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ORIGINAL ARTICLE

Serious postoperative infections following resection of common solid tumors: outcomes, costs, and impact of hospital surgical volume

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Abstract
Purpose Unlike infections related to chemotherapy-induced neutropenia, postoperative infections occurring in patients with solid malignancy remain largely understudied. Our aim is to evaluate the outcomes and the volume–outcomes relationship associated with postoperative infections following resection of common solid tumors.
Methods We used Texas Discharge Data to study patients undergoing resection of cancer of the lung, esophagus, stomach, pancreas, colon, or rectum from 01/2002 to 11/2006. From their billing records, we identified ICD-9 codes indicating a diagnosis of serious postoperative infection (SPI), i.e., bacteremia/sepsis, pneumonia, and wound infection, occurring during surgical admission or leading to readmission within 30 days of surgery. Using regression-based techniques, we estimated the impact of SPI on mortality, resource utilization, and costs, as well as the relationship between hospital volume and SPI, after adjusting for confounders and data clustering.
Results SPI occurred following 9.4 % of the 37,582 eligible tumor resections and was independently associated with nearly 12-fold increased odds of in-hospital mortality [95 % confidence interval (95 % CI), 7.2–19.5, $P<0.001$]. Patients with SPI required six additional hospital days (95 % CI, 5.9–6.2) at an incremental cost of $16,991 (95 % CI, $16,495–$17,497). Patients who underwent resection at high-volume hospitals had a 16 % decreased odds of developing SPI than those at low-volume hospitals ($P=0.03$).
Conclusions Due to the substantial burden associated with SPI following common solid tumor resections, hospitals must identify more effective prophylactic measures to avert these potentially preventable infections. Additional volume–outcomes research is needed to identify infection prevention processes that can be transferred from high- to lower-volume providers.

Keywords Postoperative infection · Solid tumors · Outcomes

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Introduction

Nosocomial infections remain one of the leading causes of morbidity and mortality among hospitalized patients, affecting about 4.5 % of all U.S. hospital admissions [1] and contributing $4.5 billion in added healthcare costs and 99,000 deaths [1]. Patients with cancer are especially vulnerable to nosocomial infections because of treatment- and disease-related changes in their immune systems. Individuals who undergo extensive tumor resections, in particular involving the respiratory and gastrointestinal (GI) tracts, are at even greater risk of developing nosocomial infections postoperatively [2]. Cancer research has yet to adequately address the occurrence of nosocomial infections among patients undergoing solid tumor resection.

Our aim is to evaluate the clinical and economic burden and the surgical volume–outcomes relationship associated with serious postoperative infection (SPI)—bacteremia/sepsis, pneumonia, and wound infection—following resection of cancer of the lung, esophagus, stomach, pancreas, colon, and rectum, which combined account for nearly 90 % of all respiratory and GI solid tumors (excluding lymphomas) newly diagnosed in the U.S. yearly [3].

Patients and methods

Study population

From the Texas Discharge Research Dataset, we identified all Texas residents 18 years or older who underwent resection of cancer of the lung, esophagus, stomach, pancreas, colon, or rectum between 01/01/2002 and 11/30/2006. This dataset contains claims information of all patients treated in all Texas hospitals, except Veterans Administration and military hospitals. We defined SPI as the presence of an ICD-9 code indicating bacteremia/septicemia, pneumonia, or wound infection in any of the secondary diagnosis fields during surgical admission or in the admitting or principal diagnosis fields of a readmission occurring within 30 days of the eligible resections. We excluded from the study (1) emergency surgical admissions and those having a diagnosis of SPI at admission, to reduce misclassification of pre-existing infections; and (2) patients with history of HIV or alcohol and drug abuse because confidentiality protection measures would not reveal subsequent readmissions. Institutional review boards of the Texas Department of State Health Services and The University of Texas MD Anderson Cancer Center approved the study.

Resource utilization and cost outcomes

Hospital length of stay (LOS) was computed as the number of initial surgical admission days plus subsequent SPI-related readmission within 30 days of surgery. Costs were determined from a provider perspective and derived from hospital charges by applying 2002–2006 Medicare cost-to-charge ratios for Texas and then inflated to 2012 U.S. dollars based on the Consumer Price Index for medical services [4–9].

