JB&JS OPEN ACCESS

Shoulder Periprosthetic Joint Infection and All-Cause Mortality: A Worrisome Association

Daniel C. Austin, MD, MS, Sarah H. Townsley, MD, Thomas H. Rogers, MD, Jonathan D. Barlow, MD, Mark E. Morrey, MD, MS, John W. Sperling, MD, MBA, and Joaquin Sanchez-Sotelo, MD, PhD

Investigation performed at the Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota

Background: Periprosthetic joint infection (PJI) can be a devastating complication following shoulder arthroplasty. PJI following hip and knee arthroplasties has been found to increase mortality. However, anatomical and bacteriologic differences could potentially result in a different trend after shoulder arthroplasties. Thus, the purpose of the present study was to determine whether there is an association between shoulder PJI and all-cause mortality.

Methods: Our institutional Total Joint Registry Database was queried to identify patients who underwent revision shoulder arthroplasty procedures between 2000 and 2018. A total of 1,160 procedures were then classified as either septic (21.8%) or aseptic (78.2%). Septic revisions were further subdivided into (1) debridement, antibiotics, irrigation, and implant retention (9.1%); (2) 2-stage reimplantation for deep infection (61.3%); (3) implant resection without reimplantation (3.6%); and (4) unexpected positive cultures at revision surgery (26.1%). The most common bacterium isolated was *Cutibacterium acnes* (64.4%). All-cause patient mortality was determined with use of our registry and confirmed with use of a nationwide mortality database. All-cause crude and adjusted mortality rates were then compared between groups.

Results: The 1-year crude mortality rate was 1.8% (95% confidence interval [CI], 0.9% to 2.6%) for the aseptic group and 2.8% (95% CI, 0.7% to 4.8%) for the septic group (p = 0.31). Multivariate Cox regression analysis demonstrated an elevated but statistically similar adjusted hazard ratio for 1-year all-cause mortality of 1.9 (95% CI, 0.8 to 4.6) when comparing the septic to the aseptic group (p = 0.17). The risk of 2-year all-cause mortality was significantly higher in the septic group, with a hazard ratio of 2.2 (95% CI, 1.1 to 4.5; p = 0.029). In univariate analyses, increased 5-year mortality in the septic revision group was associated with age, Charlson Comorbidity Index, and methicillin-resistant *Staphylococcus aureus* infection, whereas *C. acnes* infection was associated with lower mortality.

Conclusions: Shoulder PJI is associated with an adjusted 2-year all-cause mortality rate that is double that of aseptic patients. The results of the present study should be utilized to appropriately counsel patients who are considered to be at risk for infection following shoulder arthroplasty.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

The utilization of primary shoulder arthroplasty in the United States has increased dramatically over the last 2 decades and is projected to continue rising[1-3]. The incidence of shoulder periprosthetic joint infection (PJI) can be anticipated to rise accordingly[4], as this complication is observed in approximately 1% of patients[4-7]. Shoulder PJI has been associated with a number of factors including male sex, younger age, and reverse total shoulder arthroplasty[4,5,7,8], although the impact of medical comorbidities remains controversial[4-9]. The economic costs associated with 2-stage reimplantation for shoulder PJI are substantial[4,10], not to mention the considerable impact on the quality of life of patients.

The typical 2-stage reimplantation treatment algorithm for shoulder PJI requires 2 revision arthroplasty procedures and long-term intravenous antibiotics[10]. Although the short-term mortality rate following primary total shoulder arthroplasty has been reported to range between 0.16% and 1.5% at 90 days[11-13] and up to 3.8% at 1 year[12,13], rates as high as 3% have been reported at 90 days following revision shoulder arthroplasty in older patients[14]. Factors associated with mortality have included male sex and increased age[15], but the direct impact of shoulder PJI on mortality is unknown.

The lower-extremity arthroplasty literature provides strong evidence that hip and knee PJI are associated with a

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A357).

JBJS Open Access • 2022:e21.00118. openaccess.jbjs.org

1.8 to 5-fold increase in the odds of 1-year mortality[16,17]. However, this relationship has not been studied for shoulder PJI, in which anatomic and bacteriologic[5,7,16] differences may translate into different mortality rates. The purpose of the present study was to compare all-cause mortality rates between patients who underwent a surgical procedure for shoulder PJI and those who underwent a revision for aseptic failure. Further, for patients with a shoulder PJI, we sought to determine patient and infection characteristics associated with mortality. We hypothesized that PJI would increase mortality in patients undergoing revision shoulder arthroplasty.

Materials and Methods

Patient Cohort

All revision shoulder arthroplasty procedures completed between 2000 and 2018 within a multi-hospital single academic health system were retrospectively identified from our prospectively collected Total Joint Registry Database, yielding a total of 1,177 procedures. Patients were excluded if their arthroplasty was part of an oncologic reconstruction (11 patients), they had an antibiotic spacer for >1 year prior to reimplantation (5 patients), or records from referring hospitals were not available to classify them (1 patient). During this time period, 6,716 primary shoulder arthroplasty procedures were

