Incidence and Predictors of Surgical Site Infection Complications in Diabetic Patients Undergoing Lower Limb Amputation

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Background: Surgical site infections (SSIs) following lower extremity amputations (LEAs) are a major cause of patient morbidity and mortality. The objectives of this study are to investigate the annual incidence of SSI and risk factors associated with SSI after LEA in diabetic patients.
Methods: LEAs performed on diabetic patients between 2005 and 2017 were retrospectively analyzed from the American College of Surgeons National Surgical Quality Improvement Program database. Incidence rates were calculated and analyzed for temporal change. Multivariable logistic regression was conducted to identify the independent predictors of SSIs in LEA.
Results: In 21,449 diabetic patients, the incidence of SSIs was 6.8% after LEA, with an overall decreasing annual trend ($P = 0.013$). Amputation location (below-knee in reference to above-knee) [OR (95% CI): 1.35 (1.20 – 1.53), $P < 0.001$], smoking [OR (95% CI): 1.25 (1.11 – 1.41), $P < 0.001$)], female sex [OR (95% CI): 1.16 (1.03 – 1.30)], preoperative sepsis [OR (95% CI): 1.24 (1.10 – 1.40), $P < 0.001$], $P = 0.013$], emergency status [OR (95% CI): 1.38 (1.17 – 1.63), $P < 0.001$], and obesity [OR (95% CI): 1.59 (1.12 – 2.27), $P = 0.009$] emerged as independent predictors of SSIs, while moderate/severe anemia emerged as a risk-adjusted protective factor [OR (95% CI): 0.75 (0.62 – 0.91), $P = 0.003$]. Sensitivity analysis found that moderate/severe anemia, not body mass index (BMI) class, remained a significant risk factor in the development of SSIs in below-the-knee amputations; in contrast, higher BMI, not preoperative hematocrit, was significantly associated with an increased risk for SSI in above-the-knee amputations.
Conclusions: The incidence of SSIs after LEA in diabetic patients is decreasing. Overall, below-knee amputation, smoking, emergency status, and preoperative sepsis appeared to be associated with SSIs. Obesity increased SSIs in above-the-knee amputations, while moderate/severe preoperative anemia appears to protect against below-the-knee SSIs. Surgeons should take predictors of SSI into consideration while optimizing care for their patients, and future studies should investigate the role of preoperative hematocrit correction and how it may influence outcomes positively or negatively.

INTRODUCTION

Surgical site infections (SSIs) remain a major cause of patient morbidity and mortality that also impose substantial financial burden on the healthcare system despite improvements in infection control techniques in surgical practice.[1] SSIs, classified as infections arising from either incisional sites or deeper within organs/spaces after surgery are associated with a 3% mortality rate.[2,3] It is estimated that SSIs result in almost

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one million additional days of hospitalization per year, increasing the annual cost by more than three billion USD.[4,5]

Lower extremity amputation is a surgical procedure entailing high rates of postoperative morbidity, with mortality reaching up to 16% in recent reports.[6,7] Wound-related complications remain especially prominent following lower extremity amputations. [8] Diabetic patients are a particularly vulnerable population, with a higher incidence of amputations due to several indications including critical limb ischemia, diabetic foot ulcers, and gangrene.[9] In this population, SSIs not only increase the risk for mortality, but also can lead to impaired wound healing and consequently complications in prosthesis fitting.[10] This impairs the functionality of amputees and increases their dependency, which further increases long term mortality.[11,12]

Previous studies have shown an association between different preoperative factors and increased incidence of SSIs in major non-cardiac surgeries.[13,14] In LEA studies, factors such as level of amputation, disposition, smoking, body mass index (BMI), and age were found to be associated with occurrence of SSI.[8,15,16] However, these old studies came from single centers or were limited by the number of patients included, limiting their generalizability and their ability to perform risk-adjusted analysis. Hence, a contemporary analysis of a large-scale sample reflecting newer surgical and infectious control practices is needed.

