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Hypoalbuminemia increases the risk of failure following one-stage septic revision for periprosthetic joint infection

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Abstract

Purpose Malnutrition is a potentially modifiable risk factor of periprosthetic joint infection (PJI). The purpose of this study was to analyze the role of nutritional status as a risk factor for failure after one- stage revision hip or knee arthroplasty for PJI.

Methods Retrospective, single-center, case–control study. Patients with PJI according to the 2018 International Consensus Meeting criteria were evaluated. Minimum follow-up was 4 years. Total lymphocyte count (TLC), albumin values, hemoglobin, C-reactive protein, white blood cell (WBC) count and glucose levels were analyzed. An analysis was also made of the index of malnutrition. Malnutrition was defined as serum albumin < 3.5 g/dL and TLC < 1500/mm$^{3.}$ Septic failure was defined as the presence of local or systemic symptoms of infection and the need of further surgery as a result of persistent PJI.

Results No significant differences were found between increased failure rates after a one-stage revision hip or knee arthroplasty for PJI and TLC, hemoglobin level, WBC count, glucose levels, or malnutrition. Albumin and C-reactive protein values were found to have a positive and significant relationship with failure ($p < 0.05$). Multivariate logistic regression identified only hypoalbuminemia (serum albumin < 3.5 g/dL) (OR 5.64, 95% CI 1.26–25.18, $p = 0.023$) as a significant independent risk factor for failure. The receiver operating characteristic (ROC) curve for the model yielded an area under the curve of 0.67.

Conclusion TLC, hemoglobin; WBC count; glucose levels; and malnutrition, understood as the combination of albumin and TLC, were not found to be statically significant risk factors for failure after single–stage revision for PJI. However, albumin < 3.5 g/dL, alone was a statically significant risk factor for failure after single-stage revision for PJI. As hypoalbuminemia seems to influence the failure rate, it is advisable to measure albumin levels in preoperative workups.

Keywords Malnutrition · Albumin · Total lymphocyte count · Periprosthetic joint infection · Single–stage revision

Introduction

Periprosthetic joint infection (PJI) is a devastating postoperative complication following total hip arthroplasty (THA) and total knee arthroplasty (TKA) [1, 2]. Concerns about PJI have increased over the years as a result of a significant increase in the number of THAs and TKAs performed every year [3]. Several studies have demonstrated that malnutrition is associated with an increased risk of impaired wound healing, persistent wound drainage, PJI, and unsuccessful debridement, antibiotics, and implant retention (DAIR) procedures [1, 4].

The mechanism by which malnutrition may result in increased rates of PJI after THA or TKA involves the disablement of the immune system, which is rendered incapable of fighting infections caused by a decreased number of lymphocytes, and a reduction in collagen synthesis and fibroblast proliferation as a result of deficient protein reserves, which results in impaired wound healing [1, 5]. Except in severe cases, the clinical signs and symptoms of malnutrition are not easy to detect. Several methods have been developed to detect malnutrition, including the analysis of laboratory values such as serum albumin, prealbumin, total protein count, total lymphocyte count (TLC), and serum transferrin [1, 4]. However, there is currently no gold-standard laboratory test that can accurately determine

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a patient's preoperative nutritional status [1, 2]. Moreover, there are currently no guidelines recommending what patient populations to screen [4]. The most common definition of malnutrition is serum TLC < 1500 cells/mm^3 and serum albumin concentration < 3.5 g/dL [4, 6, 7]. However, doubts persist about the usefulness of TLC and several authors have pointed to hypoalbuminemia as the main risk factor for PJI in the first 30 days after surgery [8–10].

The reported outcomes of one-stage revision for the management of PJI are comparable to those of two-stage revisions [11]. On-stage revision hip and knee arthroplasty has demonstrated eradication rates ranging from 82 to 98% [11–14]. Although malnutrition is a potentially modifiable risk factor, the estimated prevalence of malnutrition in patients undergoing total joint arthroplasty ranges from 27 to 50% [4, 6]. Following the hypothesis that optimization of a patient's nutritional status (based, according to the most common definition, on TLC and albumin values) may be beneficial in reducing the risk of failure after one-stage revision PJI, the purpose of this study was to determine if nutritional status can be regarded as a risk factor for one-stage hip or knee revision for PJI.