TABLE I Comparison of Baseline Characteristics Between Cohorts

Charateristics	Septic (N = 253)	Aseptic (N = 907)	Total (N = 1,160)	P Value
Age at surgery *(yr)*				
Mean (std. dev.)	62.4 (11.4)	66.8 (11.2)	65.8 (11.4)	<0.001†
Median	63	68	67	
Interquartile range	56, 71	60, 75	59, 74	
Range	28-85	29-92	28-92	
Sex*				
Female	82 (32.4%)	514 (56.7%)	596 (51.4%)	<0.001‡
Male	171 (67.6%)	393 (43.3%)	564 (48.6%)	
Body mass index *(kg/m^2)*				
Mean (std. dev.)	30.4 (6.2)	31.0 (7.3)	30.9 (7.1)	0.287§
Median	29.9	29.7	29.7	
Interquartile range	26.1, 33.7	26.2, 34.8	26.2, 34.6	
Range	16.9-54.6	14.7-65.8	14.7-65.8	
Smoking status*				
Ever	106 (41.9%)	371 (40.9%)	477 (41.1%)	0.942‡
Never	79 (31.2%)	293 (32.3%)	372 (32.1%)	
Unknown	68 (26.9%)	243 (26.8%)	311 (26.8%)	
Charlson Comorbidity Index (severity- and age-weighted sum)				
Mean (std. dev.)	3.4 (2.7)	4.0 (2.9)	3.9 (2.8)	<0.001#
Median	3	3	3	
Interquartile range	2, 4	2, 5	2, 5	
Range	0-16	0-19	0-19	
ASA score				
Mean (std. dev.)	2.4 (0.6)	2.4 (0.5)	2.4 (0.5)	0.200‡
Median	2	2	2	
Interquartile range	2, 3	2, 3	2, 3	
Range	1-4	1-4	1-4	
Surgical treatment*				
2-stage exchange	155 (61.3%)	—	155 (61.3%)	—
DAIR	23 (9.1%)	—	23 (9.1%)	
Unexpected positive	66 (26.1%)	—	66 (26.1%)	
Resection	9 (3.6%)	—	9 (3.6%)	

*Values are given as the count with the percentage in parentheses. †Two-sample t test assuming equal variances. ‡Chi-square test. §Two-sample t test assuming equal variances conducted on log transformation. #Wilcoxon rank-sum test.

completed at our institution, highlighting that revision arthroplasty accounts for 17% of procedures within our system. All living patients had at least 2 years of postoperative follow-up, with follow-up periods of <2 years representing deaths (average follow-up, 4.4 years; range, 3 days to 5 years). Aseptic revision procedures included all surgeries that involved exchange or replacement of any prosthetic component, without suspicion or postoperative treatment for infection.

A procedure was classified as septic if the patient was presumed to have a PJI on the basis of preoperative or intraoperative findings and was treated with antibiotics for a PJI postoperatively by the orthopaedic surgeon and consulting infectious disease specialist. Septic procedures were further grouped as (1) debridement, antibiotics, irrigation, and implant retention (DAIR); (2) 2-stage explant and delayed reimplantation with a temporary antibiotic spacer; (3) implant resection without reimplantation; or (4) unexpected positive cultures at revision surgery. Patients initially treated with DAIR but then treated with a 2-stage explantation procedure within the following year were classified as having a 2-stage revision. Additionally, patients in the unexpected positive cultures group were only included in the septic cohort if they were treated postoperatively for suspected deep infection with long-term antibiotics by our infectious disease physicians. Patients who underwent multiple revisions within the 19-year collection window were grouped into either the aseptic or septic cohort according to the classification of their first revision within the period.

Altogether, a total of 1,160 revision shoulder arthroplasty procedures were included within the analysis, with 907 (78.2%) of those being classified as aseptic and 253 (21.8%) as septic (Table I). Of those in the septic group, 155 (61.3%) underwent a 2-stage exchange, 66 (26.1%) had unexpected positive cultures, 23 (9.1%) were treated with DAIR, and 9 (3.6%) had an implant resection. In the septic cohort, 85.4% of patients were found to have at least 1 positive culture. *Cutibacterium acnes* was the most common bacterium and was observed in 64.4% of infected shoulders, whereas coagulase-negative staphylococci were the second most common bacteria and were cultured in 23.6% of infections (Table II). Polymicrobial infections constituting more than 1 bacterium other than *C. acnes* were rare (n = 12, 5.6%).

TABLE II Culture Data from the Septic Cohort*

Any bacteria (n = 253)	
Any recorded	216 (85.4%)
None recorded	37 (14.6%)
C. acnes (n = 216)	
Yes	139 (64.4%)
No	77 (35.6%)
Coagulase-negative Staphylococcus (n = 216)	
Yes	51 (23.6%)
No	165 (76.4%)
MSSA (n = 216)	
Yes	13 (6.0%)
No	203 (94.0%)
MRSA (n = 216)	
Yes	11 (5.1%)
No	205 (94.9%)
Gram-negative bacteria (n = 216)	
Yes	12 (5.6%)
No	204 (94.4%)
Streptococcus (n = 216)	
Yes	7 (3.2%)
No	209 (96.8%)
Other bacteria (n = 216)	
Yes	19 (8.8%)
No	197 (91.2%)
C. acnes only (n = 216)	
Yes	114 (52.8%)
No	102 (47.2%)
Polymicrobial (n = 216)	
Yes	12 (5.6%)
No	204 (94.4%)

*Values are given as the count with or without the percentage in parentheses.

