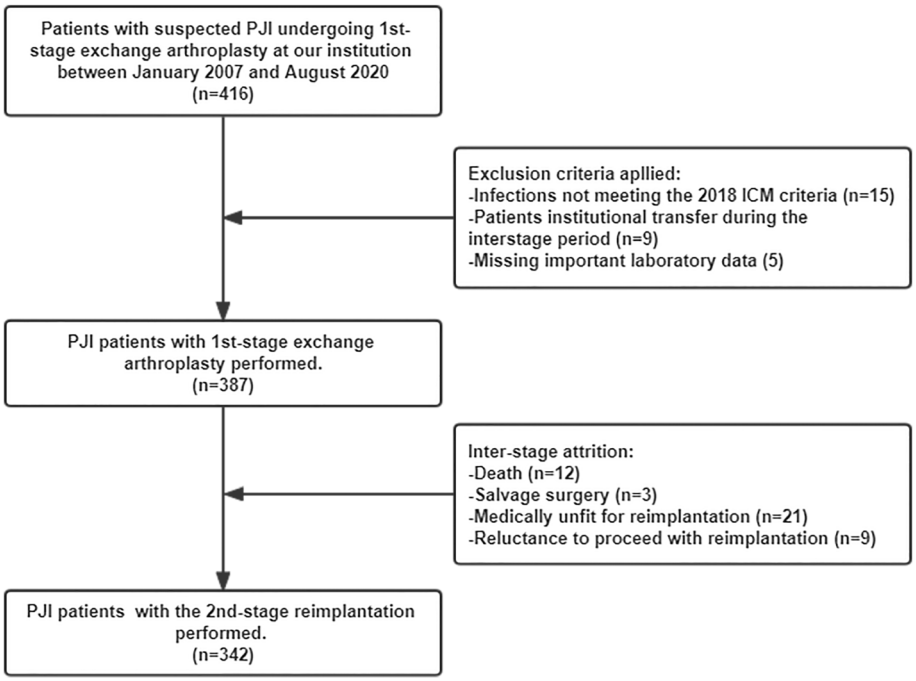

FIGURE 1 This flowchart demonstrates how patients are identified for inclusion in the final cohort. PJI, periprosthetic joint infection; ICM, International Consensus Meeting.

TABLE 1 Baseline characteristics of the study population at 1st-stage exchange.

Characteristics	Total (n = 387)
Demographic details	
Age, years	60.7 ± 13.5
Men [cases (%)]	188 (48.6)
BMI, kg/m^2	25.1 ± 4.0
Smoking [cases(%)]	33 (8.5)
CCI	2.7 ± 1.4
Disease data [cases(%)]	
Hip	214 (55.3)
Knee	173 (44.7)
Primary diagnosis [cases(%)]	
Osteoarthritis	132 (34.1)
ONFH	92 (23.8)
DDH	6 (1.6)
Inflammatory arthropathy	25 (6.5)
Fracture	89 (23.0)
Others	43 (11.1)
Pathogens [cases(%)]	
Staphylococcus aureus	40 (10.3)
Coagulase-negative staphylococcus	123 (31.8)
Entoococcus	16 (4.1)
Streptococcus	10 (2.6)
Gram-Negative bacteria	18 (4.7)
Others	25 (6.5)
Polymicrobial	60 (15.5)
Negative	95 (24.5)
Laboratory test	
C-reactive protein, mg/L	25.2 ± 26.3
ESR, mm/1 h	43.7 ± 26.5

Abbreviations: CCI, Charlson comorbidity index; DDH, developmental dysplasia of the hip; ESR, erythrocyte sedimentation rate; ONFH, osteonecrosis of the femoral head.

new prosthetic components would be reimplantation followed by re-debridement and irrigation. Finally, three hundred and forty-two patients in our cohort underwent reimplantation. Of these, 70 had positive cultures during reimplantation and were treated with 2 weeks of intravenous and 4 weeks of oral antibiotics following reimplantation. Inter-stage attrition occurred in 45 patients. Of them, 12 patients died before reimplantation, 21 were assessed as medically unfit for reimplantation, nine were reluctant to proceed with reimplantation, and three underwent salvage surgery (Figure 1).

Clinical Data Extraction

Patients were subjected to routine testing for serum albumin in the fasting state prior to the 1st- and 2nd-stage exchange. The most recent serum albumin levels before surgery were extracted. They were expressed in grams per liter (g/L), and hypoalbuminemia was defined as a serum albumin level less than 35 g/L.[9–11,35]

Relevant variables were extracted from the patients' medical records of resection and reimplantation, including demographic details, microbiological data, comorbidities, the Charlson comorbidity index (CCI), and preoperative laboratory test values of serum albumin. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were obtained to reflect the systemic inflammatory response of patients.

