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Deep Surgical Site Infection after Fracture Has a Profound Effect on Functional Outcomes

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Background: Fracture-related infection is one of the most challenging complications in orthopaedic trauma surgery. However, the effect of infection on functional and pain-related outcomes has not been well established. The aims of this study were to evaluate functional recovery for patients with fracture and a deep surgical site infection compared with patients with fracture without infection and to evaluate whether pain severity, social support, and preinjury mental health have a moderating effect on the magnitude and direction of the relationship between deep surgical site infection and functional recovery.

Methods: This is a secondary retrospective cohort study using prospectively collected data from the VANCO trial (Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection) and the OXYGEN (Supplemental Perioperative Oxygen to Reduce Surgical Site Infection After High Energy Fracture Surgery) trial. In this study, 2,116 patients with tibial plateau, pilon, or calcaneal fractures at high risk for infection were included. Patients were divided into cohorts of patients who experienced a deep surgical site infection and those who did not. The primary outcome measure was the functional outcome using the Veterans RAND 12-Item Health Survey (VR-12).

Results: After controlling for covariates, deep surgical site infection was independently associated with functional outcome, with a 3.3-point reduction in the VR-12 Physical Component Score, and pain severity was independently associated with functional outcome, with a 2.5-point reduction in the VR-12 Physical Component Score. Furthermore, the Brief Pain Inventory pain severity demonstrated an important moderating effect on the relationship between infection and functional outcome. In patients with lower pain scores, infection had a large negative impact on functional outcome, whereas, in patients with higher pain scores, infection had no significant impact on functional outcome. Furthermore, the functional outcome in the entire cohort remains at only 61% of baseline.

Conclusions: This study documents the negative impact of postoperative infection on functional recovery after injury, as well as the novel finding of pain severity as an important moderating factor. This study emphasizes not only the importance of developing effective interventions designed to reduce postoperative infection, but also the role that factors that moderate pain severity plays in limiting recovery of physical function.

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

Deep surgical site infection after fracture fixation is one of the most challenging complications in orthopaedic trauma surgery, as it is associated with serious clinical consequences and a substantial burden on resources and the cost of health care[1-5]. Soft-tissue damage adjacent to the fracture and a systematic inflammatory response from the trauma are associated with a risk of infection (2% to 10% for most closed fractures and >20% for some types of open fractures)[6-8]. Patients with postoperative infections typically require additional operations, more diagnostic testing, readmission to the hospital or a prolonged hospital stay, and the need to utilize other health-care resources[2,9]. The impact of postoperative infection may also manifest more broadly in economic terms through worse functional recovery and lost capacity and productivity of patients and their caregivers[10,11]. The effect of postoperative infection on functional and pain-related outcomes has

*A list of the Major Extremity Trauma Research Consortium members is included as a note at the end of the article.

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not been well established. Prior studies have been heterogeneous, often focused on 1 fracture type, and have typically focused primarily on direct hospital-related health-care cost rather than patient function[2,12-15]. Furthermore, psychosocial variables and access to resources have a clear and well-established impact on functional outcomes after both trauma and elective orthopaedic procedures[16-25]. However, the relationship between these psychosocial variables and the consequences of infection remains poorly defined.

There were 2 aims of this study: (1) to evaluate functional recovery for patients who experienced a deep surgical site infection compared with those who did not, and (2) to evaluate whether pain severity, social support, or preinjury mental health had a moderating effect on the magnitude and direction of the relationship between deep surgical site infection and functional recovery. Our hypothesis associated with the first aim was that patients whose recovery was complicated by infection would have significantly worse functional outcomes than those who did not develop an infection. Our hypothesis associated with the second aim was that patients' level of social support, preinjury mental health, and pain severity would each affect the strength or direction of the relationship (or moderate the relationship) between deep surgical site infection and functional recovery. Specifically, we anticipated that increased social support and lack of preinjury mental health history would be associated with more resilience to deep infection, as reflected in higher levels of functional recovery at 6 months postoperatively. Moreover, we anticipated that greater perceptions of pain severity would be associated with worse functional recovery.

