学位論文

「Preoperative sepsis is a predictive factor for 30-day mortality after major lower limb amputation among patients with arteriosclerosis obliterans and diabetes」

（術前敗血症は、閉塞性動脈硬化症と糖尿病性足壊疽患者の下肢切断術後 30 日死亡率の予測因子である）

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

Abstract

Background: While many patients with lower limb ischemia also have severe infections, few studies have investigated whether the presence of preoperative sepsis affects patient prognosis following lower limb amputation (LLA). Therefore, we investigated the factors (including sepsis as defined in SEPSIS-3) that contribute to the acute mortality rate in patients who underwent LLA due to arteriosclerosis obliterans (ASO) or diabetes mellitus (DM). Methods: In this retrospective, single-center, 10-year chart review study, 122 adult 9 patients who underwent LLA due to ASO and/or DM were identified from 56,438 surgery cases. Patient characteristics, including co-morbidities, surgical conditions, the presence/absence of sepsis, and acute physiological condition after surgery, were investigated in patients who died within 30 days of LLA and those who survived. Univariate analysis between groups was performed using the chi-square test. Comparisons of age and American Society of Anesthesiologists-Physical Status classification between groups were performed using the Mann-Whitney U test. Risk factors for 30-day mortality after LLA were examined using stepwise logistic regression (backward elimination). Statistical results were considered significant at $P<0.05$. Results: Eight cases of mortality (6.6%) were found; we identified the causes as sepsis, myocardial infarction, fatal arrhythmia, and mesenteric artery occlusive disease in 5 (62.5%), 1 (12.5%), 1 (12.5%), and 1 (12.5%) cases, respectively. Using univariate analysis, we identified that age (≥74), delirium, sepsis, intensive care unit admission, non-DM (ASO only), hemodialysis, and acute kidney injury were significantly higher in the mortality group. In logistic regression analysis, non-DM (odds ratio [OR]: 35.2, 95% confidence interval [CI]: 2.8-432) and sepsis (OR: 80.7, 95% CI: 6.7-959) were potential risk factors for 30-day mortality. Conclusions: This study suggests that cases resulting in amputation due to ASO pathology alone might have poor prognosis and that preoperative sepsis can increase perioperative mortality; hence, the decision to amputate must be considered before the development of sepsis.

Contents

Introduction

Lower limb amputation (LLA) is a potential treatment option in cases of severe gangrene resulting from arteriosclerosis obliterans (ASO) and diabetes mellitus (DM). However, the mortality rate in patients following LLA performed for lower limb gangrene is high. The 30-day mortality rate for LLA has been reported to be between 4% and 22% [1].

Some studies have suggested that the risk factors that contribute to this mortality include the surgical site (in particular, above knee amputation [AKA]), older age, and hemodialysis [2-4]. While many patients with lower limb ischemia also have severe infections, few studies have investigated whether the presence of preoperative sepsis affects patient prognosis following LLA [4-6]. Moreover, the definition of sepsis itself was recently modified with the release of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [7]. Despite this, no study to date has investigated whether there is a correlation between postoperative mortality and sepsis (especially as defined in Sepsis-3) in LLA patients. Therefore, our hypothesis was that LLA patients with preoperative sepsis are at high risk of perioperative mortality. In this study, we investigated the factors (including sepsis) that may contribute to postoperative early mortality after major LLA for cases of DM and ASO.

Methods

2.1. Patient selection and analysis

This study was approved by our local Institutional Review Board. We analyzed cases that occurred during a 10-year period from January 2007 to October 2016. Our larger data set comprised all patients who underwent LLA. Cases were identified by conducting a search for cases of "lower limb amputation" in the medical records database during the study period. Of these identified cases, those without an evidence of a major amputation were excluded from the analysis. Next, in addition to patient attributes (age, sex, body mass index, and American Society of Anesthesiologists-physical status [ASA-PS] classification), the following items were also investigated in individual medical records based on past reports [1-6]: underlying disease resulting in need for LLA, amputation site, surgical factors (anesthesia method, emergency surgery, need for blood transfusion, need for admission into the intensive care unit [ICU]), basic disease data (whether the patient was undergoing dialysis and whether they had heart disease), and perioperative complications (sepsis, acute kidney injury, delirium, respiratory insufficiency, hypoalbuminemia). Emergency surgery was defined as the operating surgeon's determination that immediate lower extremity amputation was needed to save the patient's life. We investigated these variables in a group of patients who died within 30 days of LLA and those who survived. Perioperative complications were defined as follows