Herein, we sought to investigate the nationwide temporal incidence of SSIs after lower extremity amputation, and elucidate the roles of various pre-operative factors in the development of SSIs after major lower limb amputation surgery using a large, validated database.

METHODS

Study Population

The validated American College of Surgeons National Surgical Quality Improvement Program database was used (ACS-NSQIP) for this study. Diabetic patients undergoing major lower extremity amputation (LEA) surgery between 2005 and 2017 were identified using the Current Procedural Terminology (CPT) codes for transfemoral (27590 and 27591) and transtibial (27880 and 27881) amputations. Patients undergoing re-amputations or guillotine amputations were not included. This study was exempted by the Institutional Review Board (IRB) at the American University of Beirut.

Primary Outcome and Associated Risk Factors

In this study, SSI was defined as a superficial (skin and subcutaneous tissue), deep (muscle and fascia) or organ/space infection within 30 days after surgery. Pre- and intra-operative variables studied included: age, sex, race, BMI class, preoperative hematocrit level, smoking, chronic steroid use, congestive heart failure (CHF), myocardial infection (MI), chronic obstructive pulmonary disease (COPD), dialysis, preoperative sepsis, amputation location (above-the-knee or below-the-knee), emergency surgery, and 30-day post-operative mortality. Hematocrit levels were classified, according to previous studies, into three sub-categories: normal (≥39% for men and ≥36% for women), mild anemia (hematocrit >29 – <39% for men and >29 – <36% for women), and moderate to severe (≤29% for men and women).[17,18] Additionally, BMI was classified, as per World Health Organization definition, into 3 categories: underweight (BMI <18.5 kg/ m^2), normal/overweight (BMI ≥18.5 kg/m^2 to <30 kg/ m^2), and class I/II/III obese (BMI ≥30 kg/ m^2) [19].

Statistical Analysis

Counts with percentages and means with standard deviations were used as summary statistics for categorical and continuous variables respectively. A Chi-square test was used to compare categorical variables. A multivariable logistic regression was performed to identify the independent predictors of SSI after LEA. The variables included were age, sex, BMI, hematocrit levels, smoking, COPD, CHF, MI, hypertension, dialysis, open wound, steroids, emergency status, sepsis, and amputation level. A sensitivity analysis with an additional multivariable logistic regression was performed by stratifying below and above knee amputations to elucidate the independent predictors specific to each procedure. Risk-adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated for all predictors using a backward conditional method. Furthermore, a sensitivity analysis was performed to stratify above and below knee amputations. A 2-tailed P-value < 0.05 was used to determine statistical significance. For trends, annual incidence rate analysis was performed using the Joinpoint regression model (Joinpoint 4.7.0.0). Statistical analysis was performed using the IBM SPSS statistical package (version 25, IBM Corp., Armonk N.Y., USA).

Table I. Demographic and pre-operative characteristics of the total study population and further stratified by level of amputation on univariable analysis.