Outcome Assessment

The mean follow-up time was 7.91 (median, 7.45) years after first-stage revision surgery. Clinical outcomes were assessed

according to the recently proposed Musculoskeletal Infection Society (MSIS) outcome reporting tool.[36] This tool allows for a more accurate classification using a four-tier system. In brief, infection control is considered Tier 1/2. Tier 3 represents any condition requiring surgical intervention or spacer retention. Aseptic revision and septic revision, more than 1 year from the starting point, are 3A and 3B, respectively. Similarly, aseptic and septic revisions less than 1 year from the starting point are classified as 3C and 3D, respectively. Salvage procedures such as amputation, resection arthroplasty, or arthrodesis are considered 3E. 3F indicates a retained spacer. Deaths that occur within 1 year of the starting point are classified as 4A, while deaths that occur more than 1 year after the starting point are classified as 4B. According to Borsinger *et al.*,[4] Tiers 1 and 2 were defined as successes. Overall, Tiers 3 and 4 were defined as total failures, where Tiers 3B, 3C, 3D, 3E, 3F, and 4A were failures directly related to PJI, and Tiers 3A and 4B were failures due to secondary causes. Although the suggested starting point for assessment is the 1st-stage exchange arthroplasty, we set two starting points (1st- and 2nd-stage exchange) to evaluate the impact of hypoalbuminemia in each stage.

Statistical Analysis

All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, New York). A p-value of 0.05 was considered statistically significant. We used independent-samples t-tests to evaluate differences in continuous variables between the groups. Categorical variables were compared using the chi-square test and Fisher's exact test. Paired-samples t-tests were employed to identify differences in albumin levels between the 1st- and 2nd-stage exchange. We also conducted a Pearson correlation analysis to explore the correlation between albumin levels and inflammatory parameters.

A logistic regression analysis was performed to identify independent risk factors for hypoalbuminemia at the 1st-stage exchange. Variables with a p-value < 0.1 in the univariable logistic analysis were subjected to multivariable analysis. Due to the low virulence of coagulase-negative staphylococci and the prevalence of osteoarthritis, they were set as the reference category. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off values of continuous variables. Additionally, the associations between hypoalbuminemia at the 1st- or 2nd-stage exchange and failures according to different definitions were assessed by logistic regression analysis. The models were adjusted for patient baseline characteristics such as age, gender, body mass index (BMI), microbiological findings (microbial species, negative or polymicrobial cultures), number of prior procedures, knee or hip joints, primary diagnosis, smoking, and CCI. All logistic regression analyses reported adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Also, patients were divided into four groups according to the presence or absence of hypoalbuminemia at each stage, including hypoalbuminemia at both 1st- and 2nd-stage (Group 1), hypoalbuminemia at 1st-stage only (Group 2), hypoalbuminemia at 2nd-stage only (Group 3), and no hypoalbuminemia (Group 4). The treatment failure rates were then compared among the aforementioned groups.

Results

Prevalent Trend of Hypoalbuminemia

The prevalence of malnutrition at 1st-stage exchange was 22.2% (86/387). Three hundred and forty-two individuals in the final study cohort proceeded with reimplantation. An increase in serum albumin was observed in 72% of patients during the interstage period. As illustrated in Figure S1, the serum albumin level at the 2nd-stage was significantly higher than those at the 1st-stage exchange ($p < 0.001$), with Δalbumin of 2.26 (median: 2.10) g/L. The prevalence of hypoalbuminemia at the 2nd-stage was 4.7% (16/342), which was significantly lower than that at the 1st-stage exchange (Figure S2, $p < 0.001$).

Risk Factors for Hypoalbuminemia at 1st-stage Exchange

Univariate logistic regression analysis identified age, gender, primary diagnosis, and causative pathogen as potential risk factors. A ROC curve indicated an optimal cut-off value of age was 68 years. The multivariable logistic analysis revealed age ≥ 68 years (Table 2, OR = 3.3; 95%CI, 1.9–5.7; $p < 0.001$) was an independent risk factor for hypoalbuminemia. The prevalence of hypoalbuminemia was found to be higher in patients with isolation of Staphylococcus aureus (OR = 2.7; 95%CI, 1.1–6.7; $p = 0.032$), Streptococcus (OR = 6.4; 95%CI, 1.5–26.7; $p = 0.011$), or Gram-negative bacteria (OR = 4.5; 95%CI, 1.4–14.0; $p = 0.010$). Although the result was not statistically significant, there was a trend toward a higher prevalence of hypoalbuminemia in patients with enterococcal PJI (OR = 2.9; 95%CI, 0.9–9.4; $p = 0.082$).

