Invited Commentary

# Postoperative Infection—A Pervasive Mediator of Patient Mortality

Matthew R Woeste, MD; William G. Cheadle, MD

**Postoperative infection** is responsible for approximately one-fourth of all nosocomial infections and may have an incidence as high as 5%.[1] The prevention of this morbidity remains a substantial portion of health care expenditures each year.[2] Postoperative infection increases mortality after major operations,[3] but despite this fact, much of the previous literature focuses only on its association with 30-day morbidity and mortality.

Related article

In this issue of *JAMA Surgery*, O'Brien et al[4] sought to elucidate the prolonged consequences of infection within the immediate postoperative period. They have demonstrated, through a large retrospective cohort using the Veterans Health Administration National VA Surgical Quality Improvement Program data base from 2003 to 2008, that exposure to infection in the immediate 30-day period following surgery leads to a significantly higher risk of infection and mortality in the subsequent year (hazard ratio, 3.17; 95% CI, 3.05-3.28 and hazard ratio, 1.89; 95% CI, 1.79-1.99, respectively). These findings were validated across a range of surgical specialties and infection types and were independent of patient comorbidities. For these reasons, this study should draw multidisciplinary and administrative attention, as this finding of delayed morbidity and mortality has also been shown in patients with trauma and burns.[5]

The authors acknowledge the study limitations, including the lack of diversity in their patient population and constraint to a single hospital system. It is worth reiterating their assumption of infection homogeneity equated exposures, such as surgical site infections and deep tissue or solid organ infection, presumably underestimating additional harm in an essential subgroup. To our knowledge, there is little published literature that compares postoperative infection type and mortality, highlighting a potential direction for future articles. We would also like to mention a few concerns. First, infection rates vary considerably when comparing patient levels of care with the highest reported rates within intensive care units (13%).[6] Yet, these patients were not stratified based on inpatient status. Additionally, surgical site infections were the most common exposures at 40.2% but contributed least to long-term infection and mortality. Finally, surgery occurring in days 31 to 365 was not accounted for and may be contributing to this cohort's long-term infection and mortality rate.

These data support the purpose of ongoing research in the prevention and treatment of postoperative infection. A better understanding of how infection affects patient outcomes will affect cost-benefit analyses, as O'Brien et al[4] predict. It is imperative that more studies are funded to provide prospective observations of this topic. We congratulate the authors for recognizing the need for further research that expounds on such an important topic.

## ARTICLE INFORMATION

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JAMA Surgery | Original Investigation | ASSOCIATION OF VA SURGEONS

# Association of Postoperative Infection With Risk of Long-term Infection and Mortality

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**IMPORTANCE** Surgical site infection has been shown to decrease survival in veterans by up to 42%. The association of 30-day postoperative infections with long-term infections in the overall surgical population remains unknown.

**OBJECTIVE** To determine whether exposure to 30-day postoperative infection is associated with increased incidence of infection and mortality during postoperative days 31 to 365.

**DESIGN, SETTING, AND PARTICIPANTS** In this retrospective observational cohort study, veterans undergoing major surgery through the Veterans Health Administration from January 2008 to December 2015 were included. Stabilized inverse probability of treatment weighting was used to balance baseline characteristics of the control and exposure groups. Cox proportional hazards regression was used to estimate hazard ratios of long-term infection and mortality. Data were analyzed from September 2018 to May 2019.

**EXPOSURES** Any 30-day postoperative infection (exposure group) vs no 30-day infection (control group).

**MAIN OUTCOMES AND MEASURES** Number of days between index surgery and the occurrence of death or the patient's first infection during postoperative days 31 to 365. Patients who died before having a long-term infection were censored for the infection outcome.

**RESULTS** Of the 659 486 included patients, 604 534 (91.7%) were male, and the mean (SD) age was 59.7 (13.6) years. Among these patients, 23 815 (3.6%) had a 30-day infection, 43 796 (6.6%) had a long-term infection, and 24 810 (3.8%) died during follow-up. The most frequent 30-day infections were surgical site infection (9574 [40.2%]), urinary tract infection (6545 [27.5%]), pneumonia (3515 [14.8%]), and bloodstream infection (1906 [8.0%]). Long-term infection types included urinary tract infection (21 420 [48.7%]), skin and soft tissue infection (14 348 [32.6%]), bloodstream infection (3862 [8.8%]), and pneumonia (2543 [5.8%]). Patients in the exposure group had a higher observed incidence of long-term infection (5187 of 23 815 [21.8%]) and mortality (3067 of 23 815 [12.9%]) compared with those without 30-day infection (38 789 of 635 671 [6.1%] and 21 743 of 635 671 [3.4%], respectively). The estimated hazard ratio for long-term infection was 3.17 (95% CI, 3.05-3.28) and for mortality was 1.89 (95% CI, 1.79-1.99).