・Diagnosis of preoperative sepsis

Patients with fever and an elevated inflammatory response (e.g. elevated white blood cell count, C-reactive protein, or fibrin split product) were started on antibiotics. At least two researchers determined whether to classify each case as sepsis based on the Sepsis-3 definition, which included an increase of 2 or more points on the Sequential Organ Failure Assessment (SOFA) [7]

・Definition of acute kidney injury

Acute kidney injury was determined based on serum creatinine variation (elevated by >0.3 mg/dl within 48 h or a level more than 1.5-times higher than the standard value) and timed urine volume (6 continuous hours) according to the Acute Kidney Injury Network's (AKIN) definition of acute kidney injury (AKI) [8].

・Method of diagnosing delirium

Patients were diagnosed with delirium if they were a) diagnosed with delirium by a specialist in that field or b) met at least two of the following three criteria based on physician and nurse treatment and observation records: 1) altered consciousness, 2) abnormal behavior, and 3) recent administration of an anti-psychotic (e.g. haloperidol).

・Other

Respiratory insufficiency was diagnosed when medical records showed that the patient required supplemental oxygen. Low albumin patients were defined as those with serum albumin levels ≤3.0 mg/dl.

2.2. Statistical analysis

The chi-square test was used for univariate analysis between the two groups, and the Mann-Whitney U test was used to compare age and ASA-PS classification between groups. . P <0.05 was considered statistically significant. For multivariate analysis of factors contributing to mortality, stepwise logistic regression (backward elimination based on P value) was performed, with the factors shown to exceed the level of significance in the univariate analysis used as explanatory variables. The level of significance was again set at $P < 0.05$. The analysis was performed using R software (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of 56,438 surgery cases during the study period, 185 cases of LLA were identified. Of these 185 cases, we excluded the 19 cases not involving DM or ASO (external trauma: 7 cases, necrotizing vasculitis accompanying connective tissue disease: 3 cases, burn injury: 3 cases, acute artery occlusion: 2 cases, cause unknown: 4 cases) and 44 cases involving minor amputation from the ankle and below. From this data set, 122 cases were eligible for inclusion (Figure 1). Of these, 8 patients (6.6%) died. The mean age of the subjects was 66.6 years (standard deviation [SD]: 11.0) and the male to female ratio was 81:41. The surgical site was above-knee amputation (AKA) in 51 cases (41.8%) and below-knee amputation (BKA) in 71 cases (58.2%). The pathophysiological cause of death was defined as sepsis (5 cases; 62.5%), ischemic disease (1 case; 12.5%), fatal arrhythmia (1 case; 12.5%), and mesenteric artery occlusion (1 case; 12.5%). The mortality rate was higher for AKA patients (n=5, 9.8%) than that for BKA patients (n=3, 4.2%). In total, 19 cases were identified as having sepsis; among these cases, the mortality rate was 36.8% (7/19). In terms of the primary disease, ASO was identified in 86 cases (70.4%), DM was identified in 90 cases (73.8%), and both ASO and DM were present in 53 (44.2%) of these cases. The results of the univariate analysis indicated that, compared to ASO, DM was significantly more common in the survival group, while ICU admission, hemodialysis, delirium, AKI, and sepsis were significantly more common in the mortality group (Table 1). Age was significantly higher in the mortality group, and the threshold for 8 maximum sensitivity and specificity determined using a receiver operating characteristic curve was 74 years or older (sensitivity: 0.735, specificity: 0.625, Figure 2). Stepwise logistic analysis was performed using variables that were significantly altered in the mortality group (ICU admission, hemodialysis, delirium, AKI, and sepsis), age ≥74 years, and non-DM as explanatory variables. Results of this analysis indicated that both non-DM (ASO only) and sepsis were factors that contributed to mortality (Table 2).

