Ulster Med J 2019;**88(1):**30-35

Clinical Paper

All-Cause Mortality Amongst Patients Undergoing Above and Below Knee Amputation in a Regional Vascular Centre within 2014-2015

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Accepted: 7th September 2018
Provenance: Externally peer reviewed

Keywords: Vascular Surgery; Amputation; All-Cause Mortality; Pulmonary Embolism; Deep Vein Thrombosis

Abstract

Background Major lower limb amputation remains a common treatment for patients with peripheral vascular disease (PVD) in whom other measures have failed. It has been associated with high morbidity and mortality, including risks from venous thromboembolism (VTE).

Methods A two-year retrospective cohort study was conducted involving 79 patients who underwent major lower limb amputation (below- or above-knee amputation) between January 2014 and December 2015 in a single tertiary referral centre. Amputation procedures were performed for reasons relating to complications of PVD and/ or diabetes mellitus. Patients were followed-up to investigate all-cause mortality rates and VTE events using the Northern Ireland Electronic Care Record database (mean follow-up time 17 months).

Results Of the 79 patients, there were 52 male and 27 female. Mean age at time of surgery was 72 years (range 34-99 years). Forty-six patients (58%) suffered from diabetes mellitus, 29 (35%) heart failure, 31 (39%) chronic kidney disease (CKD) and 10 (13%) chronic obstructive pulmonary disease (COPD). Twenty patients (25%) were on anticoagulant therapy, and 53 (67%) were on antiplatelet therapy.

Thirty-five patients (44%) died during follow-up; mean age at death was 74 years. No statistically significant association was found between mortality rate and the level of amputation (p=0.3702), gender (p=0.3507), or comorbid diabetic mellitus (p=0.1127), heart failure (p=0.1028), CKD (p=0.0643) or COPD (p=0.4987).

Two patients experienced radiologically-confirmed non-fatal pulmonary emboli and two patients developed radiologically-confirmed deep vein thrombosis.

Conclusions The results are in agreement with current literature that amputation is associated with significant mortality, with almost half of the study population dying during follow-up. Further work should explore measures by which mortality rates may be reduced.

INTRODUCTION

Peripheral Vascular Disease (PVD) affects up to one-fifth of patients over 75 years old[1], with higher global prevalence in diabetic patients[2]. Despite advances in revascularisation and endovascular procedures, major lower limb amputation remains a common treatment end-point.

Following major lower limb amputation, 30-day all-cause mortality has been reported as 8.6%, significantly worse for above-knee amputation (AKA) than below-knee amputation (BKA) (16.5% and 5.7% respectively, p<0.001)[3]. One- and 3-year mortality rates have been reported as high as 48% and 71% respectively[4]. Risk factors associated with increased 30-day mortality include age and comorbid cerebrovascular disease[5,6]. Additionally, diabetes mellitus has been associated with poorer five-year survival[3]. Other factors shown to be independent predictors of mortality include heart failure, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD)[7].

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Vascular patients undergoing major lower limb amputation are also known to be at significant risk of Venous-Thromboembolism (VTE); namely Deep Vein Thrombosis (DVT) and Pulmonary Embolus (PE). Amputation patients frequently have several pre-operative VTE risk factors, which are increased by surgery and post-operative immobility [8]. VTE has been shown to affect over 10% of patients in the 2 months following amputation[9].

National Institute for Clinical Excellence (NICE) guidelines suggest that vascular patients undergoing lower limb amputation should be considered for *at least* seven days of low molecular weight heparin therapy and should receive mechanical VTE prophylaxis until they no longer have significantly reduced mobility relative to their anticipated mobility[10]. Thus, the optimum duration of pharmacologic VTE prophylaxis is not standardised.

This retrospective cohort study followed up patients who underwent major lower limb amputation between January 2014 and December 2015 in the Belfast Vascular Surgery Unit and assessed overall mortality rates, causes of death and incidence of VTE. Associations with amputation level, sex, and comorbid diabetes mellitus, heart failure, CKD and COPD are reported.

METHODS

A two-year retrospective cohort study was conducted in March 2017. All 79 patients representing 90 amputation procedures who underwent major lower limb amputation (defined as below- or above-knee amputation) between January 2014 and December 2015 in a single tertiary referral centre for vascular surgery (Royal Victoria Hospital, Belfast) were followed up. The primary aim of the study was to establish all-cause mortality within the cohort; the secondary aim of the study was to examine VTE incidence post-amputation. Only patients undergoing amputation for complications relating to PVD were included; patients undergoing amputation for trauma, tumours or other indications were excluded. Level of amputation was determined based on the clinical judgement of the attending surgeon. Mean time from date of amputation to point of data collection was 17 months (range 0–38 months).