Materials and Methods

Study Design and Procedures

This secondary analysis utilized data collected in the VANCO trial (Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection)[26] and the OXYGEN (Supplemental Perioperative Oxygen to Reduce Surgical Site Infection After High Energy Fracture Surgery)[27] trial. The VANCO trial was a randomized controlled trial (ClinicalTrials.gov number NCT02227446) designed to evaluate local antibiotic therapy to reduce infection after the operative treatment of fractures at high risk for infection, and the OXYGEN trial was a randomized controlled trial (ClinicalTrials.gov number NCT01798810) designed to evaluate supplemental perioperative oxygen to reduce deep surgical site infection after high-energy fracture. The 2 studies had identical inclusion criteria and outcome variables, except that the OXYGEN trial contained calcaneal fractures and the VANCO trial did not. Patients met inclusion criteria if they were 18 to 80 years of age; had sustained a tibial plateau, tibial pilon, or calcaneal fracture treated operatively with plate-and-screw fixation; and were at high risk for infection, defined as having ≥1 of 3 characteristics: (1) treatment in a delayed fashion, with definitive fixation >3 days after the injury to allow swelling to resolve, including initial treatment of a tibial fracture with an external fixator; (2) Gustilo type-I, II, or IIIA open fractures; and (3) associated ipsilateral compartment syndrome treated with fasciotomy. Patients in the VANCO trial were randomized to receive 1 g of vancomycin powder intrawound or no vancomycin during the definitive fixation procedure. Patients in the OXYGEN trial were randomized to supplemental perioperative oxygen of 80% or standard-of-care oxygen of 30% during the definitive fixation procedure. All other decisions were left up to the treating surgeon. All outcomes were adjudicated by an independent adjudication committee for both the VANCO and OXYGEN trials.

In the present retrospective cohort study, all patients included in the VANCO and OXYGEN trials were included; no patients in these cohorts were excluded for any reason. The primary outcome measure was the Veterans RAND 12-Item Health Survey (VR-12) Physical Component Score (PCS) measured at 6 months postoperatively. The reported minimum clinically important difference (MCID) for the VR-12 is 2.5 points[28]. Pain severity was defined as the Brief Pain Inventory (BPI) pain severity score. For the main analysis, the independent variable was adjudicated deep surgical site infection. The definition of deep surgical site infection for both trials was based on the principles of the established U.S. Centers for Disease Control and Prevention (CDC)[29-31] criteria and was defined as a deep surgical site infection that was treated with operative debridement, regardless of the time after the surgery date.

Statistical Analysis

All analyses were conducted in the R environment (version 4.1.2, The R Foundation). Descriptive statistics (mean and standard deviation or number and percentage) were calculated for patient demographic variables as well as all variables included in the final model, stratified by the absence or presence of an adjudicated deep surgical site infection. Univariate differences in each variable between patients with and without surgical site infection were examined utilizing t tests or chi-square tests (Table I). Standardized mean differences were also calculated for all univariate analyses. Multiple imputation (with 50 imputations) via a bootstrapping-based algorithm[32] was employed to address bias introduced by missing data. Ordinary least squares regression was employed to examine the relationship between the 6-month VR-12 PCS outcome and predictors of interest after adjusting for patient characteristics. A nested model-building approach was taken that introduced independent variable block inclusion predicated on the timing of variable collection after the index surgical intervention. Further, a number of interaction terms were introduced to understand patient-level moderators (perceptions of pain severity, preinjury mental health scores, and social support) that impact the relationship between surgical site infection and 6-month physical functioning as reported by the patient. Significant interactions were probed by calculating simple slopes and were visualized via the pooled estimates derived from the imputation-based regression model. Significance was set at $p < 0.05$ for all tests.

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TABLE I Patient Demographic and Injury Characteristics*