Mortality

Patient survival and all-cause mortality events were captured through routine contacts by the registry, and confirmed when needed with use of a nationwide mortality database (Accurint by LexisNexis). When utilizing the nationwide database, a 6-month lag period was included in order to ensure that all deaths were given an appropriate interlude to be recorded accurately, similar to the methodology in previous studies[16]. Time-to-death calculations were performed according to the first revision surgery for patients in the aseptic, DAIR, resection, and unexpected culture groups. For patients in the 2-stage septic group, the date of reimplantation was utilized as the start of their timeline, as this was the point at which they were routinely captured by our Total Joint Registry Database. Utilization of the explantation date as the start of the mortality timeline in 2-stage patients was avoided because it could lead to an immortal time bias whereby patients were inaccurately attributed extra survival time prior to enrollment, since by definition all subjects must have survived that time period in order to be captured by the registry[18]. Baseline patient demographics, severity- and age-weighted Charlson Comorbidity Index, and infection characteristics were extracted from our registry and by chart review.

Statistical Analysis

Kaplan-Meier analyses were utilized to compare overall survivorship between groups of interest with up to 5 years of follow-up and to report mortality rates at 90 days, 1 year, 2 years, and 5

years post-revision. The log-rank test was utilized to determine if observed crude mortality rates were significantly different between cohorts within these analyses. In order to understand the independent association of shoulder PJI with mortality, Cox logistic regression was utilized in order to build multivariable models adjusted for age, sex, body mass index, smoking, American Society of Anesthesiologists (ASA) score, and severity- and age-weighted Charlson Comorbidity Index when possible, with the number of adjusters dependent on the number of mortality events within the period of interest. Finally, possible associations between patient and infection characteristics with mortality following shoulder PJI were assessed with use of univariate Cox regression with variables of interest. In all analyses, significance was set at 0.05. All statistical analyses were performed with use of SAS (version 9.4M6; SAS Institute) and R (version 3.6.2; R Foundation for Statistical Computing).

Source of Funding
No external funding was utilized for this project.

Results

The baseline patient demographics were significantly different between the cohorts (Table I). The septic cohort had a significantly lower mean age at the time of surgery (62 years) and a significantly greater proportion of male patients (68%) compared with the aseptic cohort (67 years and 43%; $p < 0.001$ for both comparisons). The severity- and age-weighted Charlson Comorbidity Index was significantly lower in the septic group. The ASA score, body mass index, and smoking status did not differ significantly between the cohorts.

A total of 26 of 253 patients in the septic cohort and 92 of 907 patients in the aseptic cohort had died at the time of the latest follow-up. Kaplan-Meier curves produced an estimated 1-year mortality rate of 2.8% (95% confidence interval [CI], 0.7% to 4.8%) in the septic cohort and 1.8% (95% CI, 0.9% to 2.6%) in the aseptic cohort; these crude rates were not significantly different ($p = 0.31$) (Table III, Fig. 1). The log-rank test did not demonstrate any significant differences between the unadjusted crude mortality rates of the groups at any point.

Multivariate Cox regression analysis demonstrated an elevated but statistically similar adjusted hazard ratio (HR) for 1-year all-cause mortality of 1.89 (95% CI, 0.77 to 4.62) for the septic compared with the aseptic cohort ($p = 0.17$) (Table IV). The 2-year risk of all-cause mortality was significantly higher in the septic group, with an HR of 2.21 (95% CI, 1.09 to 4.47; $p = 0.029$). At 5 years, the risk of all-cause mortality remained higher in the septic group (HR, 1.47; 95% CI, 0.93 to 2.32), although this trend did not reach significance ($p = 0.10$). When eliminating patients with unexpected positive cultures from the analysis, the overall results were similar except that all-cause mortality remained significantly higher in the septic group at 5 years.

In the septic cohort, univariate Cox regression analysis did not find any associations between all-cause mortality at 1, 2, or 5 years and sex, body mass index, or Gram-negative infection (see Appendix 1). As expected, patient age was associated with mortality at 2 and 5 years, whereas the Charlson Comorbidity Index were associated with increased mortality at all time intervals. Notably, infections with *C. acnes* only were associated with a significantly lower risk of mortality at 2 years (HR, 0.11; 95% CI, 0.01 to 0.83; $p = 0.033$) and at 5 years (HR, 0.29; 95% CI, 0.11 to 0.77; $p = 0.012$) (Table V). A methicillin-resistant *Staphylococcus aureus* (MRSA) infection was associated with a significantly increased risk of mortality at all time points (HR, 9.62; 95% CI, 1.87 to 49.6; $p = 0.007$ at 1 year). There was a trend toward a higher 2-year mortality rate in patients with polymicrobial infection, although this did not reach significance ($p = 0.076$). Mortality rates differed between procedure types in the septic group and were highest among patients who underwent resection (Fig. 2).

Discussion

As the number of shoulder arthroplasty procedures continues to grow[1-3], it is important to understand the potential adverse effect of shoulder PJI because the prevalence

TABLE III Estimated Crude Mortality Rates in Groups of Interest

	N		Kaplan-Meier Mortality Rates* *(%)*			
	Total	Events	90 Days	1 Year	2 Years	5 Years
All septic	253	26	0.8 (0.0-1.9)	2.8 (0.7-4.8)	4.7 (2.1-7.3)	11.5 (7.2-15.6)
Two-stage/DAIR/resection	187	23	1.1 (0.0-2.5)	3.2 (0.6-5.7)	5.3 (2.1-8.5)	13.7 (8.3-18.9)
Two-stage	155	16	0.6 (0.0-1.9)	1.9 (0.0-4.1)	3.2 (0.4-6.0)	11.8 (6.1-17.2)
DAIR	23	3	0.0 (0.0-0.0)	4.3 (0.0-12.3)	8.7 (0.0-19.5)	14.1 (0.0-27.7)
Unexpected cultures	66	3	0.0 (0.0-0.0)	1.5 (0.0-4.4)	3.0 (0.0-7.1)	5.0 (0.0-10.4)
Resection	9	4	11.1 (0.0-29.4)	22.2 (0.0-45.1)	33.3 (0.0-58.0)	44.4 (0.3-69.0)
C. acnes only	114	5	0.0 (0.0-0.0)	0.9 (0.0-2.6)	0.9 (0.0-2.6)	5.6 (0.6-10.3)
Aseptic	907	92	0.3 (0.0-0.7)	1.8 (0.9-2.6)	2.9 (1.8-3.9)	11.4 (9.1-13.6)

*Values are given as the estimated mortality rate with the 95% CI in parentheses.