Hospital surgical volume

Hospital surgical volume was categorized by dividing the data into three volume levels. Hospitals were given a percentile score according to the volume of each type of surgery performed during the 5-year study period, then ranked according to the average of their resection-specific percentile scores, and sorted into the three distinct volume categories by terciles. We adopted this approach, by Birkmeyer et al., to prevent skewing the volume rankings toward the most common procedures [10].

Independent variables

We assessed several patient- and hospital-related factors that may influence SPI outcomes. Patient demographic characteristics included age ≥75 years, gender, and race. We obtained proxy measures of socioeconomic status by linking the patients' residence ZIP codes in the claims data to ZIP code-level data on median family income and percentages of high school graduates and English speakers obtained from the 2000 U.S. Census [11]. These measures are valid proxies of socioeconomic status and are associated with SPI risk [12–15].

Clinical characteristics included (1) type of resection, (2) presence of diabetes mellitus, (3) comorbidity index based on the Dartmouth–Manitoba adaptation of the Charlson comorbidity score for administrative datasets (excluding diabetes and cancer), (3) lymph node involvement, (4) metastatic disease, and (5) concurrent in-hospital complications identified by using the algorithms developed by Iezonni et al. for administrative datasets and included pulmonary compromise, deep venous thrombosis, pulmonary embolism, reoperation of surgical site, postoperative coma or shock, acute myocardial infarction, arrhythmia, and cardiac arrest [16–22].

Hospital-level factors obtained from the 2002–2006 Texas Annual Survey of Hospitals included teaching status, ownership (i.e., for-profit vs. not-for-profit), rate of registered nurses (RN) and licensed practical nurses (LPN) per occupied bed, and availability of airborne infection isolation rooms and wound services. Hospitals located in rural counties, according to the U.S. Office of Rural Health Policy, were classified as rural hospitals [23]. Also identified were the hospitals designated as cancer centers by the National Cancer Institute (NCI) [24].

Statistical analysis

We conducted logistic regression to evaluate the multivariate association between patient- and hospital-level factors and development of SPI, influence of SPI on in-hospital mortality, and the impact of surgical volume on the risk of SPI. The parameters of each of the logistic models were estimated using multilevel mixed-effects logistic regression with two random effects to account for dependence between outcomes of multiple surgical admissions for the same patient and of patients within the same hospital.

We computed estimates of LOS and hospital costs for patients with and without postoperative infection using a mixed-effects generalized linear model, accounting for patient- and hospital-level confounders and including two random effects to account for data clusterings. Because both LOS and medical costs were highly skewed, we fitted a gamma distribution to the data using a log link, as described

by Manning et al. [25]. Excess hospital days and costs were then calculated by subtracting the estimated values for patients without infections from those with infections.

Results

Between 01/2002 and 11/2006, a total of 37,582 resections were performed on 37,064 eligible patients. The study population was predominantly non-Hispanic white (71 %), male (52 %), Medicare beneficiaries (58 %), and lived in ZIP codes with incomes above the national median (55 %); 29 % were 75 years or older and 35 % had at least one comorbidity other than cancer or diabetes (Table 1). Colon resection accounted for nearly 48 % of the procedures, lung resection for 26 %, rectal resection for 17 %, gastrectomy for 6 %, pancreas resection for 3 %, and esophagectomy for 1 % (Table 1).

Risk of SPI

As shown in Table 2, SPI occurred following 3,522 solid tumor resections (9.4 %), and SPI risk varied by resection site: esophagus (25 %), stomach (19 %), pancreas (17 %), lung (10 %), rectum (8 %), and colon (7 %). Pneumonia alone accounted for 43 % of the SPI episodes, wound infection alone for 28 %, and bloodstream infections alone for 16 %. Bacteremia/septicemia was often accompanied by pneumonia (6 % of SPI episodes) or wound infection (4 % of SPI). Pneumonia combined with wound infection, or the three infections together, accounted respectively for only 1.5 % and 1.2 % of SPI episodes. Of the 37,582 surgical admissions, 736 (2 %) were followed by infection-related readmissions; 57 % were due to wound infection, 30 % pneumonia, and the remaining 13 % to bloodstream infection. The risk of SPI-related readmission also varied by cancer site: pancreas (4.0 %), stomach (2.8 %), rectum (2.3 %), lung (1.7 %), colon (1.6 %), and esophagus (1.2 %; Table 2).

