Chronic Kidney Disease Predicts Long-Term Mortality After Major Lower Extremity Amputation

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Abstract

Background: Despite low peri-operative mortality after major lower extremity amputation, long-term mortality remains substantial. Metabolic syndrome is increasing in incidence and prevalence at an alarming rate in the USA. **Aim:** This study was to determine whether metabolic syndrome predicts outcome after major lower extremity amputation. **Patients and Methods:** A retrospective review of charts between July 2005 and June 2010. **Results:** Fifty-four patients underwent a total of 60 major lower extremity amputations. Sixty percent underwent below-knee amputation and 40% underwent above-knee amputation. The 30-day mortality was 7% with no difference in level (below-knee amputation, 8%; above-knee amputation, 4%; $P = 0.53$). The mean follow-up time was 39.7 months. The 5-year survival was 54% in the whole group, and was independent of level of amputation ($P = 0.24$) or urgency of the procedure ($P = 0.51$). Survival was significantly decreased by the presence of underlying chronic kidney disease ($P = 0.04$) but not by other comorbidities (history of myocardial infarction, $P = 0.79$; metabolic syndrome, $P = 0.64$; diabetes mellitus, $P = 0.56$). **Conclusion:** Metabolic syndrome is not associated with increased risk of adverse outcomes after lower extremity amputation. However, patients with chronic kidney disease constitute a sub-group of patients at higher risk of postoperative long-term mortality and may be a group to target for intervention.

Keywords: Chronic kidney disease, Lower extremity amputation, Metabolic syndrome, Mortality, Peripheral artery disease

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Introduction

Lower extremity amputation remains a definitive therapy for the management of ischemic disease that fails revascularization. Despite recent advances in revascularization techniques and broadening of indications, each year 55,000 to 65,000 major lower extremity amputations are performed in the USA,[1,2] making lower extremity amputation one of the most common vascular surgery procedures.

Major lower extremity amputation, either below- or above-knee amputation, is associated with significant morbidity and mortality. Multiple predictors of poor outcome after major lower extremity amputation have been reported. Patients with advanced age or coronary artery disease have poor outcomes.[3] In the Framingham Heart Study, the prevalence of metabolic syndrome doubled during a 10-year period and was associated with a three-fold increased risk in death.[4] Patients with metabolic syndrome undergoing peripheral vascular interventions have been shown to have unfavorable perioperative outcomes.[5,6] Patients who undergo above-knee amputation (AKA) have worse functional and survival outcomes compared to patients who undergo below-knee amputation (BKA).[7,8]

The aim of our study is to identify whether comorbid diseases such as metabolic syndrome are associated with either peri-operative or long-term adverse events in

patients undergoing major lower extremity amputation for ischemic disease. We have previously shown that veterans with vascular disease have more comorbid disease than non-veterans with similar diagnoses, and that these veterans form a high-risk population.[9,10] We hypothesized that these high-risk patients would have extensive comorbid diseases such as metabolic syndrome, and that peri-operative and long-term survival would be related to the presence of these risk factors. Therefore, we examined the peri-operative and long-term outcomes of veterans undergoing major lower extremity amputation.

Patients and Methods

The electronic records of all patients who underwent a major lower extremity amputation for ischemic disease at our institution between July 2005 and June 2010 were reviewed. Major lower extremity amputation was defined as amputation below the hip and above the ankle and further categorized as AKA or BKA. Amputations limited to or below the ankle or amputations for traumatic injuries were excluded.

Pre-operative, intra-operative, and post-operative data were collected. Criteria for diagnosis of metabolic syndrome were met when three or more of the following criteria were met: fasting blood glucose >110 mg/dL or previously diagnosed diabetes mellitus, BMI >30 kg/m^2, SBP/DBP >140/90 mmHg or treatment of previously diagnosed hypertension, HDL <40 mg/dL in males or <50 mg/dL in females or specific treatment for this lipid abnormality, and fasting triglycerides >150 mg/dL or specific treatment for this lipid abnormality.[11] Chronic kidney disease (CKD) was defined as stage 3 or worse, corresponding to an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation and includes patients with End-Stage Renal Disease (ESRD) on dialysis.

Patients were followed until September 2013. Early postoperative outcomes include morbidity and mortality within 30 days of surgery or the duration of the post-operative hospitalization if the patient remained in the hospital longer than 30 days. These outcomes included 30-day mortality, revision for wound failure, conversion from BKA to AKA, myocardial infarction and stroke. Late postoperative outcomes were recorded through the end of the study period and consisted of death, development of congestive heart failure, fatal, and non-fatal myocardial infarction, stroke, and progression to ESRD.