In addition, the relationship between albumin levels and patients' systemic inflammatory response was investigated. Correlation analysis revealed a negative correlation between preoperative albumin levels and either CRP (r = −0.183, $p = 0.001$) or ESR (r = −0.247, $p = 0.001$).

Association between Hypoalbuminemia and Treatment Failure

As shown in Table 3, the total failure rates with the 1st- and 2nd-stage exchange as the starting point for treatment assessment were 26.1% and 16.4%, respectively; failures directly related to PJI were 17.5% and 8.7%, respectively. After adjusting for potential confounders including patient characteristics and microbiological findings in the multivariate models, we found hypoalbuminemia at any stage was associated with worse clinical outcomes (Table 4). For patients with hypoalbuminemia at 1st-stage exchange, the risks of total failure and failure directly related to PJI were

TABLE 2 Multivariable regression analysis for predictors of hypoalbuminemia at 1st-stage exchange.

Variables	Odds ratio	95% CI	*p*
Age ≥ 68 years	3.3	1.9–5.7	**<0.001**
Female gender	1.2	0.7–2.1	0.476
Primary diagnosis			
Osteoarthritis	REF		
ONFH	0.5	0.2–1.0	0.060
Inflammatory arthropathy	1.5	0.6–4.3	0.405
Fracture	1.1	0.6–2.2	0.724
Others	0.5	0.2–1.2	0.122
Pathogens			
Coagulase-negative staphylococcus	REF		
Staphylococcus aureus	2.7	1.1–6.7	**0.032**
Entoococcus	2.9	0.9–9.4	0.082
Streptococcus	6.4	1.5–26.7	**0.011**
Gram-negative bacteria	4.5	1.4–14.0	**0.010**
Others	1.4	0.4–4.5	0.570
Polymicrobial	1.9	0.8–4.2	0.136
Negative	1.5	0.7–3.0	0.323

Abbreviations: CI, confidence interval; ONFH, osteonecrosis of the femoral head. *Note*: The Bold font indicates statistical significance ($p < 0.05$).

2.5 (95%CI, 1.4–4.5; $p = 0.002$) and 3.3 (95%CI, 1.8–6.3; $p < 0.001$) times higher than those of controls, respectively. With regard to hypoalbuminemia at 2nd-stage, the relative risks of failure were found to be elevated to 7.6 (95%CI, 2.2–25.7; $p = 0.001$) and 10.0 (95%CI, 2.2–45.6; $p = 0.003$), respectively. Meanwhile, hypoalbuminemia at 1st-stage exchange was also closely associated with attrition (OR = 2.9; 95%CI, 1.4–6.3; $p = 0.005$).

The Impact of Dynamic Change of Hypoalbuminemia

Failure rates were calculated for four subgroups based on the presence of hypoalbuminemia at each stage (Figure 2). Patients who consistently exhibited normal albumin levels had the highest success rate of 86.0% (Group 4). Nine patients (Group 1) developed persistent hypoalbuminemia throughout the two-stage exchange. The failure rate was found to be 56%, which was significantly higher than that observed in patients without hypoalbuminemia (55.6% *vs* 14.0%, Group 4, $p = 0.005$). In contrast, patients whose hypoalbuminemia was corrected (Group 2) had a substantially lower failure rate than Group 1 (20.0% *vs* 55.6%, $P = 0.036$). Additionally, a small number of patients exhibited a decline in albumin level and developed hypoalbuminemia at 2nd-stage (Group 3), with a high failure rate of 28.6%.

TABLE 3 Description of clinical outcomes using the MSIS outcome reporting tool at different starting points of treatment assessment.

MSIS outcome	1st-stage exchange (n = 387)	2nd-stage exchange (n = 342)
Tier 1/2	286 (73.9)	286 (83.6)
Tier 3		
Tier 3A	6 (1.6)	6 (1.8)
Tier 3B	4 (1.0)	4 (1.2)
Tier 3C	5 (1.3)	5 (1.5)
Tier 3D	10 (2.6)	10 (2.9)
Tier 3E	5 (1.3)	5 (1.5)
Tier 3F	33 (8.5)	
Tier 4		
Tier 4A	11 (2.8)	3 (0.9)
Tier 4B	27 (7.0)	23 (5.9)

Abbreviation: MSIS, musculoskeletal infection society.; *Note*: Tiers 3 and 4 were defined as total failures, where tiers 3B, 3C, 3D, 3E, 3F, and 4A were failures directly related to PJI, and tiers 3A and 4B were failures due to secondary causes.