**CONCLUSIONS AND RELEVANCE** At any given point during the follow-up period, patients with 30-day postoperative infection had a 3.2-fold higher risk of 1-year infection and a 1.9-fold higher risk of mortality compared with those who had no 30-day infection. Cost-benefit calculations for surgical infection prevention programs should include the increased risk and costs of long-term infection and death. Preventive efforts in the first 30 days postoperatively may improve long-term patient outcomes.

Invited Commentary

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Significant resources are expended to prevent postoperative infections, as they have both short-term and long-term consequences. Previous studies have focused on mortality following postoperative infection, and most have demonstrated that survival is decreased in patients who have infections after surgery compared with those who do not.[1,2] Specifically, sepsis and bacteremia in the postoperative period have been associated with reduced survival.[3] Surgical site infections in patients with cancer and in patients after cardiac surgery have also been associated with mortality risk.[4,5]

However, the underlying factors that confound the associations between early and later postoperative outcomes are difficult to account for. Randomization to the exposure of early infection is obviously not feasible. Thus, robust statistical methods, such as emulation of a target trial, are needed to most accurately assess the differences in infection and survival outcomes among those who do and do not have early infections in the 30-day postoperative period.

The goal of this study is to estimate the association of occurrence of 30-day postoperative infection with long-term infection and mortality up to 1 year after surgery in a large cohort of patients undergoing a broad range of surgery types during an 8-year period. We hypothesize that exposure to infection is associated with increased risk of both outcomes independent of patients' baseline characteristics and surgical factors.

### Key Points

**Question** Is infection during postoperative days 0 to 30 associated with increased incidence of infection and mortality during postoperative days 31 to 365?

**Findings** In this cohort study of 659 486 veterans, infection within 30 days after surgery was significantly associated with infection and mortality during postoperative days 31 to 365.

**Meaning** Infection after surgery is associated with long-term harm, which should be accounted for in the costs and benefits of infection prevention programs.

## Methods

### Study Design

This is a retrospective observational cohort study of patients undergoing major surgery in the Veterans Health Administration (VHA) from January 2008 to December 2015. The design uses the target trial emulation approach for inference in observational research.[6] It uses a propensity score model with stabilized inverse probability of treatment weighting (IPTW-S) to adjust for selection bias that influences a patient being in the exposure group (any 30-day postoperative infection) vs control group (no 30-day postoperative infection). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. We obtained approval from the VA Boston Institutional Review Board, which waived consent because the research involved minimal risk.

### Data Sources

The main data source was the Veterans Affairs Surgical Quality Improvement Project (VASQIP) database, which contains validated, medical record–reviewed data on a national sample of major procedures performed in 130 VHA surgical programs.[7] Procedures reviewed in the VASQIP were used to identify index events. The Surgical Package from the VHA Corporate Data Warehouse (CDW) was used to identify other operations and invasive procedures among study participants but not for identifying index procedures. The CDW also provided data on patients' clinical and demographic characteristics.

### Eligibility Criteria

The patient's first chronological VASQIP-reviewed surgery from January 2008 to December 2015 was assessed for inclusion. The surgery was excluded if the patient had any other invasive procedure in the prior 30 days. We unenrolled patients who had a subsequent surgery as well as those who died within 30 days after the index surgery, as they were not alive at the start of the outcome period. While it is an interesting research question as to whether 30-day subsequent surgery or death may be associated with the initial surgery, these outcomes are beyond the scope of our study. The final sample size was based on all available procedures meeting these criteria. It included all surgical specialties available in the source data, and we did not distinguish between implant and nonimplant procedures.

### Assessment of Exposure

After enrollment of patients based only on information known at the time of the index surgery, we determined whether each patient had an infection within 30 days using the manual medical record review assessments contained in the VASQIP database. These infections were categorized as surgical site infection (SSI), pneumonia, urinary tract infection (UTI), or bloodstream infection (BSI). Surgical site infection was defined as a VASQIP-assessed superficial, deep, or organ/space infection. Urinary tract infection and pneumonia were defined using their respective VASQIP-assessed outcomes. The VASQIP does not track the occurrence of 30-day BSI; therefore, we defined this as positive findings on a blood culture for bacterial growth, since blood is a normally sterile site. In those infections where a culture was obtained, we attempted to identify the microorganism and grouped them broadly as methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *S aureus*, other *S aureus* organisms (eg, *S epidermidis*), or as non-*Staphylococcus* organisms.