Statistical analysis

JMP® 9.0.0 software (SAS Institute, Cary, NC) was used for data analysis. Variables were represented as mean ± standard deviation. Categorical variables were compared with Chi-square analysis and continuous variables were compared with the t-test. Kaplan-Meier analysis was used for survival analysis, with comparison of groups using the log rank test. Demographic variables that predicted mortality were examined using the Cox proportional hazards model. All tests were double tailed with a type I error risk (alpha) equal to 5%.

Results

Fifty-four patients underwent a total of 60 major lower extremity amputations. All patients were male; the mean age was 65.9 years. Sixty percent (*n* = 36) underwent BKA and 40% (*n* = 24) underwent AKA. Seventy-eight percent of patients were Caucasian, 22% were African American. Eighteen percent had a prior contralateral amputation and 65% had a previous vascular intervention (endovascular, open or both). All the above-mentioned characteristics were not statistically different when compared between the BKA and AKA groups [Table 1].

The prevalence of comorbid conditions was extremely high in this population and is shown in Table 1. The most prevalent conditions were arterial hypertension (90%), diabetes mellitus (78%), metabolic syndrome (68%), history of myocardial infarction (MI, 63%), dyslipidemia (62%), chronic kidney disease (CKD, 40%), and congestive heart failure (CHF, 30%). Thirty-eight percent were dependent in their performance of activities of daily life prior to surgery. However, the prevalence of comorbidities was not statistically different between the AKA and BKA groups except that the BKA group had more patients with CKD who were dialysis-dependent than the AKA group (25% vs 4%, *P* = 0.03) [Table 1].

Operative characteristics are shown in Table 2. Forty-six percent of the amputations were performed in an urgent or semi-urgent setting for treatment of life-threatening limb disease. Forty percent were staged interventions requiring one or more additional procedure before the creation of the final amputation stump. Eighty-five percent underwent general anesthesia and 12% underwent spinal anesthesia. Amputations were equally distributed between both lower extremities; one patient required bilateral amputation during the same hospitalization as a result of worsening ischemia from multiple organ system failure following endovascular repair of aortic aneurysm. Operative characteristics were not statistically different when compared between the AKA and BKA groups. However, there was a trend toward a higher rate of staged procedures in the BKA group (50% vs 35%, *P* = 0.05) [Table 2].

Operative outcomes are shown in Table 3. Peri-operative mortality was 7% (BKA 8%, AKA 4%, *P* = 0.53). The

Table 1: Demographics and comorbidities

	All amputations (%)	BKA (%)	AKA (%)	P
N (total)	60 (100)	36 (60)	24 (40)	
Age (years)	65.9±10.3	65.5±1.7	66.5±2.1	0.74
Gender	60 (100) Male			
Race				
Caucasian	47 (78)	26 (72)	21 (88)	0.15
African-American	13 (22)	10 (28)	3 (12)	
Contralateral amputation	11 (18)	5 (14)	6 (25)	0.28
Contralateral BKA	6 (10)	4 (11)	2 (8)	0.70
Contralateral AKA	5 (8)	1 (3)	4 (17)	0.06
Previous vascular intervention	39 (65)	20 (56)	2 (6)	0.06
Surgery	18 (30)	8 (22)	10 (41)	
Endovascular	12 (20)	10 (28)	2 (8)	
Surgery + Endovascular	9 (15)	2 (6)	7 (29)	
Dependent (ADL)	23 (38)	14 (39)	9 (38)	0.91
MI, history of	38 (63)	20 (56)	18 (75)	0.13
CHF	18 (30)	13 (36)	5 (21)	0.21
Atrial fibrillation	12 (20)	7 (19)	5 (21)	0.90
CABG	17 (28)	10 (28)	7 (29)	0.91
Coronary stent	22 (37)	14 (39)	8 (33)	0.66
Stroke or TIA, history of	10 (17)	6 (17)	4 (17)	
Arterial hypertension	54 (90)	33 (92)	21 (87)	0.60
Diabetes mellitus	47 (78)	31 (85)	16 (67)	0.07
IDDM	31 (52)	22 (615)	9 (37)	0.07
NIDDM	16 (26)	9 (25)	7 (29)	0.70
Dyslipidemia	37 (62)	19 (53)	18 (75)	0.08
Metabolic syndrome	41 (68)	27 (75)	14 (58)	0.17
Chronic kidney disease	24 (40)	15 (42)	9 (37)	0.75
Dialysis dependent	10 (17)	9 (25)	1 (4)	0.03 *
COPD	10 (17)	5 (14)	5 (21)	0.48
Smoking within the previous year	22 (37)	10 (29)	12 (54)	0.09
Malignancy, history of	13 (22)	7 (19)	6 (25)	0.61
HIV seropositive	4 (7)	1 (3)	3 (12)	0.14
Hepatitis C, chronic infection	6 (10)	3 (8)	3 (12)	0.60
IV drug use	2 (3)	1 (3)	1 (4)	0.75