Materials and methods

Study design

This retrospective, single-center, case–control study was approved by the institutional review board. Data of patients diagnosed with PJI between January 2009 and December 2017 were recovered from the hospital's internal database. Hip and Knee PJI was defined according to the 2018 ICM (International Consensus Meeting) criteria [15]. Approximately 10,500 septic surgeries were performed during the study period. General indications for single-stage revision included low- virulence organisms, healthy patients with no immunocompromising systemic conditions, implant loosening, and no condition preventing direct closure of the wound after revision surgery. Previous studies found a 94% infection-free survival rate and a 75.9% surgery-free survival rate in our hospital at 10 years [16].

Inclusion and exclusion criteria

Inclusion criteria for this study were as follows: (1) Patients who experienced a septic failure after one-stage hip or knee arthroplasty for PJI. Septic failure was defined as the presence of local or systemic symptoms of infection and the need of further surgery as a result of persistent PJI. (2) Patients with at least 4 years' follow-up. The exclusion criteria included patients with no reliable preoperative albumin and TLC values. Patients diagnosed with periprosthetic fracture or dislocation, and those with malignant tumors or hematological and/or autoimmune diseases, were excluded from the study. The control group was made up entirely of patients who had undergone a one-stage revision surgery during the same period without experiencing a septic failure within at least 4 years.

Patients included in the study were stratified and divided into a "septic failure" and a "controlled infection" group. Successful infection control was defined as no clinical signs of infection, no further surgery for PJI, and no further positive cultures after the one-stage septic exchange. The potential occurrence of septic failure was monitored until December 2021, which represents a follow up of at least 4 years.

Surgical procedure

Both groups were treated with the same surgical technique according to the hospital's guidelines for one-stage revision surgery [11, 17]. These include the identification of the causative pathogen in both hip and knee PJIs. Once the organism has been identified, the one-stage technique can be performed.

One-stage surgery basically involves a complete debridement of non-viable tissues and the collection of samples for histological and cultural examination. Removal of cement and the prosthetic components, as well as further debridement and repeated lavage with saline and antibacterial solution, are mandatory. After this cleaning phase, the entire surgical team must rescrub and all sterile drapes and instruments must be exchanged before the new prosthesis is implanted with antibiotic-impregnated cement, according to the indications of the antibiogram. Intravenous antibiotic prophylaxis is administered only after collection of the samples for laboratory analysis. The patients in this study were treated and followed up in accordance with the indications of the infectious disease specialists and internal medicine doctors of our hospital.

Data collection measurements

Demographic, clinical and laboratory patient data were retrieved during hospitalization. The comorbidities in each group were evaluated, with particular consideration given to diabetes, body mass index (BMI), obesity defined as a BMI of 30 or higher, and dementia. The preoperative serum laboratory values analyzed included TLC and albumin. Hemoglobin (Hb), C-reactive protein (CRP), white blood cell count (WBC) and glucose levels were also evaluated for completeness. These data were collected as the literature overwhelmingly suggests that these parameters must be taken into consideration [6, 10, 18]. Despite the lack of a precise definition in the literature, TLC and albumin levels were considered indicators of malnutrition and therefore key

endpoints in our paper. Malnutrition was defined as serum albumin < 3.5 g/dL and TLC < 1500/mm^3 [4, 6, 7].

Statistical analysis

Statistical analyses were performed using Wizard Pro version 2.0.10 (Evan Miller, Chicago, IL, USA). Standard descriptive statistics were calculated including frequency, proportion, and measures of central tendency (mean and standard deviation (SD)). Differences between the groups with and without septic failure were analyzed. Statistical significance was set at a p value < 0.05. Chi-squared tests were used to compare the association between categorical risk factors and failure, and Student's t-test was used to compare continuous variables.

Bivariate and multivariate logistic regression analyses were performed. To analyze the predictive capacity of the model, a receiver operator characteristic (ROC) curve analysis was carried out and the area under the curve (AUC) was calculated for the risk of failure after single–stage revision for PJI.

Results

After application of the aforementioned inclusion and exclusion criteria, 165 patients were included in the study (35 knees and 41 hips). The failure group consisted of 76 patients, 40 men (60.5%) and 36 women (39.5%), Mean age was 69.9 years (standard deviation (SD) 11.1). The control group comprised 89 patients (40 knees and 49 hips) of whom 48 were men (53.9%) and 41 women (46.1%). Mean age was 67.1 (SD: 9.9). No statistically significant differences were found between the failure group and the control group regarding the demographic parameters analyzed except for BMI and obesity, where statistically significant differences were found between the groups (p = 0.004 and 0.007 respectively) (Table 1).