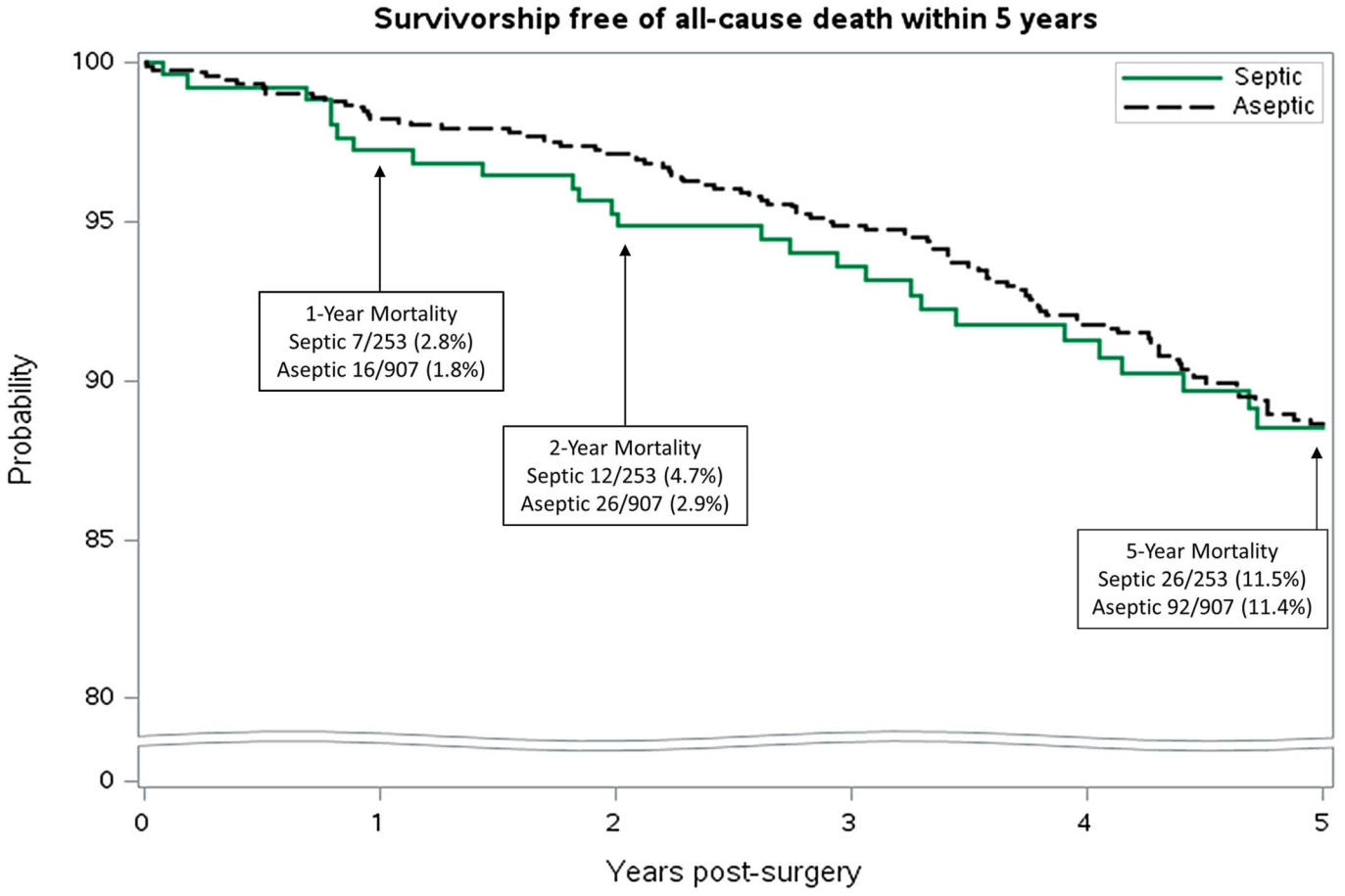

Fig. 1

Kaplan-Meier 5-year survivorship curves for the septic and aseptic cohorts. These unadjusted rates demonstrate the trend toward increased all-cause mortality in the septic cohort, although the crude rates were statistically similar ($p > 0.05$).

of this complication will certainly increase accordingly[4]. The results of the present study indicate that, after adjusting for baseline differences between cohorts, patients undergoing revision arthroplasty for shoulder PJI are more than twice as likely to die within 2 years of surgery compared with those undergoing an aseptic revision. These findings confirm our hypothesis that shoulder PJI is associated with increased mortality risk. Further, not all shoulder PJIs have an equal impact on

TABLE IV Multivariate Cox Regression Results Comparing Adjusted Mortality Rates Between the Septic and Aseptic Cohorts