Variable		Overall $n = 21449$ (%)	BKA $n = 13608$ (%)	AKA $n = 7841$ (%)	*P*-value
Age	Less than 65 years	9757 (45.5)	7099 (52.2)	2658 (33.9)	<0.001
	65 years and above	11692 (54.5)	6509 (47.8)	5183 (66.1)	
Sex	Male	13798 (64.3)	9363 (68.8)	4435 (56.6)	<0.001
Race	White	13002 (60.6)	8450 (62.1)	4552 (58.1)	<0.001
	Black	5832 (27.2)	3455 (25.4)	2377 (30.3)	
	Other	771 (3.6)	493 (3.6)	278 (3.5)	
	Unknown	1844 (8.6)	1210 (8.9)	634 (8.1)	
Body Mass Index	Underweight	757 (3.7)	333 (2.5)	424 (5.7)	<0.001
	Normal/Overweight	12102 (58.4)	7415 (56.1)	4687 (62.6)	
	Obese I/II/III	7853 (37.9)	5474 (41.4)	2379 (31.8)	
Hematocrit levels	Normal	2129 (10.0)	1213 (9.0)	916 (11.8)	<0.001
	Mild/Moderate Anemia	10832 (51.1)	6760 (50.3)	4072 (52.6)	
	Severe Anemia	8231 (38.8)	5479 (40.7)	2752 (35.6)	
Functional Status	Independent	12001 (56)	8780 (64.5)	3221 (41.1)	<0.001
	Partially Dependent	6949 (32.4)	4018 (29.5)	2931 (37.4)	
	Totally Dependent	2499 (11.7)	810 (6.0)	1689 (21.5)	
Smoking within 1 year		5138 (24)	3191 (23.4)	1947 (24.8)	0.022
Chronic Obstructive Pulmonary Disease		2387 (11.1)	1301 (9.6)	1086 (13.9)	<0.001
Congestive Heart Failure		1934 (9.0)	1161 (8.5)	773 (9.9)	0.001
Myocardial Infarction		466 (2.2)	259 (1.9)	207 (2.6)	<0.001
Percutaneous Coronary Intervention		1489 (6.9)	928 (6.8)	561 (7.2)	0.352
Hypertension		18705 (87.2)	11767 (86.5)	6938 (88.5)	<0.001
Dialysis		5254 (24.5)	3335 (24.5)	1919 (24.5)	0.956
Open Wound		16063 (74.9)	10385 (76.3)	5678 (72.4)	<0.001
Preoperative Sepsis		6302 (29.4)	3753 (27.6)	2549 (32.5)	<0.001
Emergency Case		2304 (10.7)	1361 (10.0)	943 (12.0)	<0.001
Steroids		1261 (5.9)	864 (6.3)	397 (5.1)	<0.001

BKA, Below Knee Amputation; AKA, Above Knee Amputation

RESULTS

Study Population

A total of 34,771 patients who underwent LEA were identified using the ACS-NSQIP database between 2005 and 2017. A final study population of 21,449 patients was analyzed after excluding non-diabetic patients ($n = 13,322$). Among this population, 64.3% ($n = 13,798$) patients were male, and the mean age (SD) was 66.0 (± 12.5). Ten percent of patients ($n = 2,129$) had a normal hematocrit level, 51.1% ($n = 10,832$) had mild anemia, and 38.8% ($n = 8,231$) had moderate/severe anemia. For BMI class, 3.7% ($n = 757$) patients were classified as underweight, 58.4% ($n = 12,102$) were normal/overweight, and 37.9% ($n = 7,853$) were class I/II/III obese. In addition, 24.0% ($n = 5,138$) of patients were smokers while 5.9% ($n = 1.261$) were taking steroids chronically. Of the LEAs, 63.4% ($n = 13,608$) patients underwent a BKA while 36.6% ($n = 7,841$) underwent AKA. The amputation was an emergency in 10.7% ($n = 2,304$) of cases. Table I summarizes the demographic, clinical, and operative characteristics of all patients as stratified by amputation level.

Operative Outcomes and Annual Incidence Rates of SSIs

The overall 30-day postoperative mortality was 8% ($n = 1712$). The incidence of postoperative cardiac arrest and myocardial infarction were 2.4% ($n = 512$) and 1.8% ($n = 388$) respectively, while the postoperative renal failure rate was 1.4% ($n = 297$). Superficial, deep, and organ space SSI rates were 3.9% ($n = 841$), 2.3% ($n = 484$), and 0.7% ($n = 143$) respectively. Patients undergoing AKA had significantly higher rates of postoperative mortality (P <0.001), cardiac arrest (P <0.001), and pneumonia (P <0.001) while patients undergoing BKA had significantly higher rates of superficial ($P = 0.005$) and deep SSI ($P = 0.001$) (Table II).

The overall incidence of SSIs in the study period was 6.8% ($n = 1,450$). Between 2005 and 2017, there was an overall decrease in the incidence of

Table II. Incidence of operative outcomes stratified by amputation location on univariable analysis.