Predicting factors for SPI

In logistic regression, patient age ≥75 years was associated with a 12 % increase in the odds of developing SPI compared with patients younger than 75 (Table 3). Men showed a 30 % increased odds of developing SPI relative to women, whereas Hispanics had increased odds of 22 % when compared to whites. In addition, the odds of postoperative infections were increased nearly 5-fold for every additional perioperative complication and by 48 % for every point increase in comorbidity score. Relative to segmentectomy of the lung (the baseline comparator), the odds of developing SPI varied substantially by type of resection, from 26 % increased odds following rectal resection to over 5-fold increased odds following total esophagectomy. Patients with distant metastasis had 24 % increased odds of developing SPI relative to those with no coding for metastasis. Patients who had Medicare or a commercial insurance plan, or resided in ZIP codes in which the level of

Table 1 Baseline characteristics of patients (N=37,582)

Characteristic	N (%)
Age (years)	
<74	26,648 (71 %)
≥75	10,934 (29 %)
Gender	
Female	18,111 (48 %)
Male	19,471 (52 %)
Race	
Non-Hispanic whites	26,669 (71 %)
Hispanics	5,294 (14 %)
African-Americans	3,428 (9 %)
Others	2,191 (6 %)
Charlson comorbidity score	
0	24,518 (65 %)
≥1	13,064 (35 %)
Type of resection	
Lung resection	9,891 (26 %)
Esophagectomy	265 (1 %)
Gastrectomy	2,107 (6 %)
Pancreas resection	1,211 (3 %)
Colon resection	17,877 (48 %)
Rectal resection	6,231 (17 %)
Diabetes status	
No diabetes	31,215 (83 %)
Diabetes	6,367 (17 %)
Lymph node involvement	
No	28,275 (75 %)
Yes	9,307 (25 %)
Distant metastasis	
No	31,991 (85 %)
Yes	5,591 (15 %)
Health insurance plan	
Medicaid	895 (2 %)
Medicare	21,833 (58 %)
Commercial	12,749 (34 %)
Others	2,037 (5 %)
ZIP code-level household income	
Below national median	16,683 (45 %)
Above national median	20,719 (55 %)
ZIP code-level high school graduates	
Below national median	22,317 (59 %)
Above national median	15,265 (41 %)
ZIP code-level English speakers	
Below national median	19,901 (53 %)
Above national median	17,681 (47 %)

Table 2 Distribution of solid tumor resections followed by serious postoperative infections and related readmissions

Surgical procedure	SPI	
	During surgical admission or subsequent readmission *N* (% of procedures)	SPI-related readmission only *N* (%)
Lung resection	1,020 (10 %)	175 (1.8 %)
Esophagectomy	65 (25 %)	3 (1.1 %)
Gastrectomy	390 (19 %)	60 (2.8 %)
Pancreas resection	210 (17 %)	48 (4.0 %)
Colon resection	1,335 (7 %)	305 (1.8 %)
Rectal resection	502 (8 %)	145 (1.7 %)
All procedures combined	3,522 (9.4 %)	736 (2.0 %)

SPI serious postoperative infection

education is above the national median, had decreased SPI odds compared to those who were Medicaid beneficiaries or lived in areas with low educational status. Among hospital factors, rural and for-profit statuses were the only factors statistically significantly associated with increased odds of SPI development (26 % and 19 %, respectively).

In-hospital mortality

Following the 3,522 resections in which an SPI developed, 464 in-hospital deaths occurred (unadjusted mortality=13 %), whereas 527 deaths were observed during the remaining 34,060 surgical admissions with no SPI (unadjusted mortality=1.5 %). After adjusting for patient and hospital characteristics and data clustering, SPI was independently associated with a nearly 12-fold increase in the odds of in-hospital mortality [OR=11.8; 95 % confidence interval (CI), 7.2–19.5; $P<0.001$].

Resource utilization and costs

After adjusting for confounders and data clustering, LOS for patients with solid tumors who developed SPI was 6.0 days (95 % CI, 5.9–6.2) longer than for those who did not develop such infections (Table 4). SPI was associated with $16,991 of excess hospital costs per episode of infection (95 % CI, $16,495–$17,497; Table 4). Bacteremia/sepsis in combination with wound infection was the most costly of the SPIs, resulting in 11 (95 % CI, 10–13) additional hospital days and $39,742 (95 % CI, $35,339–$44,495) in excess costs (Table 4).