ADL = Activities of daily life, AKA = Above knee amputation, BKA = Below knee amputation, CABG = Coronary artery bypass graft surgery, CHF = Congestive heart failure, COPD = Chronic obstructive pulmonary disease, HIV = Human immunodeficiency virus, IDDM = Insulin-dependent diabetes mellitus, IV = Intravenous, MI = Myocardial infarction, NIDDM = Non-insulin dependent diabetes mellitus, TIA = Transient ischemic attack

Table 2: Operative characteristics and outcomes

	All amputations (%)	BKA (%)	AKA (%)	P
N	60 (100)	36 (60)	24 (40)	
Urgent case	27 (46)	19 (53)	8 (35)	0.18
Staged procedure	24 (40)	18 (50)	6 (25)	0.05
Anesthesia				0.33
General	51 (85)	29 (80)	22 (92)	
Spinal	7 (12)	6 (17)	1 (4)	
MAC	2 (3)	1 (3)	1 (4)	
Side of surgery				0.71
Right	30 (50)	18 (50)	12 (50)	
Left	29 (48)	17 (47)	12 (50)	
Bilateral	1 (2)	1 (3)	0 (0)	

AKA = Above knee amputation, BKA = Below knee amputation, MAC = Monitored anesthesia care

rate of revision for wound failure was 10% (BKA 8%, AKA 12%, P = 0.60) and conversion from BKA to AKA occurred in one patient (2.7%). Three patients (5%) developed a non-fatal post-operative stroke. One of these patients (1.7%) had an additional non-fatal post-operative MI after BKA. All operative outcomes were not statistically different between the BKA and AKA groups [Table 3].

Long-term outcomes are shown in Table 3. The mean follow-up time was 39.7 ± 29.8 months. Through the course of the study, 50% of the patients died (BKA 56%, AKA 42%, P = 0.26). Thirty-eight percent of all patients developed a new MI, stroke, CHF or ESRD, the rates of which were comparable between AKA and BKA groups [Table 3]. Kaplan-Meier analysis showed the

1-year survival to be 73%, 3-year survival to be 61% and 5-year survival to be 54% in the whole cohort [Figure 1]. Survival was independent of level of amputation (*P* = 0.24) or urgency of the procedure (*P* = 0.51). Survival was significantly decreased by the presence of underlying chronic kidney disease (*P* = 0.04) but not by other comorbidities (history of MI, *P* = 0.79; metabolic syndrome, *P* = 0.64; diabetes mellitus, *P* = 0.56) [Figure 1]. The only variable that was a statistically significant predictor of mortality was CKD (risk ratio 2.27; 95% confidence interval 1.02-5.06; *P* = 0.0425; Table 4).

Discussion

We report a perioperative mortality of 7% after lower extremity amputation, with comparable results between the AKA and BKA groups. In this high-risk group of patients with extensive comorbid disease, 5-year survival was 54%. The presence of metabolic syndrome, history of myocardial infarction, level of amputation, or urgency of