Patients were followed up using the Northern Ireland Electronic Care Record (NIECR) database[11]. In cases where clinical details available on NIECR were unclear, inpatient notes were requested. NIECR was also utilised as a means of identifying relevant co-morbidities. DVT and PE occurrences were recorded from accessing ultrasound and computed-tomography perfusion pulmonary angiography (CTPA) reports on NIECR. Imaging was undertaken as per clinician judgement amongst patients displaying signs/ symptoms of VTE; no screening of asymptomatic patients was conducted throughout the study period. Throughout 2014-2015, practice within the Unit was that patients received pharmacological VTE prophylaxis in the form of prophylactic-dose enoxaparin throughout their inpatient stay unless contraindicated. No formal VTE risk-assessment was routinely conducted upon discharge.

Fisher's exact test[12] was carried out using 'GraphPad StatMate 2.00' and Kaplan-Meier Survival Graphs were created using 'Eureka Statistics'. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics are illustrated in **Table 1**.

TABLE 1.

Baseline patient characteristics.

Variable	Number of patients
Gender – Male	52 (66%)
Gender – Female	27 (34%)
History of diabetes	46 (58%)
History of heart failure	28 (35%)
History of renal impairment	31 (39%)
History of chronic obstructive pulmonary disease	10 (13%)
Known use of anticoagulant	20 (25%)
Known use of single or dual antiplatelet therapy	53 (67%)

There were 79 patients (52 male and 27 female) whose mean age at the time of lower limb amputation surgery was 72 years (range 34-99 years). All amputations were conducted for reasons related to PVD associated with ischaemia and/or infection or for complications related to diabetes mellitus. Of these, 37 (47%) procedures were categorised as 'elective', 37 (47%) as 'expedited' and 5 (6%) as 'urgent' as according to the National Confidential Enquiry into Patient Outcome and Death Classification of Intervention 2004[13].

Of the cohort, 46 patients (58%) were known to have diabetes (either insulin-dependent or non-insulin-dependent). Twenty-eight patients (35%) were known to have heart failure (as identified from NIECR documentation and/or pre-operative echocardiography demonstrating an ejection fraction less than or equal to 40%). Thirty-one patients (39%) were known to have CKD (as identified from NIECR documentation and/or review of peri-operative laboratory test results demonstrating an estimated glomerular filtration rate consistently below 60ml/min/1.73m^2). Ten patients (13%) were known to have COPD (as identified from NIECR documentation).

At time of follow-up, twenty patients (25%) were using anticoagulant therapy, and 53 (67%) were using single or dual antiplatelet therapy. Indications for anticoagulant therapy are detailed in **Table 2**.

Twenty patients (25%) were bilateral amputees at the time of follow-up. Ten patients (13%) had previously undergone contralateral limb major lower limb amputation prior to

TABLE 2.

Indications for anticoagulation usage amongst the cohort.

Indication	Number of patients
Indication unclear	1
Atrial fibrillation	12
Left ventricular thrombus	1
Post-operative PE	2
Pre-operative DVT	1
Recurrent DVT	1

the study period, nine (11%) underwent contralateral limb amputation during the study period and at the time of follow-up one (1%) underwent contralateral limb amputation after the study period. Only two patients (3%) underwent revision of below-knee amputation to above-knee amputation and both of these were conducted during the study period. For analysis purposes we have focused on the first procedure conducted during the two-year follow-up period.

Regarding all-cause mortality, 35 patients (44%) were found to be deceased at follow-up, as demonstrated in **Table 3** and **Figure 1**; mean age at death was 74 years (range 38-92 years).

Age of patients dying of any cause at the various time intervals is demonstrated in **Table 4**. Of those alive at the time of follow-up, mean age at time of surgery was 71 years (range 34-99 years) and mean age at time of follow-up 72 years (range 37-101 years).

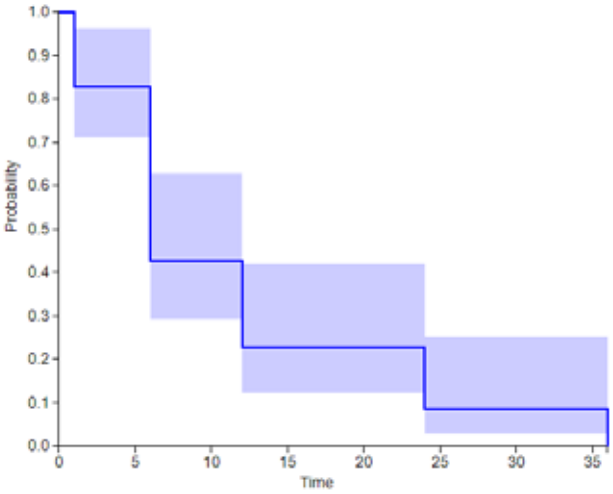

Fig 1. Kaplan-Meier survival graph considering all-cause mortality rates of 35 patients who were found to be deceased at follow-up, with 95% confidence intervals. Time is measured in months passed since operation.