	Death Within 1 Year			Death Within 2 Years			Death Within 5 Years		
	Events	Adjusted HR (95% CI)*	P Value	Events	Adjusted HR (95% CI)†	P Value	Events	Adjusted HR (95% CI)‡	P Value
Septic versus aseptic									
Septic (n = 353)	7	1.89 (0.77-4.62)	0.166	12	2.21 (1.09-4.47)	0.029	26	1.47 (0.93-2.32)	0.101
Aseptic (n = 907)	16	—	—	26	—	—	92	—	—
Surgical treatment									
Two-stage/DAIR/resection (n = 187)	6	2.10 (0.82-5.39)	0.123	10	2.34 (1.10-4.99)	0.027	23	1.74 (1.08-2.81)	0.023
Aseptic (n = 907)	16	—	—	26	—	—	92	—	—

*Adjusted for age, sex, body mass index, smoking, ASA score, and severity- and age-weighted Charlson Comorbidity Index. †Adjusted for age, ASA score, and severity/age-weighted Charlson Comorbidity Index. ‡Adjusted for severity- and age-weighted Charlson Comorbidity Index.

JBJS Open Access • 2022:e21.00118. **openaccess.jbjs.org**

TABLE V Univariate Cox-Regression Analyses Evaluating Associations with Mortality in the Septic Cohort

	Death Within 1 Year			Death Within 2 Years			Death Within 5 Years		
	Events	HR (95% CI)	P Value	Events	HR (95% CI)	P Value	Events	HR (95% CI)	P Value
Age (n = 253)	7	1.09 (1.00-1.18)	0.052	12	1.08 (1.02-1.15)	0.012	26	1.08 (1.04-1.13)	<0.001
Sex									
Female (n = 82)	2	0.82 (0.16-4.25)	0.818	4	1.04 (0.31-3.44)	0.953	9	1.09 (0.49-2.45)	0.834
Male (n = 171) (ref)	5	—	—	8	—	—	17	—	—
Body mass index (n = 253)	7	0.95 (0.83-1.09)	0.467	12	1.04 (0.95-1.13)	0.398	26	1.00 (0.94-1.06)	0.916
Smoking status									
Ever (n = 106)	2	1.51 (0.14-16.6)	0.738	4	1.00 (0.22-4.46)	0.998	13	1.88 (0.67-5.27)	0.231
Unknown (n = 68)	4	4.71 (0.53-42.1)	0.166	5	1.98 (0.47-8.29)	0.349	8	1.64 (0.54-5.04)	0.384
Never (ref)	1	—	—	3	—	—	5	—	—
Diabetes									
Present (n = 44)	0	—	—	1	0.42 (0.05-3.26)	0.407	4	0.84 (0.29-2.43)	0.746
Absent (n = 209) (ref)	7	—	—	11	—	—	22	—	—
Charlson	7	1.30 (1.10-1.54)	0.002	12	1.31 (1.14-1.51)	<0.001	26	1.27 (1.14-1.41)	<0.001
ASA score									
1-2 (n = 150)	2	0.23 (0.04-1.16)	0.075	3	0.18 (0.05-0.68)	0.011	9	0.27 (0.12-0.60)	0.001
3-4 (n = 86) (ref)	5	—	—	9	—	—	17	—	—
C. acnes only									
Yes (n = 114)	1	0.2 (0.02-1.66)	0.136	1	0.11 (0.01-0.83)	0.033	5	0.29 (0.11-0.77)	0.012
No (n = 102) (ref)	6	—	—	11	—	—	21	—	—
MRSA									
Any (n = 11)	2	9.62 (1.87-49.6)	0.007	1	8.46 (2.29-31.3)	0.001	4	4.69 (1.61-13.6)	0.005
None (n =205) (ref)	5	—	—	11	—	—	22	—	—
MSSA									
Yes (n = 13)	0	—	—	1	1.69 (0.22-13.1)	0.617	2	1.54 (0.36-6.53)	0.556
None (n =203) (ref)	7	—	—	11	—	—	24	—	—
Coagulase-negative *staphylococcus*									
Yes (n = 51)	2	1.62 (0.31-8.34)	0.565	3	1.34 (0.36-4.95)	0.661	7	1.44 (0.61-3.44)	0.406
None (n =165) (ref)	5	—	—	9	—	—	19	—	—
Streptococcus									
Yes (n = 7)	1	5.79 (0.70-48.1)	0.104	1	3.33 (0.43-25.8)	0.249	1	1.39 (0.19-10.3)	0.746
None (n = 209) (ref)	6	—	—	11	—	—	25	—	—
Gram-negative bacteria									
Yes (n = 12)	0	—	—	1	1.80 (0.23, 13.9)	0.574	1	0.78 (0.11, 5.72)	0.803
None (n = 241) (ref)	7	—	—	11	—	—	25	—	—
Polymicrobial									
Yes (n = 12)	0	—	—	2	3.96 (0.87, 18.1)	0.076	2	1.85 (0.44, 7.83)	0.404
None (n = 241) (ref)	7	—	—	10	—	—	24	—	—
Surgical treatment									
DAIR (n = 23)	1	2.22 (0.23-21.4)	0.489	2	2.75 (0.53-14.1)	0.228	3	1.30 (0.38-4.46)	0.677
Unexpected positive (n = 66)	1	0.78 (0.08-7.46)	0.826	2	0.93 (0.18-4.81)	0.933	3	0.43 (0.13, 1.48)	0.182
Resection (n = 9)	2	12.8 (2.14-76.7)	0.005	3	12.4 (2.96-52.0)	<0.001	4	5.33 (1.78-16.0)	0.003
Two-stage exchange (n = 155) (ref)	3	—	—	5	—	—	16	—	—
Treatment subgroup									
Two-stage, DAIR, resection (n = 187)	6	2.14 (0.26-17.8)	0.4801	10	1.80 (0.39-8.20)	0.4498	23	2.80 (0.84-9.32)	0.094
Unexpected positive (n = 66) (ref)	1	—	—	2	—	—	3	—	—

JBJS Open Access • 2022:e21.00118.