The failure group had significantly lower mean values of albumin (p = 0.017) and higher levels of hypoalbuminemia (p = 0.006) (Table 2). Lymphopenia, the index of malnutrition, TLC, WBC count, Hb and glucose levels did not show statistical significance (p > 0.05). Furthermore, the failure group exhibited significantly higher mean values of CRP (p = 0.018). A sub-group analysis of the risk of failure of hip and knee separated showed that BMI and obesity was a statistically significant variable in hip revisions (p = 0.006 and 0.008, respectively), but not in knee revisions (p > 0.05). Hypoalbuminemia, albumin, and CRP values was statistically significant variable for risk of failure in both hips and knees (p < 0.05) (Table 3).

In the multivariate analyses, hypoalbuminemia was the only variable with a positive and significant relationship with failure (odds ratio [OR] = 5.64, 95% CI 1.26–25.18, p = 0.023) (Table 4). The value of the area under the ROC curve of the multivariate model was 0.67 (Fig. 1).

Preoperative bacterial identification, a prerequisite for one-stage revision, was achieved for every patient in this cohort. In total, 26 different microorganisms were isolated from preoperative and surgical cultures. The most frequent

Table 1 General characteristics of the study participants

	Control Group, n = 89	Septic Group, n = 76	p value
Age (SD)	67.1 (9.9)	69.9 (11.1)	0.46
Gender			0.39
Male (%)	48 (53.9)	40 (60.5)	
Female (%)	41 (46.1)	36 (39.5)	
Side			0.41
Right (%)	48 (53.9)	36 (47.4)	
Left (%)	41 (46.1)	40 (52.6)	
Body mass index (SD)	28.6 (5.6)	30.7 (5.7)	**0.004**
Obesity (BMI ≥ 30)			**0.007**
No (%)	56 (62.9)	30 (41.7)	
Yes (%)	33 (37.1)	42 (58.3)	
Diabetes mellitus			0.132
No (%)	78 (87.6)	60 (78.9)	
Yes (%)	11 (12.4)	16 (21.1)	
Dementia			0.003
No (%)	79 (88.8)	76 (100.0)	
Yes (%)	10 (11.2)	0 (0)	

Bold indicated statistically significant differences

n number, *CI* confidence interval, % percentage, *SD* standard deviation, *BMI* body mass index

Table 2 Description of malnutrition and laboratory data of the study participants

	Control Group, n = 89	Septic Group, n = 76	p value
Lymphocytopenia			0.81
No (%)	45 (50.6)	37 (48.7)	
Yes (%)	44 (49.4)	39 (51.3)	
Hypoalbuminemia			**0.02**
No (%)	84 (94.4)	59	
Yes (%)	5 (5.6)	17	
Malnutrition			0.066
No (%)	86 (96.6)	68 (89.5)	
Yes (%)	3 (3.4)	8 (10.5)	
TLC (cells/mm^3)			
Mean (SD)	1.65 (0.64)	1.49 (0.60)	0.067
Albumin value g/L			
Mean (SD)	4.2 (0.46)	4.0 (0.49)	**0.017**
CRP value mg/L			
Mean (SD)	34.45 (43.13)	49.38 (48.49)	**0.018**
WBC count (cells/mL)			
Mean (SD)	7.98 (2.29)	8.45 (2.44)	0.148
Hemoglobin value g/L			
Mean (SD)	12.60 (1.88)	12.16 (1.79)	0.081
Glucose value mg/dL			
Mean (SD)	105.30 (33.53)	105.29 (29.10)	0.998

Bold indicated statistically significant differences

n number, *CI* confidence interval, *%* percentage, *SD* standard deviation, *CRP* c-reactive protein, *TLC* total lymphocyte count, *WBC* white blood cell, *mg* milligrams, *mm^3* cubic millimeter, *g* grams, *L* liters, *mL* milliliters, *dL* deciliters

microorganisms were *S. epidermidis* (62 patients), *S. aureus* (46 patients), *C. acnes* (24 patients), and *S. capitis* (22 patients). Eighteen patients presented with multiple bacteria.