### Outcomes

Among the patients who were enrolled and survived 30 days without subsequent surgery, the follow-up period began on postoperative day 31 and ended either on postoperative day 365 or at death. The outcomes of interest were any infection (skin and soft tissue infection [SSTI], UTI, BSI, or pneumonia) or mortality. Since the infection outcomes are beyond the 30-day window for VASQIP medical record review, we relied on a validated algorithm to identify them.[8] We defined long-term

infection as positive findings on a blood culture combined with prescription of antimicrobials within 5 days after the specimen was obtained. The outcome was classified based on the anatomical site from which the culture was taken. We attempted to identify initial infections only and rule out subsequent cultures that were likely continuations of a previous infection. In cases of UTI, BSI, and pneumonia, a subsequent positive finding on a blood culture must have occurred at least 2 weeks after the first positive findings to be counted as a new, distinct infection outcome. A subsequent positive finding on blood culture indicative of SSTI must have been from a different anatomical site than the first, regardless of time interval. We identified participants' date of death using both VASQIP data and the CDW vital status tables. Finally, we computed survival curves for both outcomes, stratified by 30-day infection type and bacteria.

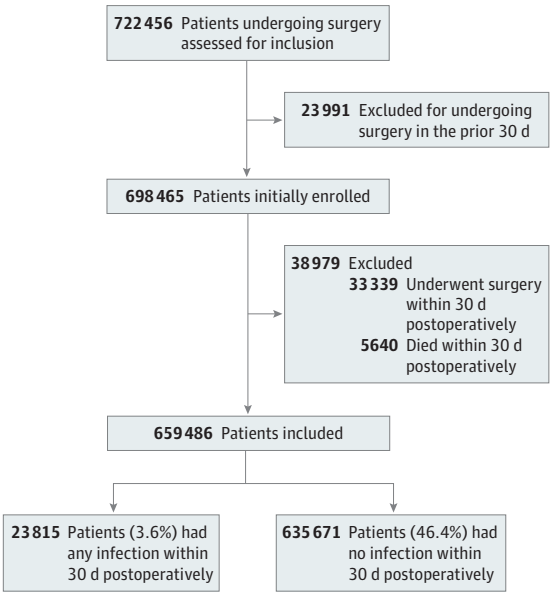
A manual medical record review performed on 415 randomly chosen outcomes allowed for correction of any topography misclassification of infection and refinement of the algorithm. The review uncovered 23 of 315 instances in which pneumonia was classified as SSI or vice versa. We updated the final algorithm to account for the surgical specialty to prevent these misclassifications. Of the 100 negative outcomes reviewed, 3 had a long-term infection, but we were unable to find data indicative of infection in the CDW microbiology database.

## Statistical Analysis

We used a propensity score model and IPTW-S to create a pseudopopulation that is balanced in the distribution of preoperative and perioperative characteristics between the exposure and control groups. The stabilization feature of the model preserves the size of the study population, avoiding the need for adjustment of standard errors in an inflated sample. Furthermore, no study participants are dropped (and statistical power lost), which is advantageous compared with propensity score matching. The model specification was based on patient and operative factors that were known at the time of the index surgery and plausibly associated with either the exposure or outcomes.[9,10] We used the twang package in R version 3.5.1 (The R Foundation) to fit a generalized boosted regression model on the participants who were enrolled and survived the 30-day exposure period. The generalized boosting model is a machine-learning algorithm that has been shown to improve propensity score estimation performance in simulations compared with logistic regression.[11] The optimal number of iterations of the model was chosen by minimizing the Kolmogorov-Smirnov statistic. The predicted probabilities of 30-day infection were then used to calculate IPTW-S.[12] The standardized mean differences (SMDs) of observed vs weighted baseline characteristics—both continuous and categorical—stratified by exposure vs control groups were calculated using the tableone package in R. We decided a priori to consider any covariates with an SMD less than 0.2 to be balanced[13] and that unbalanced covariates would be included as additional regressors in the outcome model (ie, a doubly robust specification).

Finally, an IPTW-S-weighted Cox proportional hazards model was used to estimate the hazard ratio of exposure to 30-day infection on the outcomes of long-term infection and mortality. The only effect in the model specification was the dichotomous exposure variable (yes/no), as were any baseline covariates not meeting the criterion of an SMD less than 0.2. In the long-term infection model, patients were right-censored if they died before having a long-term infection, while the mortality model had no censoring. We chose to model the 2 outcomes separately as opposed to a combined end point of infection-free survival days, as this approach allowed us to capture all mortality outcomes.