Table 3: Peri-operative and long-term outcomes

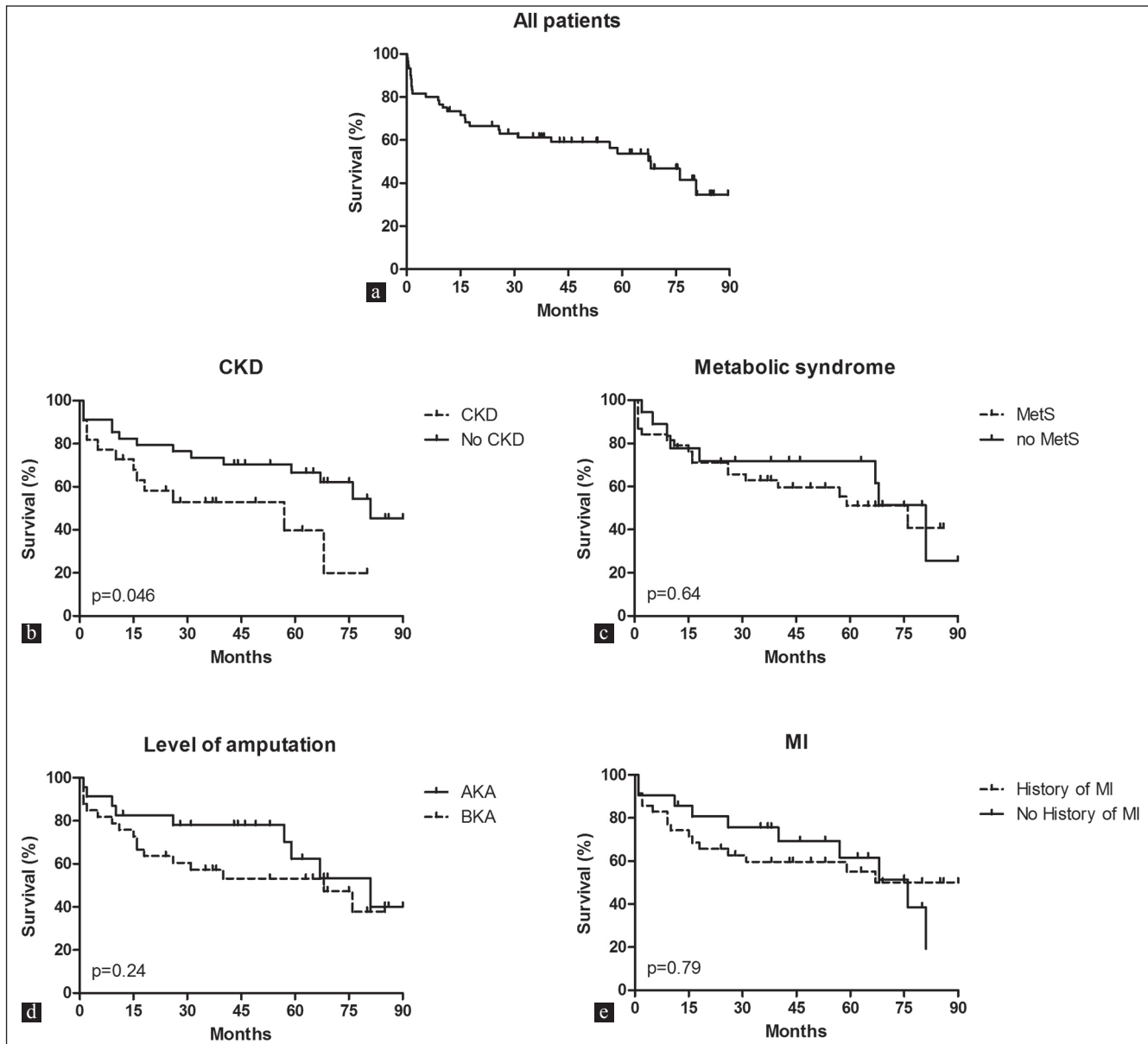|	All amputations	BKA	AKA	*P*
Peri-operative				
30-day mortality	4 (7)	3 (8)	1 (4)	0.53
Revision for wound failure	6 (10)	3 (8)	3 (12)	0.60
Conversion from BKA to AKA	1 (2.7)			
Peri-operative MI	1 (1.7)	1 (3)	0 (0)	0.41
Peri-operative stroke	3 (5)	2 (6)	1 (4)	0.81
Long term				
Mean follow-up (months)	39.7±29.8	36.2±30.2	44.9± 29.0	0.26
Death	30 (50)	20 (56)	10 (42)	0.29
CHF	6 (10)	4 (11)	2 (8)	0.73
MI, fatal	2 (3.3)	1 (3)	1 (4)	0.77
MI, non-fatal	1 (1.7)	1 (3)	0 (0)	0.41
Stroke	7 (12)	5 (14)	2 (8)	0.51
ESRD	8 (13)	6 (17)	2 (8)	0.35

AKA = Above knee amputation, BKA = Below knee amputation,
CHF = Congestive heart failure, ESRD = End-stage renal disease,
MI = Myocardial infarction

Table 4: Cox proportional hazards model

	Risk Ratio [95% confidence interval]	*P*
Chronic kidney disease	2.27 [1.02-5.06]	0.04*
History of MI	1.45 [0.68-3.27]	0.34
Metabolic syndrome	1.31 [0.61-3.08]	0.50
Level of Amputation (BKA/AKA)	1.57 [0.73-3.60]	0.25

AKA = Above knee amputation, BKA = Below knee amputation,
MI = Myocardial infarction

the procedure did not affect late survival. However, the presence of CKD prior to the amputation was associated with worse late survival [Table 4].