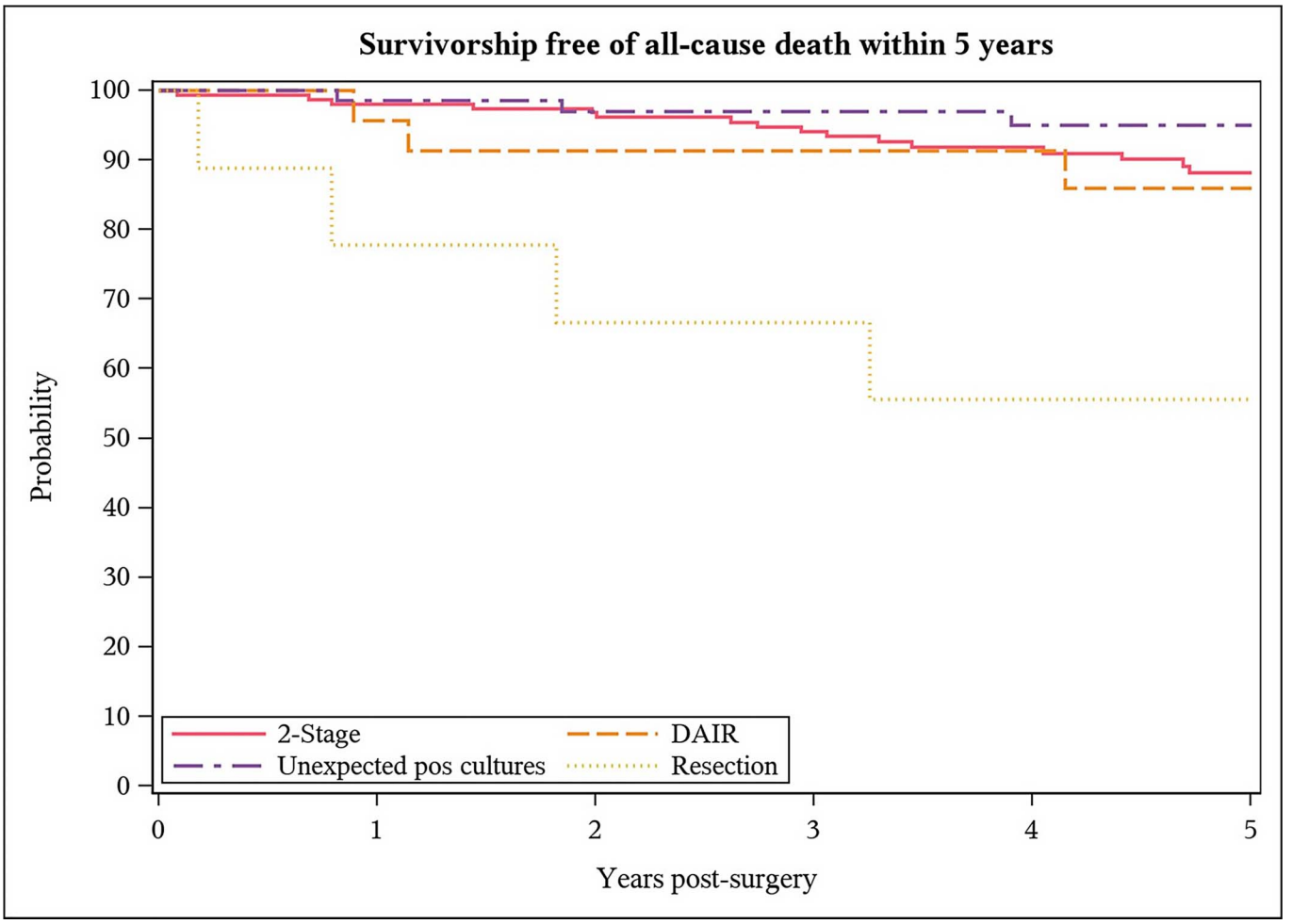

Fig. 2

Kaplan-Meier 5-year survivorship curves for procedure types in the septic cohort, demonstrating the differing mortality trends.

patients, as MRSA infections were associated with a mortality risk that was 9.6 times greater than that for other infections, and isolated *C. acnes* infections were associated with a mortality risk that was 0.1 times that for other organisms.

The lower-extremity arthroplasty literature has previously shown significantly higher mortality rates among patient with hip and knee PJI[16,17]. An institutional registry study observed an adjusted odds ratio for 1-year mortality of 5.9 in patients undergoing septic versus aseptic revision lower-extremity arthroplasty. Additionally, a study from the Danish Joint Registry observed an adjusted odds ratio for mortality of 1.87 in patients undergoing revision total hip arthroplasty for PJI[17]. We chose to utilize Cox regression and hazard ratios in our study in order to better evaluate the changes in mortality rate over time[19], making it impossible to directly compare the magnitudes of effects between studies. However, the results of the present study agree with the overall trend that PJI is associated with increased all-cause mortality.