Discussion

Main Findings of this Study

In this study, the prevalence of hypoalbuminemia was 22.2% in PJI cases, which was higher than that observed in patients with gastrointestinal cancers, such as gastric and colorectal cancer.[37,38] However, the albumin levels of these PJI cases significantly improved at the 2nd-stage exchange with a hypoalbuminemia rate of only 4.69%. Advanced age and isolation of specific highly virulent organisms may be potential risk factors for hypoalbuminemia. Hypoalbuminemia at either stage is strongly associated with failure of PJI treatment. PJI patients with persistent hypoalbuminemia (at both 1st- and 2nd-stage) had an apparently higher failure rate of 50%, while correcting hypoalbuminemia may improve prognosis following treatment for PJI.

High Prevalence of Hypoalbuminemia in Patients with PJI

The prevalence of malnutrition or hypoalbuminemia among orthopedic patients in previous studies varies considerably,

TABLE 4 The association between hypoalbuminemia and treatment failure according to different definitions.

Definitions	Total	Hypoalbuminemia		Normal		OR[a]	95% CI	*p*
		Failure	Total	Failure	Total			
Hypoalbuminemia at 1st-stage								
Total failures	101 (26.1%)	38 (44.1%)	86	63 (20.9%)	301	2.5	1.4–4.5	**0.002**
Failures directly related to PJI	68 (17.6%)	29 (33.7%)	86	39 (13.0%)	301	3.3	1.8–6.3	**<0.001**
Attrition	45 (11.6%)	22 (25.6%)	86	23 (7.6%)	301	2.9	1.4–6.3	**0.005**
Hypoalbuminemia at 2nd-stage								
Total failures	56 (16.4%)	7 (43.8%)	16	49 (15.0%)	326	7.6	2.2–25.7	**0.001**
Failures directly related to PJI	27 (7.9%)	4 (25.0%)	16	23 (7.1%)	326	10.0	2.2–45.6	**0.003**

Abbreviations: CI, confidence interval; OR, odds ratio; PJI, periprosthetic joint infection. *Note*: The Bold font indicates statistical significance ($p < 0.05$).; [a]Adjusted for baseline characteristics such as age, gender, Body Mass Index (BMI), microbiological findings (microbial species, negative or polymicrobial cultures), number of prior procedures, knee or hip joints, primary diagnosis, smoking, and comorbidities.

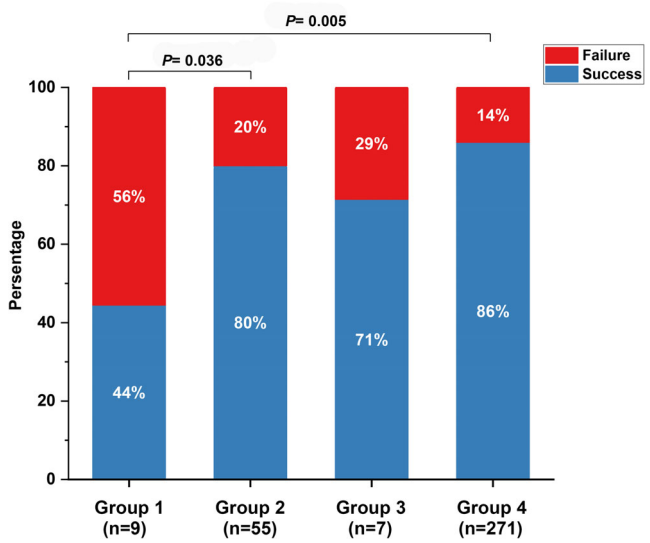

FIGURE 2 Treatment failure rates were assessed for subgroups based on the presence or absence of hypoalbuminemia at each stage, including hypoalbuminemia at both 1st- and 2nd-stage (group 1), hypoalbuminemia at 1st-stage only (Group 2), hypoalbuminemia at 2nd-stage only (Group 3), and no hypoalbuminemia (Group 4).

probably due to the differing natures of the diseases.[28,35,39,40] In a survey of the American College Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) database, hypoalbuminemia was identified in 4.0% of 49,603 patients with primary TJA and was associated with adverse outcomes such as surgical site infection and pneumonia.[41] Another study reviewed 9230 patients with revision TJA in the ACS-NSQIP database and observed hypoalbuminemia in 11.8% of patients with aseptic revision.[30] Whereas we found an increase in the prevalence of hypoalbuminemia to 22.2% in the PJI cohort. This incidence rate is alarming, even higher than that in common cancers such as gastric and colorectal cancer.[37,38] The cause of this phenomenon is still unknown. However, we speculate that it may be related to nutrition consumption in chronic infection. Also, infection is a common cause of hypoalbuminemia, and the severity of inflammatory stress could also be reflected in hypoalbuminemia. Therefore, it is important to recognize that PJI patients may be in a complicated state of combined malnutrition and inflammatory stimulation. The aforementioned evidence indicates the necessity for the routine screening of serum albumin levels in PJI patients, as it may provide clinicians with additional information about the patient's underlying health status.