TABLE 4.

Mean age of patients dying at the various time intervals.

Time interval following surgery	Mean age at time of death (years)
Within 30 days	85 years
30 days – 6 months	74 years
6 months - 1 year	74 years
1 year and 2 years	73 years
2 years and 3 three years	56 years

Mortality rates were determined by level of amputation, as demonstrated in **Figure 2.** Of the 41 patients who underwent BKA, 16 (39%) were deceased at follow-up, and of the 38 patients who underwent AKA, 19 (50%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and level of amputation (p=0.3702).

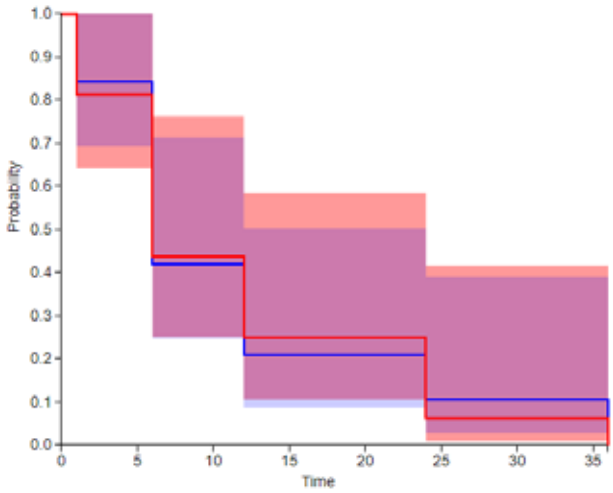

Fig 2. Kaplan-Meier survival graph for BKA (red) vs AKA (blue), with 95% confidence intervals (shaded areas). Time is measured in months passed since operation.

Of the 52 male patients, 21 (40%) were deceased at follow-up, and of the 27 female patients, 14 (52%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and

TABLE 3.

All-cause mortality rates at each of the given timeframes are demonstrated.

Timescale	Number of patients	% of those deceased (N=35)	% of overall cohort (N=79)
30-day	N=6	17%	8%
6-month	N=20	57%	25%
1-year	N=27	77%	34%
2-year	N=32	91%	41%
3-year	N=35	100%	44%

sex (p=0.3507).

Of the 46 diabetic patients, 24 (52%) were deceased at follow-up, and of the 33 non-diabetic patients, 11 (33%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and diabetic status (p=0.1127).

Of the 28 patients known to have heart failure, 16 (57%) were deceased at follow-up, and of those without known heart failure, 19 (37%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and heart failure (p=0.1028).

Of the 31 patients known to have renal failure, 18 (58%) were deceased at follow-up, and of those without renal failure, 17 (35%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and renal failure (p=0.0643).

Of the 10 patients known to have COPD, 3 (30%) were deceased at follow-up, and of those without COPD, 32 (46%) were deceased at follow-up. Fisher's exact test suggested that there was no statistically significant association between mortality rate and diabetic status (p=0.4987).

Information was available on NIECR regarding the recorded primary cause of death for 13 of the 35 deceased patients (37%); inpatient records were accessed for the remaining patients to determine likely cause of death.

Causes of death were attributed to chest/ urinary sepsis (N=6), myocardial infarction (N=4), malignancy (N=4), cardiac arrest (N=3), cardiac failure (N=3), renal failure (N=3), cerebrovascular accident (N=2), ruptured common iliac artery aneurysm (N=1) and hypoxic brain injury following hyperkalaemic cardiac arrest (N=1).

Cause of death was unclear for the remaining eight patients. Of these, six deaths were documented as 'expected' and/ or the patient was receiving palliative care. However, no clinical information relating to the event of death was available for the remaining two patients.

Incidence of VTE was then determined as a secondary aim of the study. Two patients developed contralateral radiologically-confirmed DVT; one patient at two months post-amputation and the other at 15 months post-amputation. Two patients also developed radiologically-confirmed non-fatal PE within twenty days of surgery.

DISCUSSION

This study examined all-cause mortality rates amongst patients undergoing AKA and BKA within Northern Ireland's Regional Vascular Centre within 2014-2015.

The mortality rates reported reflect the frailty of the study population, with almost one-tenth of the cohort dying within one month post-operatively.