The previous 2 studies from the lower-extremity arthroplasty literature demonstrated significantly increased mortality rates in the septic cohorts within 1 year of revision surgery, whereas the present study showed no significant difference until 2 years postoperatively. It is impossible to know if this discrepancy represents a true underlying difference between lower and upper-extremity PJI because the discrepancy could be explained by the smaller sample sizes of the present cohorts and the overall scarcity of mortality events, and because there was a nonsignificant but elevated rate of 1-year all-cause mortality in the septic cohort (HR, 1.89; 95% CI, 0.77 to 4.62; p = 0.17). However, 1 prior study found that the elevated mortality rates in the septic cohort were limited to the first postoperative year and disappeared beyond that time frame[16], whereas our observations became stronger between 1 and 2 years. These differences could be a result of the different analytic methods utilized in the present study or could highlight that shoulder PJI carries an increased risk of mortality that is smaller in magnitude but more extended in duration.

Interestingly, the previously observed 1-year mortality rates for aseptic revision total hip arthroplasty (5%; 95% CI, 4% to 6%) and septic revision total hip arthroplasty (8%; 95% CI, 6% to 11%)[17] were substantially higher than those observed at 1 year in the present study (septic cohort: 2.8%; 95% CI, 0.7% to 4.8%; aseptic cohort: 1.8%; 95% CI, 0.9% to 2.6%). This difference highlights the greater toll associated with

revision total hip arthroplasty, which is likely a result of the larger magnitude of the revision procedure; notably, the prior study highlighted that even patients undergoing aseptic revision total hip arthroplasty had higher 1-year mortality than those who did not require revision[17]. In contrast, the present study showed revision shoulder arthroplasty mortality rates that were similar to the previously reported 1-year mortality rates of 2% to 3.8% following primary shoulder arthroplasty[12,13]. Notably, the previously reported 5-year mortality rate following lower-extremity revision arthroplasty for PJI (26.1%) was substantially higher than that observed in our shoulder PJI cohort (11.5%)[16], suggesting that lower-extremity PJI may have an overall greater impact on mortality.

In the present study, patients with an MRSA infection had a substantially elevated risk of mortality (HR, 9.62). This elevated risk may be a result of the increased renal failure, hemodynamic instability, and mortality associated with MRSA versus methicillin-susceptible *S. aureus* (MSSA) bacteremia in critically ill patients[20]. In contrast, a prior study did not find a higher risk of mortality with *S. aureus,* although these authors did not separate patients into MSSA and MRSA subgroups[17]. Zmistowski et al. also did not find increased mortality rates with MRSA, but instead found polymicrobial infections to be associated with mortality[16]. In the present study, polymicrobial infections constituting multiple flora other than *C. acnes* were rare (5.6%, n = 12) but also trended toward an increased 2-year mortality rate (HR, 3.96; p = 0.076). The present results were notable for the dramatically lower mortality rates in patients with isolated *C. acnes* infections, an organism less prevalent in previous lower-extremity studies and thus not specifically analyzed previously. The unique flora in and contribution of *C. acnes* to shoulder PJI have long been known[5,7,16], but these results provide additional evidence that *C. acnes* represents a fundamentally different infection. Although shoulder PJI secondary to *C. acnes* can certainly cause pain and morbidity associated with implant failure, it does not appear to bring with it the increased mortality risk seen with other infections. Increased age and comorbidity scores were both associated with increased mortality following shoulder PJI, consistent with previous literature reporting similar associations with mortality following primary shoulder arthroplasty[12,15,21].

The strengths of the present study include the use of all revision shoulder arthroplasty procedures of interest over a 19-year period, giving us the scale necessary to evaluate mortality. However, even with this large scope, our analyses were limited by the rare nature of death following revision shoulder arthroplasty in general. We did not complete a formal power analysis because we planned to use all available patients, and it is possible that aspects of the analysis could be underpowered. This underpowering could have impacted several analyses, such as 1-year mortality, for which the number of deaths was still relatively low, making it possible to accept the null hypothesis inappropriately. Additional limitations of this study include defining patients in the septic group according to how they were treated by the infectious disease and orthopaedic surgery teams at the time, instead of by utilizing a formally defined criterion. Although the Musculoskeletal Infection Society[22] framework has proved important for lower-extremity infections, these criteria do not apply to the unique characteristics and flora of shoulder PJI and are not routinely utilized there. Instead, we ultimately relied on the decision-making of the teams treating the patients at the time of surgery to group them into the septic and aseptic cohorts. If anything, the inclusion of some patients in the septic cohort who were not truly infected would underestimate the impact of shoulder PJI on mortality. An additional limitation was our inability to complete subgroup analyses of patients on the basis of the type of implant they had prior to revision, as implant type can affect the relative invasiveness of the revision procedure. Additionally, our 2 cohorts did have baseline differences, and although we worked to adjust for these with regression analysis, a study methodology relying on matching patients would have minimized this discrepancy. A final limitation is the retrospective nature of the study, which could have led to unanticipated selection bias.