Volume–outcomes relationship

Fifteen hospitals were categorized as high-volume hospitals, 42 as intermediate volume, and 226 as low volume. Patients treated at high-volume hospitals were younger, more likely to be non-Hispanic white, less likely to have comorbidity and diabetes, and more likely to have both lymph node involvement and distant metastasis than those treated at low- or moderate-volume hospitals (Table 5). They were also more likely to live in ZIP codes with above-average income and to be covered by commercial insurance compared to patients treated at low-volume hospitals. Overall, patients treated at hospitals with intermediate surgical volume were relatively similar to those treated by low-volume providers. High-volume hospitals performed proportionally more resections of the lung, esophagus, stomach, and pancreas, but fewer colon resections than lower-volume hospitals. High-volume hospitals were more likely to be teaching hospitals, NCI-designated cancer centers, to have isolation rooms and wound services, and less likely to be rural when compared to low-volume providers (Table 5). They also had a higher RN-to-occupied bed rate, but a lower LPN-to-occupied bed rate. Overall, the distribution of the characteristics of the intermediate-volume hospitals fell in between high- and low-volume providers.

After adjusting for confounders and clustering, there was a significant decrease of 16 % in the SPI odds associated with high-volume hospitals (OR=0.84; 95 % CI, 0.72–0.98; $P=0.03$) and a non-significant 6 % odds decrease for intermediate volume (OR=0.94; 95 % CI, 0.83–1.05; $P=0.26$) when compared to low-volume hospitals.

Discussion

Our findings show that SPI is a frequent and costly complication of respiratory and GI tumor resection, occurring following nearly 10 % of all such resections and resulting in substantial mortality and excess costs. Patients at increased odds of developing SPI are 75 years or older, male, Hispanic, have other comorbidities or postoperative complications, distant metastasis, or undergo surgery in rural or for-profit hospitals. Patients undergoing resections at high-volume hospitals have a lower overall risk of developing SPI than patients treated at low-volume hospitals.

Our estimates of costs associated with SPI development following solid tumor resections suggest that these infections add a significant economic burden to U.S. healthcare providers. Given that U.S. hospitals are commonly reimbursed by third-party payers prospectively based on diagnosis-related groups (DRG), the occurrence of such infections results in millions of lost dollars to healthcare providers [26, 27]. According to Haley et al., only 5–18 % of the 9,423 nosocomial infections analyzed were found to lead the hospital admission to be reclassified to a higher-paying DRG [27]. Adding to that, only a small fraction (5 %) of the costs incurred by providers were covered by the extra payment resulting from the reclassification, leaving much of the financial burden of treating nosocomial infections to hospitals [27]. Of important note is that a large proportion of this burden may be averted as it has been estimated that 20 to 80 % of hospital-

Table 3 Predictors of serious postoperative infection following resection of respiratory and gastrointestinal solid tumors

Characteristic	Serious postoperative infection		
	Odds ratio	95 % Confidence interval	*P* value
Age (years)			
<75			
≥75	1.12	1.00–1.25	0.05
Gender			
Female			
Male	1.30	1.18–1.43	<0.001
Race			
Non-Hispanic whites			
African-Americans	1.17	0.99–1.38	0.07
Hispanics	1.22	1.06–1.41	0.01
Others	1.13	0.93–1.39	0.21
Charlson comorbidity score	1.48	1.38–1.59	<0.001
Number of other perioperative complications	4.58	3.82–5.51	<0.001
Multiple resections in the same tract			
Initial surgical procedure			
Subsequent surgical procedure	1.23	0.86–1.78	0.26
Diabetes status			
No diabetes			
Diabetes	0.92	0.81–1.04	0.17
Lymph node involvement			
No			
Yes	1.04	0.94–1.16	0.46
Distant metastasis			
No			
Yes	1.24	1.09–1.40	<0.001
Payer			
Medicaid			
Medicare	0.75	0.57–0.99	0.05
Commercial	0.64	0.49–0.85	0.002
Others	0.75	0.54–1.04	0.08
ZIP code-level household income			
Below national median			
Above national median	1.08	0.95–1.23	0.22
ZIP code-level high school graduates			
Below national median			
Above national median	0.85	0.75 – 0.97	0.01
ZIP code-level English speakers			
Below national median			
Above national median	1.03	0.93–1.14	0.55
Hospital's teaching status			
Non-teaching hospital			
Teaching hospital	0.90	0.75–1.07	0.24
Hospital's rural status			
Non-rural hospital			
Rural hospital	1.26	1.01–1.57	0.04
NCI designation			
Non NCI-designated cancer center			
NCI-designated cancer center	1.22	0.83–1.78	0.31