Outcome	Overall *n* = 21449 (%)	BKA *n* = 13608 (%)	AKA *n* = 7841 (%)	*P*-value
Death	1712 (8.0)	734 (5.4)	978 (12.5)	<0.001
Superficial SSI	841 (3.9)	572 (4.2)	269 (3.4)	0.005
Deep SSI	484 (2.3)	342 (2.5)	142 (1.8)	0.001
Organ Space SSI	143 (0.7)	95 (0.7)	48 (0.6)	0.456
Wound Disruption	344 (1.6)	270 (2.0)	74 (0.9)	<0.001
Pneumonia	873 (4.1)	461 (3.4)	412 (5.3)	<0.001
Pulmonary Embolism	88 (0.4)	39 (0.3)	49 (0.6)	<0.001
Renal Failure	297 (1.4)	200 (1.5)	97 (1.2)	0.160
Cardiac Arrest	512 (2.4)	274 (2.0)	238 (3.0)	<0.001
Myocardial Infarction	388 (1.8)	238 (1.7)	150 (1.9)	0.385

BKA, Below Knee Amputation; AKA, Above Knee Amputation; SSI, Surgical Site Infection

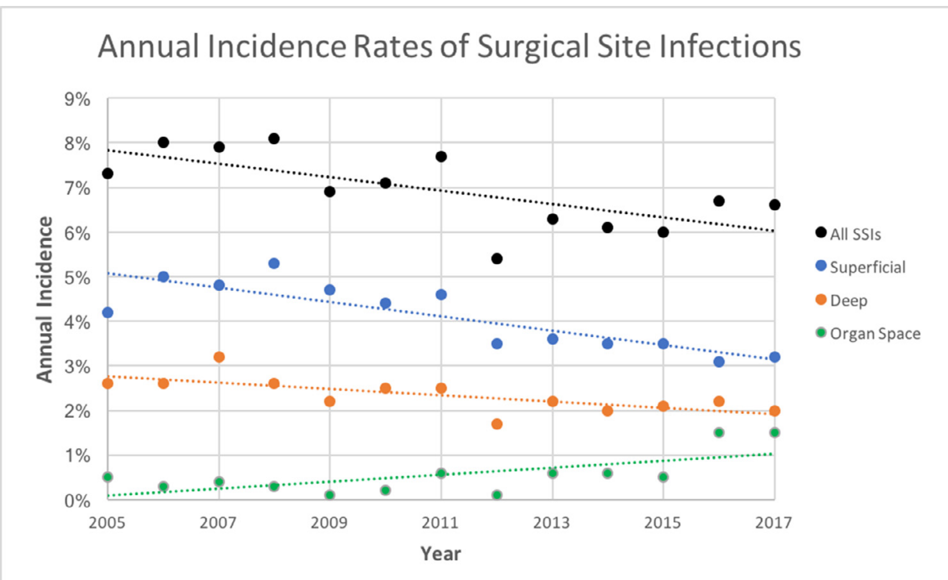

Fig. 1. Annual incidence rate of surgical site infections in diabetic patients after lower extremity amputation from 2005 to 2017 stratified by type.

SSIs (Fig. 1) ($P = 0.013$). After stratification by SSI type, superficial SSIs ($P < 0.001$) and deep SSIs ($P < 0.001$) were noted to have an overall decreasing annual trend while organ space SSIs did not have a significant trend ($P = 0.069$) (Supplement Table S1).

Predictors of SSI

On multivariable analysis, BKA (as opposed to AKA) [OR (95% CI): 1.35 (1.20 – 1.53), $P < 0.001$], smoking [OR (95% CI): 1.25 (1.11 – 1.41), $P < 0.001$), female sex [OR (95% CI): 1.16 (1.03 – 1.30)], preoperative sepsis [OR (95% CI): 1.24 (1.10 – 1.40), $P < 0.001$], and emergency status [OR (95% CI): 1.38 (1.17 – 1.63), $P < 0.001$] were associated with higher odds of SSI (Table III). Higher BMI was also associated with increased odds of developing a SSI, specifically patients with class I-III obesity [OR (95% CI): 1.60 (1.12 – 2.27), $P = 0.009$]. Lower hematocrit levels were associated with lower risk of developing SSI. Patients with moderate/severe anemia [OR (95% CI): 0.75 (0.62 – 0.91), $P = 0.003$] had lower odds of SSI as compared to patients without anemia.