Risk Factors for Hypoalbuminemia

A significant conclusion of this study is that it may assist in identifying associations between hypoalbuminemia and patient or microbial characteristics. Previous literature has shown that patients with high or low BMI, malabsorption, and hypermetabolic states are at an elevated risk for malnutrition in TJA.[42] However, to our knowledge, there are currently no reports on predictors of hypoalbuminemia in PJI patients. The results of multivariate logistic regression analysis revealed for the first time a potential association between hypoalbuminemia at the 1st-stage exchange and advanced age or infection with specific highly virulent organisms. Although the present findings are preliminary, they are still interesting and warrant the attention of surgeons, as they emphasize the importance of further close monitoring of serum albumin levels in high-risk patients. In addition, further investigation of the association between these factors and hypoalbuminemia may contribute to our improved understanding of the pathogenesis of hypoalbuminemia in infectious diseases. In a study by Schwarzkopf *et al.*,[43] no correlation was found between nutritional status and nasal staphylococcal colonization in TJA patients. However, the combination of Staphylococcus aureus and poor nutritional status led to intense transcription of such innate immunity components and could induce extensive tissue injury.[44] Our results indicated that infection with specific highly virulent

pathogens may induce more severe inflammatory stress, which in turn may lead to increased hypoalbuminemia.

Strong Association between Hypoalbuminemia and PJI Treatment Failure

A substantial body of research indicates a correlation between potential malnutrition and unfavorable outcomes after TJA.[28–30,39,41,45,46] A previous study found that preoperative albumin level was the most valuable nutritional predictor of PJI after primary TJA.[29] Furthermore, our findings revealed a robust association between treatment failure and preoperative hypoalbuminemia during the two-stage exchange arthroplasty. Compared to total failures, hypoalbuminemia demonstrated a more excellent predictive value for failures directly related to PJI, indicating the critical impact of nutritional status on PJI. Chronic conditions associated with hypoalbuminemia can complicate treatment by second hit phenomena,[47] which may explain the higher risk of failure in PJI patients with concomitant hypoalbuminemia. Also, attrition represents patients who did not receive the expected reimplantation in a two-stage exchange. These patients have been substantially overlooked in the past and are now defined as treatment failures by the latest MSIS outcome reporting tool.[36] A previous study identified several independent risk factors for attrition, including higher CCI score, liver disease, the presence of sinus tract, spacer exchange, and the prior revision.[48] We further identified an approximately twofold increased risk of attrition in patients with hypoalbuminemia. These findings may assist surgeons in gaining a deeper understanding of this comorbidity.

It is disheartening to note that the treatment failure rate for patients with persistent hypoalbuminemia exceeded 50%. On the contrary, most patients corrected their hypoalbuminemia after 1st-stage, and their treatment success rate improved significantly. This result suggests that hypoalbuminemia due to infection may be reversible in the majority of cases, indicating that the nutritional status of patients can be enhanced after infection control by the 1st-stage exchange. On the other hand, our findings show that improved albumin levels before reimplantation may positively impact the prognosis of PJI. To date, the literature on nutritional intervention and its effects on orthopedic patients is limited.[42] Several studies have evaluated the impact of special diets on length of stay and postoperative complications after TJA, yielding mixed results.[40,49–51] Further assessment of the potential benefits of various nutritional interventions is still needed. Furthermore, our findings indicated that hypoalbuminemia at reimplantation was more closely related to treatment failure. In general, patients' albumin levels would increase after the infection was eradicated by 1st-stage exchange. However, the presence of hypoalbuminemia at reimplantation may suggest that the infection has not been adequately controlled or that the patient may have other serious disease states, as it has been suggested that hypoalbuminemia may be a physiological state resulting from a combination of malnutrition and inflammation.[52] These data suggest that greater attention should be paid to the patient's albumin level before reimplantation, which could provide additional information about treatment outcomes.

Notably, hypoalbuminemia can lead to altered antibiotic pharmacokinetics as evidenced by an increase in the apparent total volume of distribution and clearance of the drug, thereby decreasing antibacterial exposure.[53] This could compromise the attainment of pharmacodynamic targets, especially for time-dependent antimicrobials. On the one hand, it may be one of the potential causes of the higher treatment failure rate in PJI patients with hypoalbuminemia; on the other hand, it indicated the importance of detecting antibiotic blood concentrations in this group of patients. Limited by the availability of data, we were not able to investigate the changes and impact of antibiotic blood concentrations in the present study, thus more in-depth studies will be needed in the future.