Table 3 (continued)

Characteristic	Serious postoperative infection		
	Odds ratio	95 % Confidence interval	*P* value
Hospital's profit-seeking status			
Not-for-profit			
For-profit	1.19	1.04–1.35	0.01
Availability of airborne isolation rooms			
No			
Yes	0.90	0.77–1.04	0.17
Availability of wound management services			
No			
Yes	0.98	0.87–1.12	0.83
RN staffing			
Low RN-to-occupied bed ratio			
High RN-to-occupied bed ratio	0.98	0.88–1.09	0.72
LVN staffing			
Low LVN-to-occupied bed ratio			
High LVN-to-occupied bed ratio	1.00	0.88–1.12	0.96

acquired infections are preventable, with approximately one third potentially prevented by merely adhering to established infection control guidelines [28, 29].

To the best of our knowledge, this is the first population-based study to describe the outcomes and volume–outcomes relationship associated with three of the most common and serious types of hospital-acquired infections in this patient population. This study is also the first to include infection-related readmissions occurring within 30 days of surgery. Other population-based studies have focused on a single infection diagnosis and relied on a broad cross-section of cancer and non-cancer patients, and the few ones to explore volume–outcomes relationship have solely focused on postoperative wound infection [30–39]. Our results are consistent with findings from another population-based study conducted by Thompson et al., which exclusively focused on the outcomes of postoperative pneumonia occurring during admissions for elective intra-abdominal surgeries in the general population [34]. In their study, pneumonia occurred following 1,511 (8.0 %) of the 18,838 gastrectomies and 5,446 (2.1 %) of the 259,338 colorectal resections analyzed. In our study, the risk of postoperative pneumonia following gastrectomy and colorectal resection were 10 and 2.7 %, respectively [34].

Our study has several limitations. We used hospital discharge data, which are based on claims for reimbursement, and as such are subject to coding errors. As a result, we may have underestimated the rate of SPI-related readmission since a diagnosis other than infection might have been coded as the admitting diagnosis for optimization of reimbursement. In addition, by exclusively analyzing in-hospital deaths, we have probably underestimated the real impact of SPI on mortality, as we were not able to analyze the deaths occurring after hospital discharge. By omitting costs incurred by patients, such as deductibles and other non-covered expenses, and by excluding indirect costs such as the costs of productivity loss associated with longer hospital stays and infection-related

Table 4 Excess resources and costs associated with serious postoperative infections overall and by type of infection following resection of solid tumors

Type of infection	Excess hospital bed days[a] Mean (95 % CI)	Excess costs[a] (2012 US$) Mean (95 % CI)
Any serious postoperative infection	6.0 (5.9–6.2)	$16,991 ($16,495–$17,497)
Pneumonia alone	3.7 (3.3–3.9)	$10,187 ($9,496–$10,900)
Wound infection alone	5.8 (5.5–6.2)	$11,256 ($10,422–$12,122)
Bacteremia/sepsis alone	6.0 (5.4–6.5)	$20,639 ($19,070–$22,280)
Bacteremia/sepsis and pneumonia	7.1 (6.2–8.0)	$19,362 ($17,175–$21,705)
Bacteremia/sepsis and wound infection	11.3 (10.0–12.8)	$39,742 ($35,339–$44,495)
Pneumonia and wound infection	11.6 (9.5–13.9)	$25,727 ($20,785–$31,318)
Bacteremia/sepsis, pneumonia, and wound infection	13.0 (10.3–16.1)	$33,868 ($27,039–$41,730)

CI confidence interval

[a] Adjusted for patient and hospital factors and accounting for clustering of surgical admissions within the same patient and of patients within hospitals