Figure 1. CONSORT Diagram




# Results

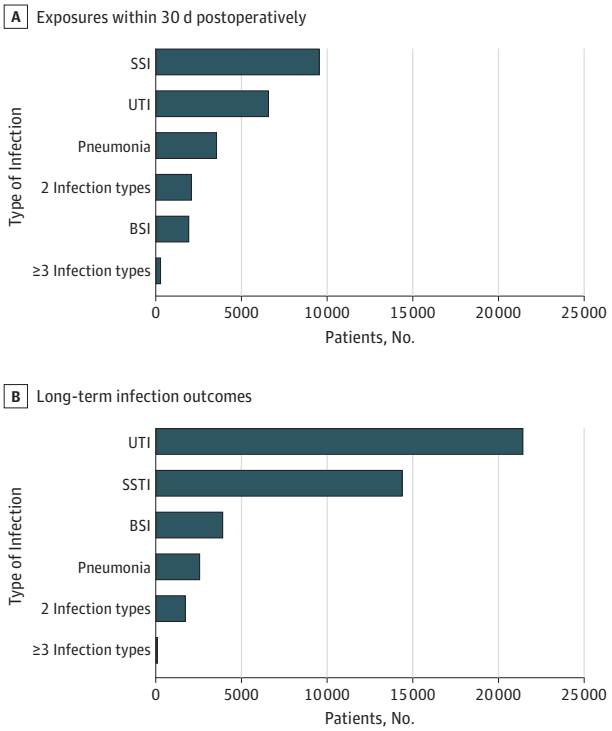
## Study Population

The enrollment process is illustrated in **Figure 1**. We assessed 722 456 patients who underwent a procedure during the study period for inclusion in the study. Among these, 23 991 (3.3%) were excluded for having an invasive procedure in the prior 30 days. Among the 698 465 initially enrolled patients, we disenrolled 33 339 patients (4.8%) who had another invasive procedure within 30 days and 5640 (0.8%) who died within 30 days. The remaining 659 486 patients were those who survived the full 30-day exposure period without having subsequent surgery. In the final study population, 604 534 patients (91.7%) were male and 418 928 (63.5%) were white. The most common surgical specialties were orthopedics (191 414 [29.0%]), general surgery with a clean wound (133 158 [20.2%]), and general surgery with a clean-contaminated or dirty wound (89 868 [13.2%]).

## Exposure to Postoperative Infection

We identified occurrence of postoperative infection in 23 815 patients (3.6%). The most frequent types were SSI (9574

Figure 2. Frequency of Postoperative and Long-term Infection Types




BSI indicates bloodstream infection; SSI, surgical site infection; UTI, urinary tract infection.

[40.2%]), UTI (6545 [27.5%]), pneumonia (3515 [14.8%]), and BSI (1906 [8.0%]). The remainder of postoperative infections were a combination of 2 or 3 infection types at any time during the 30 days (**Figure 2**).

Characteristics of patients stratified by exposure group vs control group are shown in **Table 1.** Compared with those with no postoperative infection, those with any postoperative infection were older (mean [SD] age, 64.9 [12.2] vs 59.5 [13.7] years), more frequently had an American Society of Anesthesiologists score greater than 2 (85.0% [20 247 of 23 815] vs 65.0% [413 116 of 635 671]), more likely to have underwent emergent surgery (11.4% [2710 of 23 815] vs 4.0% [25 412 of 635 671]), and more likely to have underwent surgery with a duration in the highest quartile (45.3% [10 784 of 23 815] vs 23.3% [148 302 of 635 671]).

In 12 610 of 23 815 patients (52.9%) with 30-day VASQIP-assessed infection, no culture was performed or there was no growth. Growth of non-*Staphylococcus* bacteria was observed in 7149 patients (30.0%), methicillin-sensitive *S aureus* was observed in 1729 (7.3%), coagulase-negative *S aureus* was observed in 1401 (5.9%), and methicillin-resistant *S aureus* was observed in 926 (3.9%).

## Outcomes of Long-term Infection and Mortality

The incidence rate of infection during postoperative days 31 to 365 was 6.7% (43 976 initial infections in 659 486 patients) (Figure 2). The most frequent types were UTI (21 420 [48.7%]), SSTI (14 348 [32.6%]), BSI (3862 [8.8%]), pneumonia (2543 [5.8%]), or a combination of 2 or 3 types simultaneously (1803 [4.1%]). In patients in the exposure group, 5187 of 23 815 (21.8%) had a long-term infection compared with 38 789 of 635 671 (6.1%) in the control group. The median (interquartile range) interval between index surgery and the first occurrence of long-term infection was 78 (44-165) days in the exposure group compared with 132 (65-232) days in the control group.