4. Discussion

4.1. General discussion

The perioperative mortality rate associated with LLA in this study was 6.6%, which is a lower 30-day mortality rate than that reported in a systematic review of previous studies (4-22%) [1]. Nelson et al. [3] reported that the 30-day postoperative mortality rate following AKA was two-fold higher than that following BKA. Subramaniam et al. [2] also reported that the amputation site (AKA OR: 4.35) was a risk factor for higher 30-day mortality rates. While our study did not reveal a significant difference in the mortality rates between different surgical sites, the mortality rate for AKA was twice that for BKA, similar to observations in previous reports [2,3]. The fact that slightly 9 more BKA cases were included in our analysis (58.2%) may have contributed to the lower 30-day mortality rate. Many reports have suggested that increased age is a risk factor for mortality in LLA surgery [4-6, 9-10]. While age was not found to be an independent risk factor for mortality in our study, the average age of the mortality group was relatively higher, and the risk threshold was found to be at 74 years (and above). In a retrospective study, Scott et al. [11] cited age as a factor contributing to the 30-day mortality rate in LLA patients, with the OR for patients aged 74–79 years at 3.8 compared to those of 74 years or younger, and 4.08 for those aged 79 years or older. López-Valverde et al. [12] also conducted a retrospective study of outcomes in LLA surgery for patients with DM and identified that being 74 years or older was a risk factor for 30-day mortality. Another study [5] indicated that while the odds ratio for 30-day mortality was 1.61 for patients aged 69–79 years, it was 3.14 for those 80 years or older. While these results cannot be directly compared, as all three of these studies were retrospective and targeted different areas and ethnicities, it appears that the age at which risk increases is in the mid-70s. Preoperative sepsis developed in 7 (87.5%) of the 8 patients who died. Sepsis was 10 diagnosed as the postoperative cause of death in 5 (62.5%) of these cases. Sepsis patients generally have a high mortality rate, reportedly around 10% [5]. It has previously been suggested that sepsis is a risk factor for LLA, and many reports have investigated this relation. Easterlin et al. [5] reported in an investigation of 30-day mortality risk in 9,244 patients who underwent major amputation that the OR for sepsis was 1.84 (95% CI: 1.51-2.24). Nelson et al. [4] found that while the mortality rate for AKA was twice that for BKA, the OR was higher for BKA if sepsis was present prior to surgery (AKA: OR of 1.69 [95% CI: 1.36-2.09], BKA: OR of 2.09 [95% CI: 1.63-2.69]). In both these reports, analysis was performed using the database of the American College of Surgeons National Surgical Quality Improvement Program. The presence of sepsis was diagnosed based on the applicable International Classification of Diseases 9th Revision, Clinical Modification, code included in medical records. As a result, the cases were not necessarily extracted using completely standard criteria. Moreover, while the definition of sepsis was revised in 2016, no studies have investigated sepsis as a risk factor for postoperative mortality in LLA patients using the SOFA score as required under the new Sepsis-3 diagnostic criteria. To the best of our knowledge, we are the first to identify potential risk factors for 30-day mortality after LLA using factorial analysis based on the latest diagnostic criteria. We also identified absence of diabetes as a risk factor contributing to mortality in LLA patients. The result does not reveal that the coexistence of DM improves the prognosis of LLA patients; on the contrary, it suggests that patients with LLA due to ASO alone have a poor prognosis based on the study population. In the present study, DM patients accounted for 70.4% of cases. A systemic review by van Netten et al. [1] indicated that this ratio varies greatly, ranging from 39% to 89%. They suggest that this variation is due to differences in the types of subjects included in different studies; for instance, some targeted only BKA cases, while others targeted all major amputation cases. The analysis by van Netten et al. [1] also specifically noted two studies in which, similar to our results, the presence of DM lowered the 30-day mortality rate [13,14]. It should be noted there are many studies in which no effect of DM status was identified [5,9,12,15,16]. Thus, while the absence of DM was an independent risk factor for 30-day mortality in our study, careful consideration must be applied if this is to be used as a risk factor clinically. Our results suggest that cases resulting in amputation due to ASO pathology alone may have a poor prognosis. Past reports have indicated that hemodialysis is also a risk factor for mortality in LLA 12 patients [4-6, 9]. While hemodialysis was found to be significantly more common in the mortality group in our study, it was ultimately excluded in the stepwise logistic analysis (backward elimination). The small sample size may have affected our results.