Characteristic	Deep Surgical Site Infection		P Value†	Standardized Mean Difference
	No (N = 1,934)	Yes (N = 182)		
Study cohort†			0.556	0.052
VANCO	900 (46.5%)	80 (44.0%)		
OXYGEN	1,034 (53.5%)	102 (56.0%)		
Age§ *(yr)*	45.29 ± 14.08	48.22 ± 13.48	**0.007**	0.212
Race†			0.359	0.173
Hispanic	156 (8.1%)	17 (9.3%)		
Non-Hispanic White	1,368 (70.7%)	136 (74.7%)		
Non-Hispanic Black	267 (13.8%)	16 (8.8%)		
Other	81 (4.2%)	6 (3.3%)		
Unknown or refused	62 (3.2%)	7 (3.8%)		
Male sex†	1,251 (64.7%)	134 (73.6%)	**0.019**	0.195
Education†§			0.520	0.237
No high school or GED	287 (15.1%)	40 (22.3%)		
High school graduate or GED	622 (32.7%)	61 (34.1%)		
Some college	590 (31.0%)	45 (25.1%)		
4-year college graduate	249 (13.1%)	24 (13.4%)		
Graduate education	154 (8.1%)	9 (5.0%)		
Tobacco†§			**0.008**	0.247
Current	699 (36.5%)	82 (45.1%)		
Former	402 (21.0%)	44 (24.2%)		
Never	814 (42.5%)	56 (30.8%)		
BMI# *(kg/m^2)*	29.19 ± 6.78	29.45 ± 6.56	0.613	0.040
ASA classification†			0.891	0.078
1	283 (14.6%)	28 (15.4%)		
2	1,125 (58.2%)	107 (58.8%)		
3 to 5	526 (27.2%)	47 (25.8%)		
Injury Severity Score# *(points)*	7.78 ± 7.71	6.73 ± 6.05	0.087	0.152
Fracture type†§			0.400	0.105
Calcaneal	240 (12.5%)	21 (11.7%)		
Pilon	788 (40.9%)	83 (46.1%)		
Plateau	897 (46.6%)	76 (42.2%)		
Open fracture†	304 (15.7%)	55 (30.2%)	**<0.001**	0.350
Social support#	4.54 ± 0.90	4.54 ± 0.96	0.949	0.005
Social support level†§			0.541	0.139
Never	47 (2.5%)	7 (3.9%)		
Rarely	40 (2.1%)	3 (1.7%)		
Sometimes	133 (7.0%)	8 (4.5%)		
Usually	289 (15.3%)	29 (16.3%)		
Always	1,383 (73.1%)	131 (73.6%)		
Preinjury scores#				
VR-12 MCS	54.99 ± 10.01	54.99 ± 10.09	0.994	0.001
VR-12 PCS	51.87 ± 8.12	51.09 ± 8.26	0.220	0.095

*GED = general educational development test, BMI = body mass index, and ASA = American Society of Anesthesiologists. †Significant values are shown in bold. †The values are given as the number of patients, with the percentage in parentheses. §Some variables had missing data and therefore do not total the total for each column. #The values are given as the mean and the standard deviation.

TABLE II Six-Month Patient-Reported Outcome Measures

	Deep Surgical Site Infection			
	No (N = 1,934)	Yes (N = 182)	P Value*	Standardized Mean Difference
VR-12 MCS				
Mean† *(points)*	52.59 ± 12.61	50.10 ± 14.05	**0.016**	0.187
Decrease from preinjury† *(points)*	2.4 ± 11.31	4.89 ± 12.07	0.09	
Percent of preinjury	96.34%	90.92%		
VR-12 PCS				
Mean† *(points)*	36.12 ± 10.58	31.10 ± 9.26	**<0.001**	0.505
Decrease from preinjury† *(points)*	15.75 ± 9.35	19.99 ± 8.76	**<0.001**	
Percent of preinjury	69.64%	60.87%		
BPI pain† *(points)*				
Severity	2.90 ± 2.32	3.53 ± 2.57	**0.001**	0.257
Interference	3.50 ± 2.88	4.59 ± 3.05	**<0.001**	0.367

*Significant differences are shown in bold. †The values are given as the mean and the standard deviation.

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Results

In this study, 980 patients from the VANCO trial and 1,136 patients from the OXYGEN trial were included. Among the 2,116 patients included, 182 developed a deep surgical site infection (8.6%). There were differences between patients with and without infection with regard to age, sex, tobacco use, and open fracture (Table I). There was no significant difference with regard to preinjury Mental Component Score (MCS) or PCS (Table I). Univariate analysis demonstrated a significant difference between the groups without and with infection with regard to the mean VR-12 MCS (52.59 ± 12.61 compared with 50.10 ± 14.05; $p = 0.016$), mean VR-12 PCS (36.12 ± 10.58 compared with 31.10 ± 9.26; $p < 0.001$), mean BPI pain severity[33] (2.9 ± 2.32 compared with 3.53 ± 2.57; $p = 0.001$), and mean BPI pain interference (3.5 ± 2.88 compared with 4.59 ± 3.05; $p < 0.001$) at 6 months (Table II). At 6 months, patients without infection had recovery of the MCS to 96% of their preinjury baseline and of the PCS to 70% of baseline. Patients whose course was complicated by infection had recovery of the MCS to 91% of their preinjury baseline and of the PCS to 61% of baseline.