Overall, 24 810 patients (3.8%) died during follow-up. The observed mortality rate in those in the exposure group was 12.9% (3067 of 23 815) compared with 3.4% (21 743 of 635 671) in the control group. The median (interquartile range) interval between index surgery and death was 129 (61-234) days in the exposure group compared with 183 (100-272) days in the control group.

## Propensity Score Weights and Outcome Model

The weighted baseline characteristics of study participants is shown in Table 1. Prior to weighting, 8 of 20 characteristics had an SMD greater than 0.2, as would be expected between the arms of a nonrandomized study. After weighting, all characteristics became well-balanced between the exposure and control groups, with the largest SMD being surgical specialty (0.04)—still well below our prespecified threshold of 0.2. Therefore, the only effect in the Cox proportional hazards model was exposure to 30-day infection.

The estimated hazard ratio of long-term infection as a function of postoperative infection exposure was 3.17 (95% CI, 3.05-3.28) (**Table 2**). The hazard ratio for long-term mortality was 1.89 (95% CI, 1.79-1.99). Since none of the weighted baseline characteristics had an SMD greater than 0.2, we did not include any of those terms in the model.

## Observed Outcomes by Infection Type and Bacteria

The cumulative incidence rates of long-term infection and mortality stratified by 30-day infection type and bacteria are shown in **Figure 3.** Among patients with a 30-day infection, those with a BSI experienced the highest rate of long-term infection, and those with an SSI experienced the lowest rate. Those with any 30-day methicillin-resistant *S aureus* infection had the highest rate of long-term infection compared with other organisms. In the 5187 patients who had both a postoperative and long-term infection, the most common infection types were UTI with subsequent UTI (1231 [23.7%]), SSI with subsequent SSTI (929 [17.9%]), SSI with subsequent UTI (388 [7.4%]), and pneumonia with subsequent UTI (229 [4.4%]).

# Discussion

In this national cohort of patients undergoing surgery, we applied robust statistical methods to emulate a target trial and demonstrate that infections occurring in the 30-day postoperative period have long-term consequences of repeated infection and reduced survival over the following year. These associations were not only statistically significant but also clinically meaningful, with more than a tripling of late infection and nearly a doubling of mortality rates among patients who had 30-day postoperative infections. The strength of this

Table 1. Observed and Weighted Baseline Characteristics of Veterans Undergoing Surgery Stratified by Exposure to 30-Day Postoperative Infection