4.2. Limitations

This retrospective, single facility study had a relatively small sample size; therefore, careful interpretation of results is necessary. Moreover, ICU admission and the choice of anesthesia methods, which were investigated in this study, were left to the discretion of the anesthesiologist in charge of each case. As APACHE II and SOFA scores were not measured in cases admitted to the ICU, we were unable to compare the severity of each case. In addition, AKI was defined according to the AKIN criteria, even though the KDIGO criteria are more frequently used in contemporary practice. Further research needs to be conducted by means of a prospective, multicenter study with methodical tracking of patient severity to determine the factors contributing to perioperative mortality in LLA. While many studies focus on the 5-year mortality rate, our study focused on the 30-day mortality rate only. This was to determine the factors that might indicate the need for intensive care during perioperative management. We used this study design to 13 focus particularly on whether the presence of an acute pathology of sepsis affects the 30-day mortality rate. While conditions such as acute disseminated intravascular coagulation and clotting disorders were also considered as parameters for investigation, we ultimately excluded them from the study; these conditions commonly accompany sepsis (coagulopathy: 50-70%, disseminated intravascular coagulopathy: 35%) [17,18]and were unlikely to be independent factors.We retrospectively investigated the 30-day mortality rate and associated risk factors using the new definition (Sepsis-3) for sepsis in patients who underwent LLA due to lower limb gangrene as a result of ASO or DM. The 30-day mortality rate was 6.6%, and we identified that the presence of sepsis and the non-DM status of the patient as significant risk factors for mortality. Our results suggest that cases resulting in amputation due to ASO pathology alone may have a poor prognosis; as preoperative sepsis could increase perioperative mortality, it is necessary to decide whether amputation is needed before the development of sepsis. These cases require strict perioperative management when complicated with preoperative sepsis.

Conflict of interest:

None

References

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Figure 1.

Patient selection flow chart for the analysis of potential risk factors for 30-day mortality after lower leg amputation.