Table 5 Characteristics of patients and hospitals across different surgical volume groups

Characteristic	Surgical volume terciles			*P* value
	Low volume	Intermediate volume	High volume	
Patient characteristic (%)				
Age ≥75 years	32 %	30 %	26 %	<0.001
Male	52 %	52 %	51 %	0.29
Non-Hispanic white	69 %	68 %	76 %	<0.001
African-American	9 %	8 %	10 %	<0.001
Hispanic	16 %	18 %	8 %	<0.001
Charlson comorbidity score >1	46 %	46 %	43 %	<0.001
Diabetes	18 %	17 %	15 %	<0.001
Lymph node involvement	23 %	25 %	27 %	<0.001
Distant metastasis	14 %	16 %	15 %	<0.001
Concomitant complications	11 %	12 %	11 %	0.01
ZIP code-level household income above U.S. median	52 %	51 %	62 %	<0.001
ZIP code-level high school graduates above U.S. median	37 %	39 %	46 %	<0.001
ZIP code-level English speakers above U.S. median	51 %	42 %	48 %	<0.001
Medicaid	3 %	3 %	2 %	<0.001
Medicare	60 %	60 %	54 %	<0.001
Commercial	30 %	31 %	40 %	<0.001
Others	6 %	5 %	5 %	<0.001
Lung resection	20 %	27 %	32 %	<0.001
Esophagectomy	0.3 %	0.7 %	1.1 %	<0.001
Gastrectomy	5 %	6 %	7 %	<0.001
Pancreas resection	1 %	2 %	6 %	<0.001
Colon resection	58 %	48 %	37 %	<0.001
Rectal resection	15 %	17 %	17 %	<0.001
Hospital characteristic (%)				
Teaching hospital	4 %	10 %	56 %	<0.001
NCI-designated cancer centers	1 %	2 %	14 %	<0.001
Rural hospital	4 %	2 %	0 %	<0.001
Isolation rooms	79 %	85 %	89 %	<0.001
Wound services	62 %	75 %	91 %	<0.001
High RN-to-occupied bed rate	40 %	46 %	63 %	<0.001
High LVN-to-occupied bed rate	65 %	54 %	30 %	<0.001

deaths, we have underestimated the true economic burden of SPI following resection of solid tumors. Additionally, since administrative datasets do not supply information on important processes of care provided perioperatively, such as patterns of prophylactic antibiotic and respiratory therapy use, we were unable to adequately account for these factors to assess the possible mechanisms underlying the volume–outcomes relationship for SPI development. Furthermore, administrative data also lack detailed clinical information such as obesity level and in-hospital surgical delay, which have both been shown to be associated with increased risk of postoperative infection [40, 41]. Finally, clinical characteristics that affect susceptibility to infection among cancer patients, such as history of prior treatment with chemotherapy and radiation therapy, are also not attainable with claims-based inpatient data. Nevertheless, it is worth noting that since patients treated at high-volume hospitals were more likely to have more advanced disease, they might have been more likely to have a history of prior immunosuppressive cancer therapy. If that is the case, failure to adequately adjust for such a risk factor may have led to an underestimated effect of surgical volume on the risk of SPI. Future studies with clinical data sources are necessary to refine the predictors of postoperative infection presented herein. In addition, to elucidate the mechanisms underlying the volume–outcomes relationship for postoperative infection found in our study, emphasis should be given to the role played by

measurable and well-established preventive measures such as administration of prophylactic antibiotics within 60 min prior to surgery, appropriate selection of prophylactic antibiotic regimen, and use of respiratory therapy perioperatively.

Conclusions

Serious postoperative infection is a frequent, deadly, and costly complication of respiratory and GI tumor resection. Patients undergoing resections at high-volume hospitals have a lower risk of developing SPIs than those at low-volume hospitals. Under current reimbursement practices, most of this heavy burden is borne by hospitals. Averting preventable infections following solid tumor resections and the associated financial burden will require hospitals to comply with established infection control guidelines and to identify more cost-effective prophylactic measures. Further volume–outcomes research incorporating additional patient-level risk factors and patterns of infection prevention processes is warranted. A better understanding of the mechanisms underlying the volume–outcomes relationship for SPI could lead to improved outcomes if future research identifies infection prevention processes that can be transferred from high- to low-volume providers.

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