In the multivariable model controlling for covariates, the most important predictor of functional outcome was deep infection. Deep infection was associated with a 3.3-point reduction in VR-12 PCS (Table III), which is larger than the MCID of 2.5[28]. BPI pain severity was also independently associated with functional outcome (2.5-point reduction in VR-12 PCS). The preinjury MCS was independently associated with the 6-month functional outcome (each 10-point reduction in the preinjury MCS was associated with a 0.7-point reduction in 6-month PCS) (Table III). Note that an early iteration of this model (without the BPI severity variable) demonstrated a nonsignificant finding for the preinjury MCS (see Appendix Supplemental Table 1).

The relationship between deep surgical site infection and functional outcome was moderated by BPI pain severity, in that there was a significant difference in function between those without infection and those with infection only among patients with lower pain severity ($p < 0.001$). Patients with higher pain severity demonstrated worse function overall, but with no significant difference between those with and without infection (Figure 1, Table III). Preinjury mental health and social support did not moderate the relationship between deep surgical site infection and the self-reported physical function outcome.

Discussion

This study documents the negative association between postoperative infection and functional recovery after fracture using data derived from 2 large prospectively collected data sets with adjudicated outcomes. Our findings suggest that, among patients operatively treated for a high-risk fracture, postoperative infection was independently associated with a clinically relevant 3.3-point reduction in VR-12 PCS at 6 months. For context, this reduction is larger than the MCID for the VR-12 PCS (2.5 points) and is more severe than that associated with angina (2.53 points) or diabetes (3.05 points)[28,34]. This analysis also suggested that pain plays a role in the relationship between deep surgical site infection and physical function. Pain was independently associated with decreased functional outcome and exerted a moderating effect on the relationship between infection and function by affecting its magnitude. Patients with less pain severity

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TABLE III Multivariable Ordinary Least Squares Regression Model for the 6-Month Functional Outcomes*

	Estimate†	P Value‡	Fraction of Missing Information§
(Intercept)#	37.893 ± 1.164		0.186
Age	−0.059 ± 0.016	**<0.001**	0.186
Race			
Hispanic	Reference		
Non-Hispanic White	−0.790 ± 0.792	0.319	0.257
Non-Hispanic Black	1.382 ± 0.954	0.148	0.269
Other	−0.211 ± 1.280	0.869	0.258
Sex			
Female	Reference		
Male	−0.744 ± 0.446	0.095	0.155
Tobacco			
Current or past use	Reference		
Never	0.843 ± 0.434	0.052	0.141
BMI	−0.126 ± 0.032	**<0.001**	0.156
ASA classification			
1	Reference		
2	−0.195 ± 0.604	0.747	0.115
3 to 5	−0.363 ± 0.725	0.617	0.116
Injury Severity Score	−0.086 ± 0.031	**0.006**	0.255
Fracture type			
Calcaneal	Reference		
Pilon	−0.995 ± 0.719	0.167	0.160
Plateau	−1.107 ± 0.703	0.116	0.160
Fracture			
Closed	Reference		
Open	−1.998 ± 0.599	**0.001**	0.186
Social support	−0.097 ± 0.259	0.708	0.201
Study			
OXYGEN	Reference		
VANCO	0.201 ± 0.438	0.647	0.127
Adjudicated deep surgical site infection			
No	Reference		
Yes	−3.308 ± 0.734	**<0.001**	0.090
BPI severity	−2.523 ± 0.100	**<0.001**	0.188
Preinjury VR-12 MCS	−0.068 ± 0.024	**0.005**	0.208
Interaction of an adjudicated deep surgical site infection with			
BPI severity	0.815 ± 0.301	**0.007**	0.092
Preinjury VR-12 MCS	−0.052 ± 0.081	0.521	0.151
Social support	0.431 ± 0.823	0.601	0.163