A sensitivity analysis was performed by stratifying below and above knee amputations. Interestingly, moderate/severe anemia remained a robust protective factor in the development of SSIs in the BKA group [OR (95% CI): 0.74 (0.58 – 0.93), $P = 0.011$] (Supplement Table S2) while BMI class was no longer significantly associated with SSIs. In the AKA group, higher BMI category

Table III. Risk-adjusted independent predictors of surgical site infection after lower extremity amputation by multivariable logistic regression.

Variable	Adjusted OR (95% CI)	*P*-value
Amputation Location		
AKA	Reference	
BKA	1.354 (1.200 – 1.527)	<0.001
Sex		
Male	Reference	
Female	1.157 (1.032 – 1.298)	0.013
Smoker		
No	Reference	
Yes	1.250 (1.105 – 1.414)	<0.001
Sepsis		
No	Reference	
Yes	1.242 (1.103 – 1.399)	<0.001
Emergency		
No	Reference	
Yes	1.383 (1.172 – 1.631)	<0.001
BMI Category		
Underweight	Reference	
Normal/Overweight	1.384 (0.976 – 1.961)	0.068
Class I/II/III Obese	1.595 (1.121 – 2.268)	0.009
Hematocrit Category		
Normal	Reference	
Mild Anemia	0.932 (0.777 – 1.117)	0.444
Moderate/Severe Anemia	0.753 (0.623 – 0.911)	0.003

BKA, Below Knee Amputation; AKA, Above Knee Amputation

(class I/II/III obese) was significantly associated with an increased risk for SSI [OR (95% CI): 1.79 (1.08 – 2.94), $P = 0.023$)]. Preoperative hematocrit level was not a significant risk factor in this group (Supplement Table S3).

DISCUSSION

Postoperative SSIs remain a substantial burden on everyday surgical care.[1] In this study, we found that the overall annual incidence rate of all SSIs, although decreasing, remains high at 6.8%. The decreasing trend in superficial and deep SSIs after lower limb amputations spanning the study period from 2005 – 2017 may largely be attributed to increased surveillance of bacterial and antibiotic susceptibility and optimizing modifiable risk factors and prophylactic measures.[14] Yet, the finding supports the tenant that SSIs remain highly prevalent and that efforts must continue to further minimize them. Our study leveraged the multi-institutional cohort of diabetic lower limb amputation patients from the ACS NSQIP to further investigate the preoperative risk factors associated with SSIs.

Significant predictors of SSI following LEA included level of amputation, female sex, smoking, preoperative sepsis, emergency status, and obesity. The increased odds of SSI following BKA, as compared to AKA, could be explained by decreased blood perfusion to the more distal parts of the extremity. In addition, as suggested by Hasanadka et al., BKA is in close proximity to the infected foot in cases of gangrene, which tend to occur distally.[15] Moreover, the higher rates of hematoma in BKA makes it more susceptible to infection.[16]

Smoking was also found to be an independent predictor of SSI, consistent with previous studies.[20,21] Substances such as nicotine, nitric oxide, and carbon monoxide inhaled from smoking disrupt the endothelial lining of blood vessels and impair immune response, leading to delayed wound healing and increased susceptibility to infection.[22,23] Emergency status and preoperative sepsis were also independently associated with the occurrence of SSI in LEA. Both conditions place the incision under high risk of infection due to suboptimal preoperative preparation and the increased presence of the infecting organism in the body.