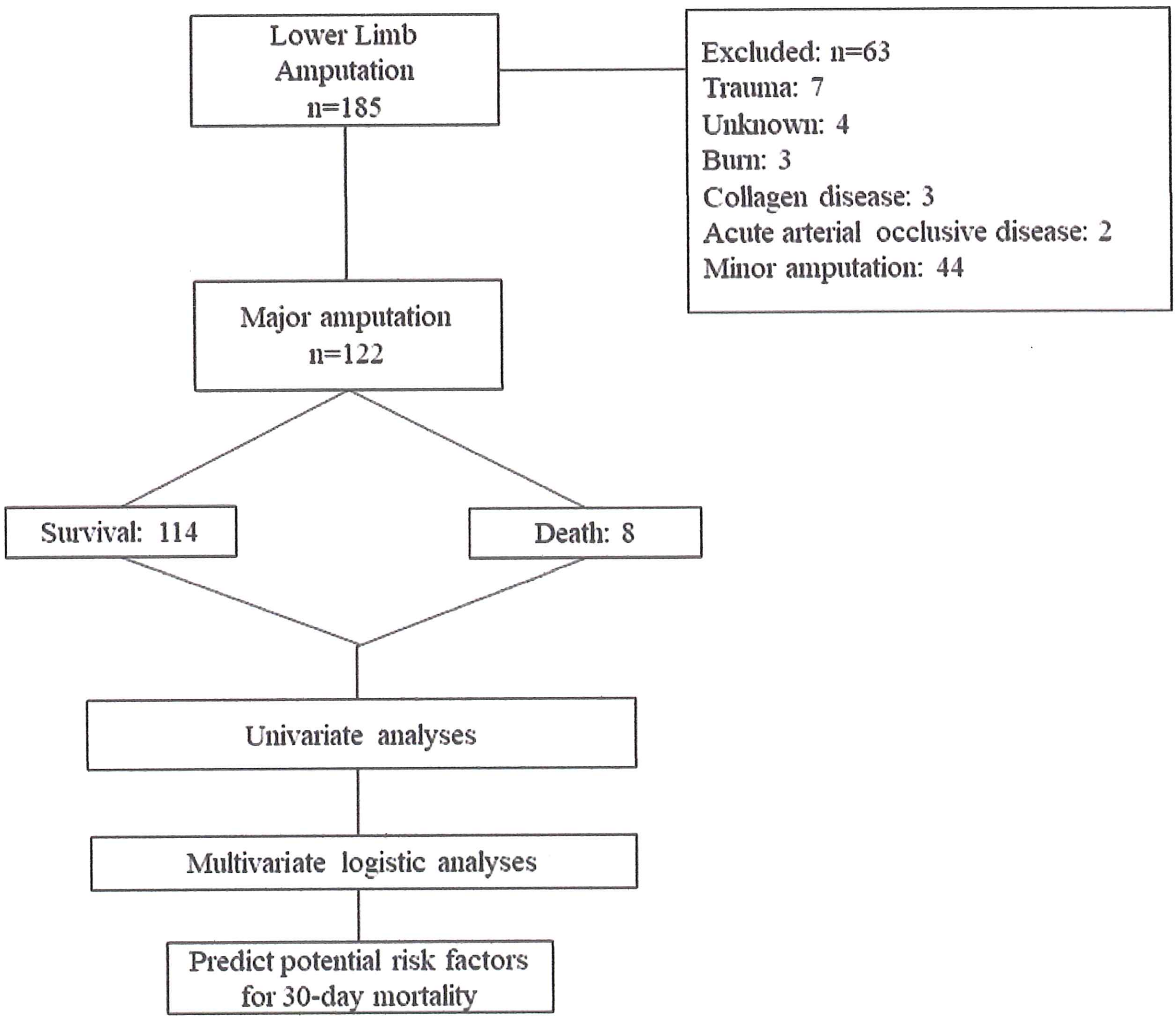

Figure 2.

Receiver operating characteristic curve for patient age as a predictor of 30-day mortality. A threshold value at which the sum of sensitivity and specificity is maximized is obtained for identification of an age threshold where a value at or above is considered as positive factor.