*BMI = body mass index and ASA = American Society of Anesthesiologists. †The values are given as the estimate and the standard error. ‡Significant p values are shown in bold. §All continuous predictors were centered on the mean. #The intercept is the mean VR-12 score when all covariates in the model are set to zero, and each estimate represents the slope (change in VR-12 score associated with a 1-unit increase in that specific covariate).

demonstrated a significant reduction in functional outcome with infection. In contrast, among those with worse pain severity, functional outcome was much worse but there was no difference in function according to whether or not patients had an infection (Figure 1). This suggests that a patient with a deep surgical site infection and less pain is more likely to have better physical

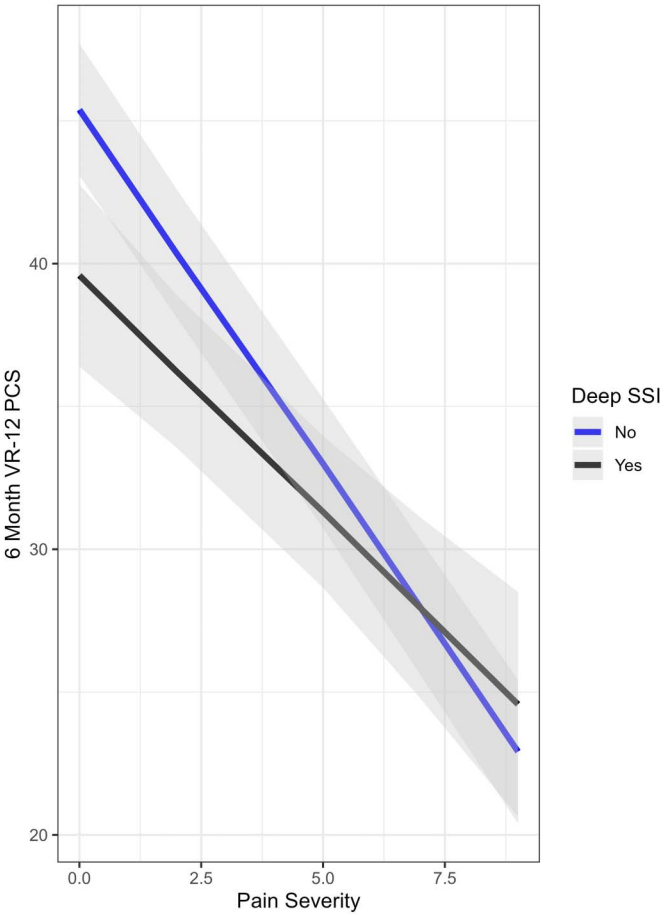

Fig. 1

Interaction between pain severity and deep surgical site infection (SSI), demonstrating the moderating effect of pain severity on the relationship between deep SSI and functional outcome. In patients with less pain severity, there was a significant reduction in functional outcome in patients who experienced an infection (black line) compared with those who did not (blue line). The shading indicated 95% confidence intervals. Among those with worse pain severity, functional outcome was much worse in both patient cohorts and there was no difference in physical function between patients who had and had not experienced an infection.

function than a patient without a deep surgical site infection but with greater than average perceptions of pain. Although it is likely that pain is in the causal pathway for physical function, this observational study cannot provide evidence for a causal relationship. Neither preinjury baseline MCS nor social support moderated the relationship between infection and functional outcome, meaning that neither of these variables influenced the strength or direction of the relationship between infection and functional outcome. Additionally, this analysis demonstrated that substantial functional deficits, below population norms and below patients' baseline, persist at the 6-month mark, with neither group recovering to >70% of their baseline function.

These results are consistent with current literature and clinical experience. In the military population, infectious complications were associated with an increased rate of disability and reduced rate of return to duty[35]. Furthermore, in this population, infection and pain represent the top reasons for late amputation[36]. In the civilian population, postoperative infection after surgical fracture treatment has a substantial economic impact on both the patient and the health-care system as well as negative functional consequences[15,37]. Several retrospective studies have demonstrated the negative impact of fracture-related infection on the quality of life[11,15,38-40]. The economics of fracture-related infection are clearly substantial, with several studies demonstrating extraordinarily high health-care expenditures[2,11,12,15]. Beyond health-care expenditures, infection has a profound and persistent effect on patient-specific economics. O'Hara et al. demonstrated that patients with fracture who developed infection had a persistent deficit in income even 6 years after a traumatic injury, as well as a 6.6% increase in the risk of catastrophic wage loss and a 45% increase in the odds of receiving Social Security benefits[37]. It is likely that deficits in physical function mediate the relationship between injury and wage loss, accounting for a substantial proportion of persistent disability.