| Characteristic | No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Observed | | | IPTW-S | | |
| | No Infection Within 30 d | Any Infection Within 30 d | SMD | No Infection Within 30 d | Any Infection Within 30 d | SMD |
| No. of procedures | 635 671 | 23 815 | NA | 635 628.2 | 22 639.6 | NA |
| Male | 582 172 (91.6) | 22 362 (93.9) | 0.089 | 582 760.9 (91.7) | 20 486.5 (90.5) | 0.042 |
| Age, mean (SD), y | 59.50 (13.65) | 64.88 (12.20) | 0.416 | 59.69 (13.64) | 59.81 (13.50) | 0.009 |
| Race | | | | | | |
| White | 403 475 (63.5) | 15 453 (64.9) | 0.034 | 403 765.3 (63.5) | 14 596.9 (64.5) | 0.021 |
| Black | 94 973 (14.9) | 3543 (14.9) | | 94 957.7 (14.9) | 3239.9 (14.3) | |
| Other/missing | 137 223 (21.6) | 4819 (20.2) | | 136 905.2 (21.5) | 4802.7 (21.2) | |
| American Society of Anesthesiologists class | | | | | | |
| 1-2 | 221 137 (34.8) | 3543 (14.9) | 0.475 | 216 550.6 (34.1) | 7419.6 (32.8) | 0.028 |
| 3-5 | 413 116 (65.0) | 20 247 (85.0) | | 417 688.8 (65.7) | 15 171.6 (67.0) | |
| Missing | 1418 (0.2) | 25 (0.1) | | 1388.8 (0.2) | 48.4 (0.2) | |
| Surgical specialty | | | | | | |
| General surgery (clean) | 130 700 (20.6) | 2458 (10.3) | 0.696 | 128 337.4 (20.2) | 4619.2 (20.4) | 0.031 |
| General surgery (not clean) | 81 655 (12.8) | 8213 (34.5) | | 86 601.6 (13.6) | 3147.9 (13.9) | |
| Neurosurgery | 34 172 (5.4) | 1098 (4.6) | | 33 990.5 (5.3) | 1198.7 (5.3) | |
| Orthopedics | 188 090 (29.6) | 3324 (14.0) | | 184 499.3 (29.0) | 6329.7 (28.0) | |
| Other | 39 708 (6.2) | 1053 (4.4) | | 39 291.3 (6.2) | 1386.5 (6.1) | |
| Peripheral vascular | 44 962 (7.1) | 2528 (10.6) | | 45 778.6 (7.2) | 1600.4 (7.1) | |
| Plastic surgery | 15 247 (2.4) | 350 (1.5) | | 15 030.4 (2.4) | 541.1 (2.4) | |
| Podiatry | 7530 (1.2) | 150 (0.6) | | 7403.5 (1.2) | 255.6 (1.1) | |
| Thoracic surgery | 16 055 (2.5) | 1302 (5.5) | | 16 725.6 (2.6) | 619.6 (2.7) | |
| Urology | 77 552 (12.2) | 3339 (14.0) | | 77 970.0 (12.3) | 2941.0 (13.0) | |
| Dialysis | 4891 (0.8) | 337 (1.4) | 0.062 | 5034.8 (0.8) | 183.1 (0.8) | 0.002 |
| Renal failure | 1335 (0.2) | 161 (0.7) | 0.070 | 1434.6 (0.2) | 52.5 (0.2) | 0.001 |
| Chemotherapy | 2263 (0.4) | 261 (1.1) | 0.087 | 2429.4 (0.4) | 95.6 (0.4) | 0.006 |
| Radiation therapy | 2176 (0.3) | 425 (1.8) | 0.141 | 2499.9 (0.4) | 91.8 (0.4) | 0.002 |
| Steroids | 9755 (1.5) | 724 (3.0) | 0.101 | 10 089.7 (1.6) | 367.7 (1.6) | 0.003 |
| Smoking | 207 318 (32.6) | 8342 (35.0) | 0.051 | 207 848.6 (32.7) | 7460.8 (33.0) | 0.005 |
| COPD | 71 961 (11.3) | 4785 (20.1) | 0.243 | 73 956.3 (11.6) | 2683.4 (11.9) | 0.007 |
| Obesity | 242 422 (38.1) | 8631 (36.2) | 0.039 | 241 964.0 (38.1) | 8956.4 (39.6) | 0.031 |
| Diabetes | 126 455 (19.9) | 6702 (28.1) | 0.194 | 128 345.1 (20.2) | 4712.6 (20.8) | 0.015 |
| Surgery relative value units | | | | | | |
| <10 | 266 315 (41.9) | 4100 (17.2) | 0.637 | 260 645.7 (41.0) | 9145.8 (40.4) | 0.029 |
| 10-<20 | 214 637 (33.8) | 8127 (34.1) | | 214 672.6 (33.8) | 7502.7 (33.1) | |
| ≥20 | 154 679 (24.3) | 11 587 (48.7) | | 160 270.0 (25.2) | 5990.4 (26.5) | |
| Missing | 40 (<0.1) | 1 (<0.1) | | 39.8 (<0.1) | 0.7 (<0.1) | |
| Emergent surgery | 25 412 (4.0) | 2710 (11.4) | 0.280 | 27 094.3 (4.3) | 1042.4 (4.6) | 0.017 |
| Operating duration quartile | | | | | | |
| First (lowest) | 163 647 (25.7) | 2902 (12.2) | 0.529 | 160 543.4 (25.3) | 5835.2 (25.8) | 0.026 |
| Second | 161 766 (25.4) | 4366 (18.3) | | 160 111.1 (25.2) | 5458.7 (24.1) | |
| Third | 161 956 (25.5) | 5763 (24.2) | | 161 634.4 (25.4) | 5765.1 (25.5) | |
| Fourth (highest) | 148 302 (23.3) | 10 784 (45.3) | | 153 339.3 (24.1) | 5580.6 (24.6) | |
| Preoperative serum albumin quartile | | | | | | |
| First (lowest) | 92 228 (14.5) | 7672 (32.2) | 0.464 | 96 255.9 (15.1) | 3566.5 (15.8) | 0.022 |
| Second | 140 182 (22.1) | 5475 (23.0) | | 140 389.6 (22.1) | 5079.0 (22.4) | |
| Third | 82 560 (13.0) | 2572 (10.8) | | 82 055.0 (12.9) | 2858.8 (12.6) | |
| Fourth (highest) | 136 372 (21.5) | 3692 (15.5) | | 135 010.0 (21.2) | 4706.1 (20.8) | |
| Not known | 184 329 (29.0) | 4404 (18.5) | | 181 917.7 (28.6) | 6429.1 (28.4) | |
| 48-h Preoperation sepsis | 3900 (0.6) | 619 (2.6) | 0.158 | 4344.5 (0.7) | 150.5 (0.7) | 0.002 |
| Open wound/wound infection | 17 375 (2.7) | 1639 (6.9) | 0.195 | 18 319.7 (2.9) | 680.1 (3.0) | 0.007 |