Discussion

It is a known fact that malnutrition increases the rate of peri- and post-operative complications [1, 19]. However, a great deal of confusion exists regarding the role of malnutrition in orthopedics and specifically in prosthetic joint surgery. Traditionally, an excessive number of parameters have been taken into consideration, leading to a significant waste of time and money [6]. The main finding in our paper was that BMI, obesity, *hypoalbuminemia*, and albumin and CRP values did exhibit a positive and significant relationship with failure. However, the TLC and the index of malnutrition did not exhibit any relationship with failure after one-stage revision hip or knee arthroplasty for PJI. In a sub-group analysis of the risk of failure of hip and knee separated showed that BMI and obesity was a statistically significant variable in hip revisions, but not in knee revisions, however hypoalbuminemia, albumin and CRP values was statistically significant variable for risk of failure in both hips and knees. Despite this, the multivariate logistic regression analysis identified *hypoalbuminemia* (serum albumin < 3.5 g/dL) to be a significant independent risk factor for failure after single–stage revision for PJI (p = 0.02).

The most commonly used definition for malnutrition is a serum albumin level < 3.5 g/dL and a serum TLC < 1500 cells/mm^3 [6, 8]. However, although serum albumin concentrations and the TLC have been reported as valid and reliable markers of malnutrition, their cutoff levels and predictive values for PJI in patients undergoing total joint arthroplasty (TJA) remain questionable [8, 18, 19]. In our study the prevalence of altered albumin values or TLC was 55.2%. The prevalence of malnutrition, according to the definition provided above, was nevertheless 6.7%, with no statistical significance regarding the risk of failure after one-stage revision for PJI. Our results are similar to those reported by Morey et al. in their study of 3169 primary TKAs. These authors found that the prevalence of malnutrition as per the serum albumin level < 3.5 g/dL or serum TLC < 1500 cells/mm^3 was 21% and dropped to 1.6% when malnutrition was defined as serum albumin < 3.5 g/dL "and" TLC < 1500/mm^3, indicating an overlap between the two markers. The authors did not find an association between malnutrition and surgically-treated wound complications (OR 1.38; 95% CI 0.30–6.36; p = 0.676). In our study, TLC < 1500 cells/mm^3 did not achieve the expected statistical significance, and indeed these low levels were distributed equally between the two groups, with about half of the total patient sample exhibiting such concentrations [8]. Based on the findings of this study it can therefore be said that TLC is not a decisive predictor of failure after one-stage revision. Although this minor role of TLC has also been reported by other authors, TLC continues to be one of the mainstays in the evaluation and the definition of malnutrition [18, 19].

Conversely, as shown in the literature, albumin is a fundamental parameter that must be evaluated in the preoperative period. Blevins et al. showed that albumin alone is the predictive biomarker with the highest specificity (95% CI 97.8–98.4%), the highest positive predictive value (7.3%, 95% CI 4.4–11.8%) and the largest AUC (0.61, 95% CI 0.55–0.67) for PJI following primary TJA when compared to other markers like hemoglobin, white blood cells or platelets [10]. In a multivariate analysis, Ryan et al., found both hypoalbuminemia and the ASA score to be significant (p < 0.05) predictors of complications such as death, superficial infection, pneumonia, renal insufficiency, reintubation, transfusion, readmission, and reoperation after TJA. Furthermore, they found that hypoalbuminemia was a more robust risk factor to predict deep infections in THA patients,

Table 3 Description of general characteristics of the study participants. A sub-group analysis of the risk of failure of hip and knee patients separated