Multiple studies have evaluated specific comorbid diseases associated with reduced survival after major lower extremity amputation. Frequently, more than one comorbid condition have been identified, including congestive heart failure[12-14], renal disease[12,13,15,16], cerebrovascular disease[12], chronic obstructive pulmonary disease[13], preoperative pneumonia,[13] diabetes mellitus[16], age >75[13], and admission through the emergency department.[8] In addition, AKA was previously found to be associated with worse survival compared to BKA.[16]

Metabolic syndrome has a high prevalence in our patient population (68%) similar to the one reported in patients with peripheral artery disease.[17] It is a pro-inflammatory and pro-thrombotic state accompanied by an increased risk for cardiovascular disease and type 2 diabetes mellitus.[18] At the endothelial level, it is associated with altered intima-media thickness and impaired myocardial perfusion which are independent predictors of adverse cardiovascular outcomes.[19] Two of the components of the metabolic syndrome, elevated fasting plasma glucose and microalbuminuria, are predictors of peripheral vascular disease.[20] In patients undergoing hemodialysis access placement, metabolic syndrome is associated with worse survival and secondary patency.[11] However, we did not find an association between metabolic syndrome and long-term mortality after major lower extremity amputation [Table 4]. The lack of association of metabolic syndrome with outcome after amputation may be related to several factors. First, patients with metabolic syndrome may be treated for their condition, including multiple medications that address the glucose as well as the lipid abnormalities. Second, metabolic syndrome may not be a statistically significant factor compared to others, such as CKD or cardiac disease that have significant effects on perioperative mortality. Third, our sample size may be insufficient to detect such an effect.

Several studies reported an association between renal disease and survival after amputation. Aulivola *et al.* reported significantly decreased survival among patients with diabetes mellitus, serum creatinine >2 mg/dL or ESRD. Interestingly, patients with elevated creatinine without ESRD had decreased survival similarly to those with ESRD.[16] Mayfield *et al.* reported on a large series from a veteran population and found that patients with renal disease have worse survival during the first year after amputation. Other predictors of worse mortality were proximal level of amputation, cerebrovascular disease and congestive heart failure.[12] Feinglass *et al.* reported on survival from the NSQIP database. Multiple

Figure 1: Survival analysis. (a) Survival of entire cohort; (b) Survival stratified by presence or absence of chronic kidney disease; (c) Survival stratified by presence or absence of metabolic syndrome; (d) Survival stratified by level of amputation; (e) Survival stratified by presence or absence of history of myocardial infarction

preoperative comorbidities were associated with worse perioperative and late survival including BUN > 40 mg/dL and ESRD.[13] Dossa *et al.* reported a hospital mortality of 24%, a 1-year survival of 38% and a 2-year survival of 20% among patients with ESRD, advocating for aggressive foot care and patient education to prevent amputation.[15] How CKD contributes to worse survival is unclear. One study reported an association between preoperative CKD and postoperative malnutrition in patients undergoing open vascular surgery.[21] It might be of value to examine the nutritional status of this subgroup of patients and determine whether malnutrition is a common underlying factor.

Major lower extremity amputation is associated with significant mortality. Our peri-operative mortality of 7% is consistent with previously reported data ranging from 4 to 17%.[2,16,22-24] Peri-operative mortality was similar between the AKA and BKA groups, in contrast to previous reports of higher peri-operative mortality after AKA.[25,26] Post-operative surgical complications are not uncommon after major lower extremity amputation. We report a rate of wound revision and conversion that is lower than the rates reported in larger series where wound revision ranged between 13.2% and 15.4% and conversion ranged between 9% and 20%.[16,27,28] Also, we did not find a higher rate of local wound complications in the BKA group compared to the AKA group, which

is different from previous reports.[22,29] The lower rate of local wound complications could be explained by the relatively high rate of staged procedures in our series (40%), since 46% of the procedures were performed in the setting of limb-threatening wet gangrene; two-stage amputation has fewer wound complications than one-stage amputation performed for wet gangrene.[30]

Our analysis is limited by the relatively small size of the population and retrospective nature of the study. It includes only veterans and lacks female patients who may have health characteristics different from the general population.[9,10] Due to the population size, we could not determine whether the observed decreased survival in patients with CKD is related to the subgroup of patients with ESRD. In addition, it is not known how the medical management of comorbid conditions evolved during the study period. Further studies are required to determine if better control of specific comorbid disease improves outcomes after lower extremity amputation.

In conclusion, major lower extremity amputation for ischemic disease is characterized by substantial perioperative mortality and morbidity. Metabolic syndrome is not associated with increased risk of adverse outcomes after lower extremity amputation. However, patients with chronic kidney disease constitute a sub-group of patients at higher risk of postoperative long-term mortality and may be a group to target for intervention to improve outcomes.

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