Abbreviations: COPD, chronic obstructive pulmonary disease; IPTW-S, stabilized inverse probability of treatment weighting; NA, not applicable; SMD, standardized mean difference.

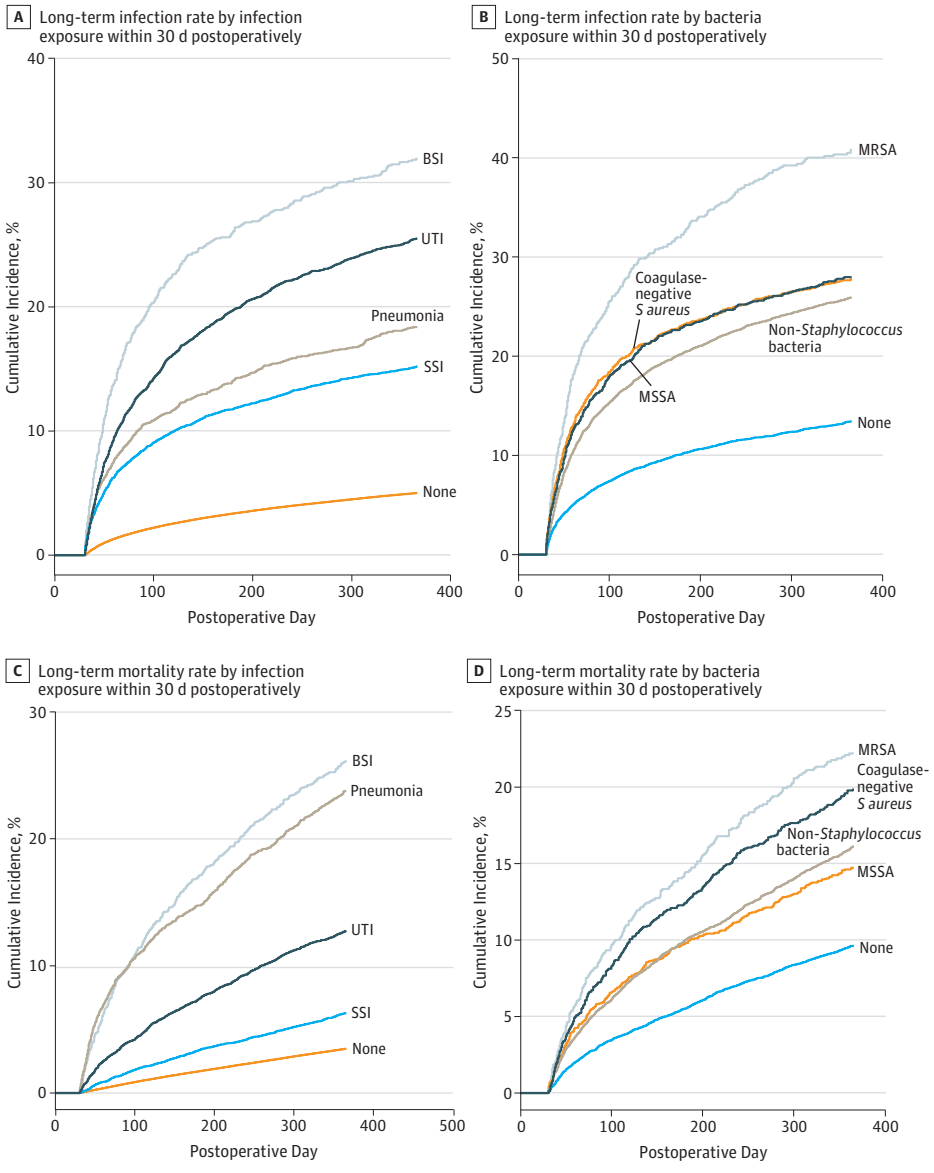
finding is bolstered by the use of inverse-weighted propensity score analysis, a methodology used to emulate randomization in the exposed and unexposed groups and particularly useful for investigations such as this one in which randomization would otherwise be impossible and unethical. By creating cohorts balanced by clinical and surgical risks, we are able to demonstrate the independent association of postoperative infection with long-term outcomes and significantly add to the understanding of the consequences of postoperative infections across surgical procedure types and infection types.