	Total hip arthroplasty			Total knee arthroplasty		
	Failure			Failure		
	NO, n = 49	YES, n = 41	p value	NO, n = 40	YES, n = 35	p value
Age (SD)	65.7 (9.6)	68.0 (10.3)	0.28	68.8 (10.1)	65.8 (11.9)	0.24
Gender			0.17			0.80
Male (%)	25 (51)	15 (36.6)		24 (60)	20 (57.1)	
Female (%)	24 (49)	26 (63.4)		16 (40)	15 (42.9)	
Body mass index (SD)	27.7 (5.7)	31.3 (6.1)	**0.006**	29.6 (5.3)	30.8 (5.6)	0.33
Obesity (BMI ≥ 30)			**0.008**			0.28
No (%)	35 (71.4)	16 (43.2)		21 (52.5)	14 (40.0)	
Yes (%)	14 (28.6)	21 (56.8)		19 (47.5)	21 (60.0)	
Diabetes mellitus			0.63			0.13
No (%)	38 (77.6)	30 (73.2)		38 (95.0)	30 (85.7)	
Yes (%)	11 (22.4)	11 (26.8)		2 (5.0)	5 (14.3)	
Lymphocytopenia			0.50			0.71
No (%)	25 (51)	18 (43.9)		20 (50)	19 (54.3)	
Yes (%)	24 (49)	23 (56.1)		20 (50)	16 (45.7)	
Hypoalbuminemia			**0.04**			**0.006**
No (%)	44 (89.8)	30 (73.2)		40 (100)	29 (82.9)	
Yes (%)	5 (10.2)	11 (26.8)		0 (0)	6 (17.1)	
Malnutrition			0.1			0.28
No (%)	46 (93.9)	34 (82.9)		40 (100)	34 (97.1)	
Yes (%)	3 (6.1)	7 (17.1)		0 (0)	1 (2.9)	
CRP value mg/L						
Mean (SD)	29.8 (35.5)	44.5 (41.4)	**0.03**	34.1 (50.9)	44.7 (44.0)	**0.04**
TLC (cells/mm^3)						
Mean (SD)	1.7 (0.7)	1.5 (0.5)	0.10	1.6 (0.6)	1.6 (0.6)	0.94
Albumin value g/L						
Mean (SD)	4.2 (0.5)	3.9 (0.5)	**0.04**	4.2 (3.9)	3.8 (5.3)	**0.04**
WBC count (cells/mL)						
Mean (SD)	7.9 (2.1)	8.1 (2.8)	0.84	8.0 (2.5)	7.8 (2.0)	0.63
Hemoglobin value g/L						
Mean (SD)	12.7 (1.9)	12.4 (1.7)	0.38	12.4 (1.9)	11.7 (1.4)	0.07
Glucose value mg/dL						
Mean (SD)	103.2 (35.1)	107.6 (38.7)	0.57	107.9 (31.8)	101.1 (24.4)	0.31

Bold indicated statistically significant differences

n number, % percentage, *SD* standard deviation, *CRP* c-reactive protein, *TLC* total lymphocyte count, *WBC* white blood cell, *mg* milligrams, *mm*^{3} cubic millimeter, *g* grams, *L* liters, *mL* milliliters, *dL* deciliters

as well as superficial infections in TKA patients, than the ASA score [5]. In their study of the National Surgical Quality Improvement Program database, Bohl et al. found that patients with hypoalbuminemia undergoing aseptic revision arthroplasty were twice as likely to develop subsequent PJI (4.5% versus 2.1%; relative risk [RR] 2.1, 95% CI 1.2–3.5, p = 0.005), and patients with hypoalbuminemia were over 3 times more likely to have a septic indication for revision than patients with normal albumin levels (42.8% versus 11.8%; RR 3.6, 95% CI 3.2–4.1, p < 0.001). However, these authors did not clarify if patients with hypoalbuminemia had a higher risk of reinfection after one-stage treatment of PJI [9]**.** Yuwen et al., conducted a meta-analysis where they also found that patients with an albumin level < 3.5 g/dL had an almost 2.5-times higher risk of developing orthopedic surgical site infections (2.96% versus 1.00%; RR 2.39, 95% CI 1.57–3.64, p < 0.0001) [20]. It seems that albumin values alone can indicate an inadequate nutritional status, which can compromise both primary arthroplasty and certainly revision surgery. In view of this, malnutrition could perhaps be equated with a low level of serum albumin [2, 6, 9]. The reason why malnutrition and hypoalbuminemia deserve attention is because they are associated with the risk of post-surgical complications, which translate into longer

Table 4 Risk factors related to failure after single–stage revision for periprosthetic joint infection. Multivariate analysis

Failure one-stage revision	OR	95% CI	p value
Age	0.98	0.95–1.02	0.47
Gender	1.53	0.77–3.05	0.22
BMI	1.10	0.96–1.16	0.23
Obesity (BMI ≥ 30)	1.50	0.51–4.39	0.46
Hypoalbumin (serum albumin < 3.5 g/dL)	5.64	1.26–25.18	**0.023**
Albumin value g/L	1.01	0.91–1.13	0.86
CRP mg/L	1.00	0.99–1.01	0.59

Bold indicated statistically significant differences

OR odds ratio, *CI* confidence interval, *%* percentage, *BMI* body mass index, *g* gram, *dL* deciliters, *mg* milligrams, *L* liter