Strengths and Limitations

There are some strengths to this study. First, we reported for the first time the risk factors of hypoalbuminemia in patients with PJI. Second, the association between hypoalbuminemia and treatment outcomes throughout the two-stage exchange (both 1st- and 2nd-stage) was revealed. Our study also has several limitations. First, the design was retrospective, and the inherent biases of such studies must be acknowledged. Second, although institutional guidelines for therapy have been established, differences still exist in the management of patients over a 14-year period. However, we did not observe a substantial improvement in PJI treatment success at our institution during this period. Future prospective studies may provide additional information. Third, the details of dietary and other nutritional support for hypoalbuminemia are not available. Therefore, a further assessment of the prognostic impact of different nutritional interventions is warranted. Fourth, postoperative serum albumin variations were unavailable, and thus we were unable to investigate their impact on the outcome. However, based on the findings of this study preoperative hypoalbuminemia may be safely labeled as a prognostic factor for PJI treatment. This implies that we should consider more detailed treatment decisions in such patients. Finally, although we included patients' CCI in logistic regression models, further detailed analyses of underlying disease and hypoalbuminemia in the future may strengthen our conclusions.

Conclusions

Overall, the prevalence of hypoalbuminemia among PJI patients is relatively high. Advanced age and infection with specific highly virulent organisms may be risk factors for hypoalbuminemia. Besides, during the treatment decision-making process for PJI, patients should be counseled on the higher risk of failure if hypoalbuminemia is present. Further work should focus on the outcomes after corrective measures have been taken to offset hypoalbuminemia in PJI patients.

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None.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Ethics Statement

Ethical approval for this study was obtained from the Institutional Review Board (Number: S2021-015-01). The research only uses existing medical records and does not require any additional testing or specimen collection from the subjects.

Author Contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. L.Z.Y. and L.Z. were responsible for formal analysis and manuscript writing. X.C. and F.J. were responsible for material preparation and data collection. M.Z. and H.L.B. were responsible for data collection and visualization. C.J.Y. and Z.Q.M were responsible for the conceptualization, methodology, supervision, and project Administration. All authors read and approved the final manuscript.

Authorship Declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher's web-site:

Figure S1. Serum albumin levels at the 2nd-stage exchange were significantly higher than those at the 1st-stage.-**Figure S2.** Evolution of the prevalence of hypoalbuminemia during the two-stage exchange.