The prevention of postoperative infections is a high priority in clinical practice, as these can lead to increased morbidity, need for reoperation and hospitalization, and, in some cases, mortality.[14] A systematic review of European studies[15] found that SSI was associated with a range of long-term harm to the patient, including prolonged surgical length of stay, rehospitalization, and decreased quality of life. We believe that any causal pathway between early and late infection or mortality would be most likely indirect. For example, the initial infection could cause absence from work, leading to financial hardship, reduced quality of life, and inability to meet medi-

Table 2. Estimated Cox Proportional Hazard Ratios of Infection and Mortality at 1 Year as a Function of Exposure to 30-Day Postoperative Infection

| Long-term Outcome | Hazard Ratio (95% CI) |
|---|---|
| Infection | 3.17 (3.05-3.28) |
| Mortality | 1.89 (1.79-1.99) |

Figure 3. Observed Cumulative Incidence of Infection and Mortality at 1 Year Stratified by Exposure to Infections and Bacteria Within 30 Days Postoperatively




BSI indicates bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SSI, surgical site infection; UTI, urinary tract infection.

cal needs,[16] leading to poor outcomes. A 2008 Australian study[17] found that patients with infection following hip and knee surgery experienced reduced mobility and independence as well as worsened psychological health.

While there is little prior literature on the occurrence of long-term infection, our results are comparable with previous work describing the risk of mortality. In a 2013 Canadian study of patients with lung cancer undergoing surgery with curative intent,[18] the 5-year survival rate in patients with any postoperative infectious complication was 62.8% compared with 73.8% in those without a complication ($P < .001$). A large population-based Veterans Affairs (VA) study[19] described increased risk of long-term mortality in veterans who had deep wound infection (odds ratio, 1.1; 95% CI, 1.1-1.2) and pneumonia (odds ratio, 1.3; 95% CI, 1.2-1.5). In a study of 211 patients undergoing colorectal resection for cancer,[20] postoperative infection was associated with increased risk of 5-year mortality (hazard ratio, 2.13; 1.18-3.83). Another colorectal surgery study[21] found a 1-year mortality rate of 13% in patients with postoperative infection compared with 4% in those without ($P = .04$). Finally, in propensity-matched patients who underwent cardiac surgery, the adjusted 1-year survival rate in those with postoperative infection was 83% compared with 86% in those without ($P = .008$).[22]

## Strengths and Limitations

This study has several notable strengths. The large data set of medical record–reviewed procedures allowed us to perform statistical inference on an exposure that has a low baseline incidence. The national database of laboratory microbiology results allowed for an automated assessment of the outcome using a previously validated algorithm. The VA is one of the few organizations where such a study can be performed.

The study also has several limitations. Like most VHA population studies, most participants were men; therefore our results may lack external validity for other populations. We made a simplifying assumption of homogeneity of the exposure, ie, the models did not account for the likely additional harm of an organ/space SSI relative to a superficial SSI or UTI. Modeling a heterogenous effect, perhaps with a multinomial propensity score or even taking into account the effect of different bacteria species cultured in the postoperative infection, is an interesting question but would be difficult—even in our large population—given the low baseline exposure rate (ie, the curse of dimensionality). It is possible that we are undercounting long-term infections in cases where the patient was treated at hospitals outside the VA, as we do not have access to non-VA data. We also do not control for postexposure confounders that might have a causal relationship with long-term infection or mortality, as this is limited by our data sources and retrospective study design. Although we attempted to control for selection bias for the exposure, it is possible that there are other unmeasured or unobservable confounders. Additionally, implicit in the Cox proportional hazards model is the assumption that the ratio of hazards in the 2 groups is constant over time, which may not reflect the true relationship. Visual examination of the Kaplan-Meier curves shows that the groups' curves do not cross and the slopes are reasonably parallel; therefore we believe this risk is minimal.

## Conclusions

The novel contribution of this study is that the occurrence of a postoperative infection, independent of patient characteristics and surgery factors, is associated with increased likelihood of having a subsequent infection and mortality up to 1 year after the initial surgery. The increased harm and cost of long-term infections should be included in the cost-benefit calculus of infection prevention initiatives.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*Acquisition, analysis, or interpretation of data*: All authors.
*Drafting of the manuscript*: O'Brien, Itani.
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*Statistical analysis*: O'Brien.
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