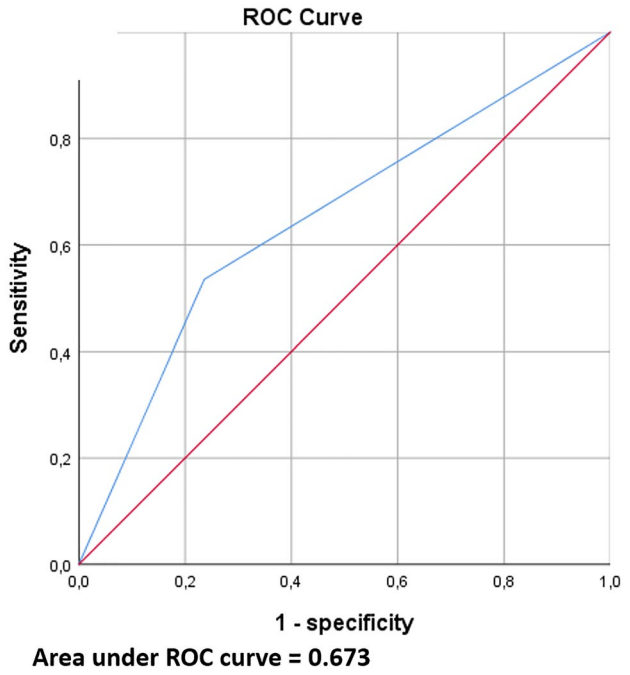

Fig. 1 Multivariate logistic regression model. The receiver operating characteristic (ROC) curve for the multivariate model exhibited a very good discriminatory power with an area under the curve (AUC) of 0.67 (95% CI 0.018–2.69), and a specificity of 82.02%

hospital stays, and the need for further hospitalizations [21]. Bala et al., estimated the cost of a patient suffering from malnutrition for the health system at approximately US$ 3,875 in the first 90 days following TJA ($p < 0.001$) [2]. As hypoalbuminemia seems to influence the failure rate, we think it is advisable to measure albumin levels in preoperative workups.

Currently, the most common definition of malnutrition in orthopaedics is serum TLC < 1500 cells/mm^3 and serum albumin concentration < 3.5 g/dL [4, 6, 7]. Although, nowadays the role of TLC in malnutrition definition has been questioned as in our study, and despite the role of hypoalbuminemia often coincides with a negative nutrient balance, the relationship between albumin and nutritional status is nowadays somewhat controversial. It is believed that, rather than reflecting undernutrition per se, hypoalbuminemia is more a reflection of the extent of physiological stress resulting from disease [22, 23]. We think that the meaning of malnutrition and the used of TCL and albumin as indicators for a malnutrition state should be evaluated in future studies. Finally, CRP is known to be an acute phase reactant, and a minor diagnostic marker for PJI (ICM—2018). At our hospital, CRP tests are performed routinely both preoperatively and during the follow-up period [24, 25]. The analysis of the two groups examined revealed statistically significant CRP values ($p = 0.018$) which, in our opinion, indicates that, in addition to a diagnostic marker, CRP ought to be considered a predictive criterion. Recent studies have recently linked albumin with CRP values, demonstrating how the CRP/albumin ratio (CAR) can be considered a valid and economical predictor of periarticular infection [24, 26]. The validity of CAR, however, is rather contradictory. Fury et al. found that a high preoperative CAR was associated with an increased risk of reinfection and 30- and 60-day readmissions ($p < 0.01$) [24]. Hong et al., in a retrospective study of two-stage PJI revision, did not find that CAR was an applicable value ($p = 0.766$) [27]. Given these contradictions, we think that CAR should be the subject of more detailed analysis in future studies.

This study is not without limitations. Firstly, one should mention the limitations inherent in a retrospective cohort design. It must be said, however, that other studies dealing with malnutrition and serum values have used a similar approach. Second, only serum albumin and TLC levels were used as serological markers. Other commonly used laboratory parameters with shorter half-lives such as serum transferrin, pre-albumin, and the retinol-binding protein were not included, as their determination was not feasible in our patients. The literature, nevertheless, supports our selection as serum albumin levels and TLC are consistently used in previous studies on the subject.

Conclusion

TLC, hemoglobin; WBC count; glucose levels; and malnutrition, understood as the combination of albumin and total lymphocyte count, were not found to be statically significant risk factors for failure after single–stage revision for PJI. However, albumin < 3.5 g/dL, alone was a statically significant risk factor for failure after single-stage revision for PJI. As hypoalbuminemia seems to influence the failure

rate, it is advisable to measure albumin levels in preoperative workups.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Giacomo Traverso, Jorge H. Nuñez, Thorsten Gehrke and Mustafa Citak declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval This material is the authors' own original work, which has not been previously published elsewhere. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Informed consent Not applicable according to the nature of the retrospective study with use of non-identifiable data and according to the ethical approval waived by the local Ethics Committee. Informed consent was obtained from all individual participants for whom identifying information is included in this article.

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