Consistent with previous studies, we found that the risk of developing a SSI increases in a stepwise manner with obesity.[24,25] The etiology of wound complications in obese individuals is multifactorial, involving both local and systemic factors. Locally, factors contributing to poor wound healing include the relative hypo-vascularity of subcutaneous adipose tissue, which may also reduce antibiotic delivery and increase wound tension. Poor skin perfusion also makes obese individuals susceptible to pressure-induced injuries, which can be aggravated by difficulties in repositioning and increased shearing during movement.[26,27] After stratification by amputation location, this trend was significant in the above knee amputation cohort but was no longer apparent in the below knee amputation cohort. This finding, consistent with the study by Hasanadka et al., can be partially explained physiologically by the greater concentration of adipose tissue around the thigh than around the ankles and calves.[15] A second contributory explanation is that the wound size in above-the-knee amputations is larger due to the greater circumference of the limb which requires a larger incision within the less vascularized, more adipose tissue. Accordingly, special considerations in the dosing of antibiotics might be warranted in obese patients undergoing AKA, and further research should investigate the role of increasing the antibiotic dosage in this population.

Surprisingly, we found that preoperative hematocrit level was inversely proportional to the risk of developing an SSI: as the severity of anemia increased, the odds of developing SSI decreased. This contradicts the hypothesis that lower hematocrit levels would cause decreased tissue oxygenation and hence impede wound healing leading to a higher infection rate. In fact, a study that investigated the relationship between hematocrit and gangrene in BKAs found that higher hematocrit was in fact associated with increased risk for insipidus gangrene.[28] Another small study that assessed the predictors of healing after lower limb amputation surgery found that patients with hemoglobin >120 g/L (normal) had a higher risk of wound healing failure compared to patients with hemoglobin <120 g/L.[29] These findings were attributed to one main theory. Higher hematocrit is associated with an increase in blood viscosity which impedes oxygen delivery and inflammatory factors washout in the microvasculature, while lower hematocrit is a product of hemodilution which increases tissue perfusion and oxygen tension. In fact, a relatively high hematocrit is a known risk factor for tissue ischemia.[30,31].Also, hemodilution has been shown to increase blood flow and decrease claudication in patients with peripheral arterial disease.[32] This effect was evident in the BKA group after sensitivity analysis. Perhaps this effect is mitigated in the more proximal AKAs with larger caliber vessels that are less susceptible to occlusion, while accentuated in more distal amputations where much narrower vessels predominate.

Although this study does not allow us to confidently draw conclusions on the necessity of preoperative correction of hematocrit level, it does provide evidence that aggressive preoperative optimization does not carry clear-cut benefits when it comes to SSI prevention in lower limb amputation surgeries. In fact, large meta-analysis by Hill et al. found that an allogenic blood transfusion increases the risk of postoperative bacterial infection.[33] Thus, from a different vantage point, this study supports that finding.

Deploying the international-scale ACS NSQIP database permits for powerful, validated and generalizable studies; however, some limitations persist. The individual patient characteristic are mostly preoperative variables and there is limited intraoperative factors which can influence the post-operative risk of SSI. The database does not capture variables relevant to our discussion such as glycemic control, antibiotics administration and the presence of peripheral vascular disease. Anemia is a major point of discussion in our study and is associated with preoperative blood transfusion which can affect the outcome. Future studies should look at how the correction of preoperative hematocrit may influence outcomes. BMI was used as an indicator of adiposity as opposed to percent body fat. Percent body fat is a better determinant of adiposity and would have been a more accurate representation, however this variable is scarcely screened prior to surgery and was not in the dataset we used in our analysis. Additionally, substantial surgical judgement is used when deciding upon the level of amputation and potential selection bias may exist for AKA based on patient mobility status. Furthermore, due to the large study population, some associations may demonstrate statistical significant but may be clinically insignificant.

CONCLUSION

Although decreasing, annual SSI rates after LEA in diabetic patients remains high. This study found below-the-knee amputation, smoking, obesity, emergency status, and preoperative sepsis to be associated with SSIs. Obesity specifically exacerbates the risk of developing postoperative surgical site infections in patients undergoing above-the-knee but not below-the-knee amputation surgery. Alternatively, lower hematocrit was found to be an unexpected protective factor in developing SSI in below-the-knee amputations. Future studies should further explore novel antibiotics regimens in obese patients undergoing AKA as well as elucidate the role of preoperative hematocrit correction and how it may influence the development of SSI after BKA.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.avsg.2021.09.040.

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