Conclusions

Shoulder PJI was associated with an increased adjusted 2-year all-cause mortality rate, which was particularly magnified in patients with MRSA infections. This information can be helpful for counseling patients considered at risk for infection and when discussing the prognosis with patients with a shoulder PJI. Additional studies are needed to further understand the mechanisms associated with increased mortality and shoulder PJI so that new interventions can be developed to mitigate this risk.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A358). ■

Daniel C. Austin, MD, MS[1]
Sarah H. Townsley, MD[1]
Thomas H. Rogers, MD[1]
Jonathan D. Barlow, MD[1]
Mark E. Morrey, MD, MS[1]
John W. Sperling, MD, MBA[1]
Joaquin Sanchez-Sotelo, MD, PhD[1]

[1]Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota

Email for corresponding author: Sanchezsotelo.joaquin@mayo.edu

References

1. Wagner ER, Farley KX, Higgins I, Wilson JM, Daly CA, Gottschalk MB. The incidence of shoulder arthroplasty: rise and future projections compared with hip and knee arthroplasty. J Shoulder Elbow Surg. 2020 Dec;29(12):2601-9.

2. Best MJ, Aziz KT, Wilckens JH, McFarland EG, Srikumaran U. Increasing incidence of primary reverse and anatomic total shoulder arthroplasty in the United States. J Shoulder Elbow Surg. 2021 May;30(5):1159-66.

3. Day JS, Lau E, Ong KL, Williams GR, Ramsey ML, Kurtz SM. Prevalence and projections of total shoulder and elbow arthroplasty in the United States to 2015. J Shoulder Elbow Surg. 2010 Dec;19(8):1115-20.

4. Padegimas EM, Maltenfort M, Ramsey ML, Williams GR, Parvizi J, Namdari S. Periprosthetic shoulder infection in the United States: incidence and economic burden. J Shoulder Elbow Surg. 2015 May;24(5):741-6.

5. Richards J, Inacio MC, Beckett M, Navarro RA, Singh A, Dillon MT, Sodl JF, Yian EH. Patient and procedure-specific risk factors for deep infection after primary shoulder arthroplasty. Clin Orthop Relat Res. 2014 Sep;472(9):2809-15.

6. Bohsali KI, Wirth MA, Rockwood CA Jr. Complications of total shoulder arthroplasty. J Bone Joint Surg Am. 2006 Oct;88(10):2279-92.

7. Singh JA, Sperling JW, Schleck C, Harmsen WS, Cofield RH. Periprosthetic infections after total shoulder arthroplasty: a 33-year perspective. J Shoulder Elbow Surg. 2012 Nov;21(11):1534-41.

8. Morris BJ, O'Connor DP, Torres D, Elkousy HA, Gartsman GM, Edwards TB. Risk factors for periprosthetic infection after reverse shoulder arthroplasty. J Shoulder Elbow Surg. 2015 Feb;24(2):161-6.

9. Wagner ER, Houdek MT, Schleck C, Harmsen WS, Sanchez-Sotelo J, Cofield R, Sperling JW, Elhassan BT. Increasing Body Mass Index Is Associated with Worse Outcomes After Shoulder Arthroplasty. J Bone Joint Surg Am. 2017 Jun 7;99(11):929-37.

10. Baghdadi YMK, Maradit-Kremers H, Dennison T, Ransom JE, Sperling JW, Cofield RH, Sánchez-Sotelo J. The hospital cost of two-stage reimplantation for deep infection after shoulder arthroplasty. JSES Open Access. 2017 Apr 19;1(1):15-8.

11. White CB, Sperling JW, Cofield RH, Rowland CM. Ninety-day mortality after shoulder arthroplasty. J Arthroplasty. 2003 Oct;18(7):886-8.

12. Dacombe P, Harries L, McCann P, Crowther M, Packham I, Sarangi P, Whitehouse MR. Predictors of mortality following shoulder arthroplasty. J Orthop. 2020 May 4;22:179-83.

13. Amundsen A, Rasmussen JV, Olsen BS, Brorson S. Mortality after shoulder arthroplasty: 30-day, 90-day, and 1-year mortality after shoulder replacement—5853 primary operations reported to the Danish Shoulder Arthroplasty Registry. J Shoulder Elbow Surg. 2016 May;25(5):756-62.

14. Alentorn-Geli E, Clark NJ, Assenmacher AT, Samuelsen BT, Sánchez-Sotelo J, Cofield RH, Sperling JW. What Are the Complications, Survival, and Outcomes After Revision to Reverse Shoulder Arthroplasty in Patients Older Than 80 Years? Clin Orthop Relat Res. 2017 Nov;475(11):2744-51.

15. Li X, Veltre DR, Cusano A, Yi P, Sing D, Gagnier JJ, Eichinger JK, Jawa A, Bedi A. Insurance status affects postoperative morbidity and complication rate after shoulder arthroplasty. J Shoulder Elbow Surg. 2017 Aug;26(8):1423-31.

16. Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic joint infection increases the risk of one-year mortality. J Bone Joint Surg Am. 2013 Dec 18;95(24):2177-84.

17. Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. Increased mortality after prosthetic joint infection in primary THA. Clin Orthop Relat Res. 2017 Nov;475(11):2623-31.

18. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010 Mar 12;340:b5087.

19. George A, Stead TS, Ganti L. What's the Risk: Differentiating Risk Ratios, Odds Ratios, and Hazard Ratios? Cureus. 2020 Aug 26;12(8):e10047.

20. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus. Arch Intern Med. 2002 Oct 28;162(19):2229-35.

21. Waterman BR, Dunn JC, Bader J, Urrea L, Schoenfeld AJ, Belmont PJ Jr. Thirty-day morbidity and mortality after elective total shoulder arthroplasty: patient-based and surgical risk factors. J Shoulder Elbow Surg. 2015 Jan;24(1):24-30.

22. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, Garvin KL, Mont MA, Wongworawat MD, Zalavras CG. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011 Nov;469(11):2992-4.