References

1. Corvec S, Portillo ME, Pasticci BM, Borens O, Trampuz A. Epidemiology and new developments in the diagnosis of prosthetic joint infection. Int J Artif Organs. 2012;35(10):923–34.
2. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Jt Surg Am. 2007;89(4):780–5.
3. Kurtz SM, Higgs GB, Lau E, Iorio RR, Courtney PM, Parvizi J. Hospital costs for unsuccessful two-stage revisions for periprosthetic joint infection. J Arthroplasty. 2022;37(2):205–12.
4. Borsinger TM, Pierce DA, Hanson TM, Werth PM, Orem AR, Moschetti WE. Is the proportion of patients with "successful" outcomes after two-stage revision for prosthetic joint infection different when applying the musculoskeletal infection society outcome reporting tool compared with the Delphi-based consensus criteria? Clin Orthop Relat Res. 2021;479(7):1589–97.
5. Petrie MJ, Panchani S, Al-Einzy M, Partridge D, Harrison TP, Stockley I. Systemic antibiotics are not required for successful two-stage revision hip arthroplasty. Bone Jt J. 2023;105(5):511–7.
6. Li Z, Xu C, Chen J. Articulating spacers: what are available and how to utilize them? Arthroplasty. 2023;5(1):22.
7. Drain NP, Bertolini DM, Anthony AW, Feroze MW, Chao R, Onyekweli T, et al. High mortality after Total knee arthroplasty periprosthetic joint infection is related to preoperative morbidity and the disease process but not treatment. J Arthroplasty. 2022;37(7):1383–9.
8. Cross MB, Yi PH, Thomas CF, Garcia J, Della Valle CJ. Evaluation of malnutrition in orthopaedic surgery. J Am Acad Orthop Surg. 2014;22(3):193–9.
9. Stauder R, Augschoell J, Hamaker ME, Koinig KA. Malnutrition in older patients with hematological malignancies at initial diagnosis - association with impairments in health status, systemic inflammation and adverse outcome. Hemasphere. 2020;4(1):e332.
10. Chamogeorgakis T, Mason DP, Murthy SC, Thuita L, Raymond DP, Pettersson GB, et al. Impact of nutritional state on lung transplant outcomes. J Heart Lung Transplant. 2013;32(7):693–700.
11. Sze S, Pellicori P, Zhang J, Weston J, Clark AL. The impact of malnutrition on short-term morbidity and mortality in ambulatory patients with heart failure. Am J Clin Nutr. 2021;113(3):695–705.
12. Bossi P, Delrio P, Mascheroni A, Zanetti M. The Spectrum of malnutrition/cachexia/sarcopenia in oncology according to different cancer types and settings: a narrative review. Nutrients. 2021;13(6):1980.
13. Bullock AF, Greenley SL, McKenzie GAG, Paton LW, Johnson MJ. Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis and meta-analysis. Eur J Clin Nutr. 2020;74(11):1519–35.
14. Wiedermann CJ. Hypoalbuminemia as surrogate and culprit of infections. Int J Mol Sci. 2021;22(9):4496.
15. Li Z, Maimaiti Z, Fu J, Li ZY, Hao LB, Xu C, et al. The superiority of immune-inflammation summary index for diagnosing periprosthetic joint infection. Int Immunopharmacol. 2023;118:110073.
16. Fulks M, Stout RL, Dolan VF. Albumin and all-cause mortality risk in insurance applicants. J Insur Med. 2010;42(1):11–7.
17. Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8–12.
18. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med. 2010;36(10):1657–65.
19. Doucette K, Percival ME, Williams L, Kandahari A, Taylor A, Wang S, et al. Hypoalbuminemia as a prognostic biomarker for higher mortality and treatment complications in acute myeloid leukemia. Hematol Oncol. 2021;39(5):697–706.
20. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020;383(23): 2255–73.
21. Ferrer R, Mateu X, Maseda E, Yebenes JC, Aldecoa C, De Haro C, et al. Non-oncotic properties of albumin. A multidisciplinary vision about the implications for critically ill patients. Expert Rev Clin Pharmacol. 2018;11(2):125–37.
22. Hoth JJ, Smith LM, Furdui CM, Wells JD, Yoza BK, McCall CE. Antioxidant treatment after injury suppresses second hit immune priming. J Trauma Acute Care Surg. 2018;85(2):367–74.
23. Bao YC, Yu M, Tang L, Ning HY, Zhang WL. Changes in serum prealbumin and incision complications following spinal tuberculosis surgery: a preliminary study. Orthop Surg. 2021;13(2):501–5.
24. Siddiqui SS, Chakraborty N, Muzaffar SN, Gurjar M. Albumin kinetics in sepsis and COVID-19. Crit Care Explor. 2022;4(3):e0651.
25. Li Z, Maimaiti Z, Li ZY, Fu J, Hao LB, Xu C, et al. Moderate-to-severe malnutrition identified by the controlling nutritional status (CONUT) score is significantly associated with treatment failure of periprosthetic joint infection. Nutrients. 2022;14(20):4433.
26. Zhang J, Li X, He R, Zheng W, Kwong JS, Lu L, et al. The effectiveness of clinical pharmacist-led consultation in the treatment of infectious diseases: a prospective, multicenter, Cohort study. Front Pharmacol. 2020;11:575022.
27. Chen C, Zhang Y, Zhao X, Tao M, Yan W, Fu Y. Hypoalbuminemia - An indicator of the severity and prognosis of COVID-19 patients: a multicentre retrospective analysis. Infect Drug Resist. 2021;14:3699–710.
28. Yi PH, Frank RM, Vann E, Sonn KA, Moric M, Della Valle CJ. Is potential malnutrition associated with septic failure and acute infection after revision total joint arthroplasty? Clin Orthop Relat Res. 2015;473(1):175–82.
29. Blevins K, Aalirezaie A, Shohat N, Parvizi J. Malnutrition and the development of periprosthetic joint infection in patients undergoing primary elective Total joint arthroplasty. J Arthroplasty. 2018;33(9):2971–5.
30. Bohl DD, Shen MR, Kayupov E, Cvetanovich GL, Della Valle CJ. Is hypoalbuminemia associated with septic failure and acute infection after revision Total joint arthroplasty? A study of 4517 patients from the National Surgical Quality Improvement Program. J Arthroplasty. 2016;31(5):963–7.
31. Green CC, Valenzuela MM, Odum SM, Rowe TM, Springer BD, Fehring TK, et al. Hypoalbuminemia predicts failure of two-stage exchange for chronic periprosthetic joint infection of the hip and knee. J Arthroplasty. 2023;38(7): 1363–1368.