The importance of psychosocial factors in recovery after trauma has been clear for many years. The Lower Extremity Assessment Project study suggested that functional outcomes were driven more by psychosocial factors than by patient, injury, or treatment factors[41-43]. This has been confirmed through multiple subsequent studies demonstrating that increased psychological stress, depression, anxiety, pain catastrophizing, and social support can have profound impacts on functional recovery[16-25]. This is consistent with our findings that perceptions of pain severity and the preinjury mental score were independently associated with functional outcome. However, not only did pain impact the functional outcome independently, but it also influenced the magnitude of the relationship between infection and functional outcome. This emphasizes the importance of developing effective integrated models of pain and rehabilitation and of applying them to patients at the highest risk, such as those with infectious complications.

There were several limitations associated with this study. First, the data set included functional scores before and 6 months after injury. Although clinically relevant differences in the postinjury functional score between patients with and without infection were detected at the 6-month time point, the longitudinal time course remains unclear. Prior research has demonstrated a functional recovery plateau occurring anywhere from 6 months to 5 years after the original injury, and so it should be assumed that patients in this cohort are continuing to improve beyond 6 months[44-47]. Second, it was possible that, over a longer time course, patients who develop an infection catch up, particularly because many patients remain under active treatment near to or during this 6-month time point. This limited the conclusions that could be drawn from this analysis. Patients who develop infection have, at best, substantially delayed functional recovery, given that their 6-month functional outcomes are so much worse than the otherwise similar cohort. However, based on prior literature, it is likely

that these functional deficits do persist. Previous smaller retrospective studies have demonstrated that these deficits persist at 1 year or even a mean of 4.2 years[11,15,38,39]. More research is needed to document functional recovery at additional time points to determine the relative persistence of the functional deficits as well as the normal time course for function to plateau. Third, although there were demographic differences between the cohorts, these differences were controlled for using multivariable modeling. Fourth, the results of this study may not have been generalizable to all institutions because data were derived from 2 prospective studies at hospital centers with funded research infrastructure. It is possible that institutions with strong research infrastructure are better resourced, which may impact patient functional recovery. However, these data derived from multiple centers across North America represent the greatest diversity of sites examining these issues to date. Fifth, because neither the VANCO trial nor the OXYGEN trial was designed to assess the relationship between infection and functional recovery, the patient cohorts were not evenly distributed and there were differences between patient cohorts. Rigorous statistical methods, including multivariable regression, were used to control for these differences, as is indicated for observational research. Sixth, given that the cohorts for this analysis were derived from 2 prospective trials randomizing patients to 1 of 2 different treatments, there was the potential for a survivorship bias or a bias in which the "survivors" who were "saved" from an infection by virtue of 1 of the interventions were inherently different and potentially weaker than patients who were never going to develop an infection. However, this bias was likely to be quite limited; it was unlikely that those who were saved from developing an infection were any different with regard to physical function than those who never would have developed an infection. Moreover, even if that cohort was inherently weaker in terms of physical function, this would have biased the noninfected cohort toward a worse functional score, thus making it harder to detect a difference. In that case, the difference that we detected would have overcome this bias and the true difference might actually be even larger than reported.

There are several strengths associated with this study. The study leveraged a high-quality, prospectively collected, adjudicated data set, which has advantages in terms of validity over prior research using retrospective chart review or administrative data, which are subject to issues with inconsistent reporting and coding inaccuracies or biases associated with research at a single center[48,49]. The multicenter nature of this study improves its external validity. Furthermore, all outcomes were adjudicated by an independent adjudication committee.

In conclusion, this study documents the negative impact of postoperative infection on functional recovery after a lower-extremity fracture at high risk for developing infection, with pain severity being an important moderating factor affecting the magnitude of the relationship between infection and functional outcomes. This work emphasizes not only the importance of developing effective interventions designed to reduce postoperative infection, but also the role of factors such as pain severity, which moderate the impact of infection on functional recovery.

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/A591). ■

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