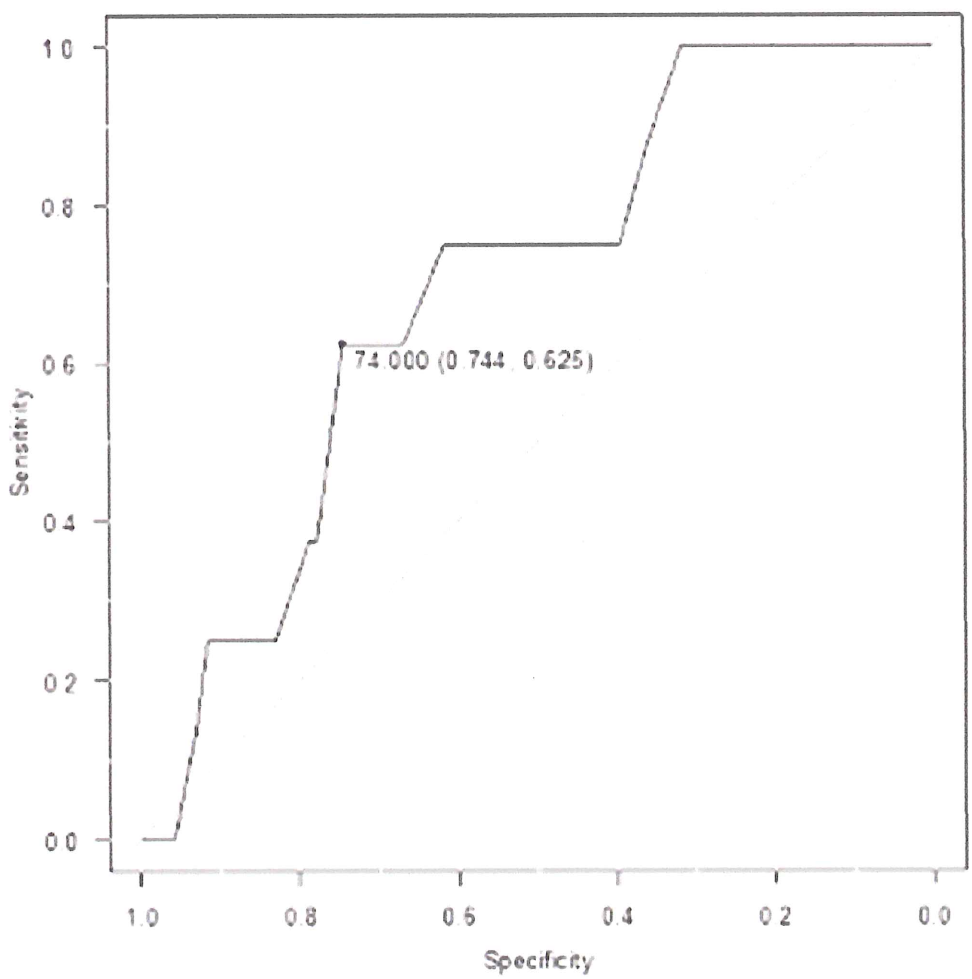

Table 1.

Characteristics of the study population and univariate analyses of potential risk factors for 30-day mortality after major lower limb amputation.

	Total n(%)	Survival Group n(%)	Non-survival group n(%)	P value
No.of patients	122	114	8	
Age in years, mean±SD	66.6±11.0	66.2±11.1	73.1±7.2	0.011
Male gender	81(66.4%)	75(65.8%)	6(75%)	0.88
Obesity(BMI≧30kg/m²)	5(4%)	5(4.4%)	0(%)	0.75
ASA-PS≧4	18(14.8%)	11(9.6%)	7(87.5%)	0.19
Arteriosclerosis obliterans	86(70.4%)	78(68.4%)	8(100%)	0.13
Diabetes mellitus	90(73.8%)	89(78%)	1(12.5%)	<0.001
Above-Knee amputation	51(41.8%)	46(40.3%)	5(62.5%)	0.39
Below-Knee amputation	71(58.2%)	68(59.6%)	3(37.5%)	0.39
Emergency surgery	56(45.9%)	51(44.7%)	5(62.5%)	0.54
General anesthesia	49(39.2%)	44(38.6%)	5(62.5%)	0.33
Transfusion	44(36.1%)	40(35.1%)	4(50%)	0.63
ICU admission	28(22.9%)	21(18.4%)	7(87.5%)	0.001
Heart disease	57(46.7%)	51(44.7%)	6(75%)	0.17
COPD	1(0.8%)	1(0.9%)	0(0%)	0.08
Hemodialysis	50(40.1%)	44(38.6%)	6(75%)	0.03*
Delirium	11(9%)	6(5.3%)	5(62.5%)	<0.001
Respiratory failure	7(5.7%)	5(4.4%)	2(25%)	0.1
Acute kidney injury	14(12%)	11(9.6%)	3(37.5%)	<0.001
Hypoalbuminemia	70(57%)	64(56%)	6(75%)	0.53
Sepsis	19(15.2%)	12(10.5%)	7(87.5%)	<0.001

ASA-PS: America society of anesthesiologists physical status, COPD: Chronic Obstructive Pulmonary Disease, SD: Standard deviation, BMI: Body mass index, ICU: Intensive care unit,

Table 2

Multivariate logistic analysis of the potential risk factors for 30-day mortality in patients after major lower limb amputation.

	Odds ratio	95%CI	P value
Non-DM	35.2	2.8-432	0.005
Sepsis	80.7	6.7-959	<0.001

DM: Diabetes mellitus, CI: confidence interval