32. Shohat N, Bauer T, Buttaro M, Budhiparama N, Cashman J, Della Valle CJ, et al. Hip and knee section, what is the definition of a periprosthetic joint infection (PJI) of the knee and the hip? Can the same criteria be used for both joints?: proceedings of international consensus on orthopedic infections. J Arthroplasty. 2019;34(2S):S325–7.
33. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. Lancet. 2016;387(10016):386–94.
34. Aggarwal VK, Bakhshi H, Ecker NU, Parvizi J, Gehrke T, Kendoff D. Organism profile in periprosthetic joint infection: pathogens differ at two arthroplasty infection referral centers in Europe and in the United States. J Knee Surg. 2014; 27(5):399–406.
35. Bohl DD, Shen MR, Hannon CP, Fillingham YA, Darrith B, Della Valle CJ. Serum albumin predicts survival and postoperative course following surgery for geriatric hip fracture. J Bone Jt Surg Am. 2017;99(24):2110–8.
36. Fillingham YA, Della Valle CJ, Suleiman LI, Springer BD, Gehrke T, Bini SA, et al. Definition of successful infection management and guidelines for reporting of outcomes after surgical treatment of periprosthetic joint infection: from the workgroup of the musculoskeletal infection society (MSIS). J Bone Jt Surg Am. 2019;101(14):e69.
37. Haskins IN, Baginsky M, Amdur RL, Agarwal S. Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients. Clin Nutr. 2017;36(5):1333–8.
38. Zheng HL, Lu J, Li P, Xie JW, Wang JB, Lin JX, et al. Effects of preoperative malnutrition on short- and long-term outcomes of patients with gastric cancer: can we do better? Ann Surg Oncol. 2017;24(11):3376–85.
39. Ellsworth B, Kamath AF. Malnutrition and Total joint arthroplasty. J Nat Sci. 2016;2(3):179.
40. An X, Wang J, Shi W, Ma R, Li Z, Lei M, et al. The effect of passive smoking on early clinical outcomes after Total knee arthroplasty among female patients. Risk Manage Healthcare Policy. 2021;14:2407–19.
41. Bohl DD, Shen MR, Kayupov E, Della Valle CJ. Hypoalbuminemia independently predicts surgical site infection, pneumonia, length of stay, and readmission after Total joint arthroplasty. J Arthroplasty. 2016;31(1):15–21.
42. Golladay GJ, Satpathy J, Jiranek WA. Patient optimization-strategies that work: malnutrition. J Arthroplasty. 2016;31(8):1631–4.
43. Schwarzkopf R, Russell TA, Shea M, Slover JD. Correlation between nutritional status and staphylococcus colonization in hip and knee replacement patients. Bull NYU Hosp Jt Dis. 2011;69(4):308–11.
44. Gomes de Morais N, Barreto da Costa T, Bezerra de Lira JM, da Cunha Goncalves de Albuquerque S, Alves Pereira VR, de Paiva Cavalcanti M, et al. TLR and NLRP3 inflammasome expression deregulation in macrophages of adult rats subjected to neonatal malnutrition and infected with methicillin-resistant Staphylococcus aureus. Nutrition. 2017;33:174–80.
45. Greene KA, Wilde AH, Stulberg BN. Preoperative nutritional status of total joint patients. Relationship to postoperative wound complications. J Arthroplasty. 1991;6(4):321–5.
46. Li Z, Maimaiti Z, Yang F, Fu J, Li ZY, Hao LB, et al. Incidence, associated factors, and outcomes of acute kidney injury following placement of antibiotic bone cement spacers in two-stage exchange for periprosthetic joint infection: a comprehensive study. Front Cell Infect Microbiol. 2023;13:1243290.
47. Lasanianos NG, Kanakaris NK, Dimitriou R, Pape HC, Giannoudis PV. Second hit phenomenon: existing evidence of clinical implications. Injury. 2011;42(7): 617–29.
48. Wang Q, Goswami K, Kuo FC, Xu C, Tan TL, Parvizi J. Two-stage exchange arthroplasty for periprosthetic joint infection: the rate and reason for the attrition after the first stage. J Arthroplasty. 2019;34(11):2749–56.
49. Botella-Carretero JI, Iglesias B, Balsa JA, Arrieta F, Zamarron I, Vazquez C. Perioperative oral nutritional supplements in normally or mildly undernourished geriatric patients submitted to surgery for hip fracture: a randomized clinical trial. Clin Nutr. 2010;29(5):574–9.
50. Harsten A, Hjartarson H, Toksvig-Larsen S. Total hip arthroplasty and perioperative oral carbohydrate treatment: a randomised, double-blind, controlled trial. Eur J Anaesthesiol. 2012;29(6):271–4.
51. Schroer WC, LeMarr AR, Mills K, Childress AL, Morton DJ, Reedy ME. 2019 Chitranjan S. Ranawat Award: elective joint arthroplasty outcomes improve in malnourished patients with nutritional intervention: a prospective population analysis demonstrates a modifiable risk factor. Bone Jt J. 2019;101(Suppl 7): 17–21.
52. Eckart A, Struja T, Kutz A, Baumgartner A, Baumgartner T, Zurfluh S, et al. Relationship of nutritional status, inflammation, and serum albumin levels during acute illness: a prospective study. Am J Med. 2020;133(6):713–22.
53. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99–110.