The overall 30-day mortality rate of 8% was comparable to that found by Aulivola et al[3], which is somewhat lower than rates of 22-30% demonstrated in other studies[5,6,14]. This may reflect differences in both patient demographics within the study groups and practice between the different centres, including exclusion criteria regarding high-risk patients, time from decision to amputate to surgery being conducted, and the use of amputation as a means of pain relief at the end stages of care.

In contrast to findings from Aulivola et al[3], no statistically significant association between mortality rate and level of amputation, that is, below- or above-knee, was found. Aulivola et al, however, studied a larger cohort of patients (N=788) for a longer period (11 years). Their cohort also contained a relatively higher proportion of patients undergoing BKA than ours, with 73.4% of their cohort having undergone BKA and 26.6% AKA, as opposed to 51.9% and 48.1% of our cohort undergoing BKA and AKA respectively. Fortington et al[6] also found no significant difference regarding level of amputation and we note that their ratio of AKA to BKA appears more equivocal to ours.

Similar to the findings of Fortington et al[6] and Tentolouris et al[15], but in contrast to Aulivola et al[3], no statistically significant association between mortality rate and diabetic status was found. This may represent differences between study populations but also in diabetic classification and management between centres. Although our numbers of patients are too small to make meaningful comparisons, we note 13% of the diabetic cohort as opposed to 0% of the non-diabetic cohort were deceased at 30-days. We believe that further study regarding the relationship between diabetes duration and mortality is advisable, as longer duration of diabetes has previously been associated with increased all-cause mortality post-amputation amongst diabetic patients[15].

Unlike Jones et al[7], who found heart failure to be an independent predictor of mortality following major lower limb amputation, we did not identify a significant association between the two variables. We note that Jones et al used data relating to a much larger cohort, and as not all patients routinely undergo pre-operative screening echocardiography within the Unit, patients with milder degrees of ventricular impairment may not have been identified. Furthermore, due to the small sample size, it has not been possible to examine the relationship between degree of severity of heart failure and all-cause mortality.

The findings of Aulivola et al[3], Fortington et al[6], and Jones et al[7], indicated an association between CKD and all-cause mortality following major lower limb amputation. Our results suggested a trend but this was not statistically significant. This may relate to differences in cohort size, but also to patient selection and definition of chronic kidney disease. Due to small numbers of dialysis-dependent patients it was not possible to examine differences in all-cause mortality between those with dialysis-dependent CKD and non-dialysis-dependent CKD. However, we feel that this represents an

area for future investigation with a larger cohort.

Only ten patients within the cohort were known to have COPD from NIECR documentation. Although the sample size was too small to make meaningful statistical analyses, our results would suggest that no association exists between COPD and all-cause mortality following major lower limb amputation. This finding is in keeping with that of Fortington et al[6] who did not identify an association between chronic lung disease and 30-day, one-year or five-year mortality rates. We also note that many of the cohort may have had undiagnosed COPD at the time of surgery, and that as pulmonary function tests were not readily available on NIECR we were relying on potentially incomplete information. Smoking status was not readily available on NIECR which may be associated with increased all-cause mortality due to compromised respiratory clearance mechanisms in patients with already compromised mobility.

Almost half of our cohort was deceased at three years. However, it must be remembered that limb amputation may prevent sepsis-related deaths and improve quality of life in patients affected by PVD not amenable to other treatment measures. From our data, no clear determinants of the three-year survivors were found but further investigation of this group is suggested. We also feel, given the profile of the causes of death seen, further work is warranted regarding the effects of pre-operative care and rehabilitation services on mortality.

As a secondary aim of the study, the incidence of VTE post-amputation was examined. Two patients developed radiologically-confirmed DVT and two patients developed radiologically-confirmed PE. However, PE could not be excluded amongst the three patients who died following sudden cardiac arrest (particularly as one of these patients developed bilateral PE whilst inpatient post-amputation) and amongst those for whom no cause of death was recorded.

In their prospective study following 49 patients undergoing amputation in 2007-2009, Struijk-Mulder et al[9] found that two of their patients developed confirmed DVT (one of whom was symptomatic), and six patients developed confirmed PE (four of which were symptomatic including two fatal PE). However, Struijk-Mulder et al[9] screened for DVT and PE at approximately two weeks post-procedure and did not follow-up their patients for VTE occurrence post-procedure. This meant that their work facilitated detection of asymptomatic VTE, whilst VTE events occurring at later dates remain unknown. Ultrasound screening for DVT at both one week and two weeks post-procedure has been reported in other studies but there is insufficient evidence for this in the literature to advise incorporation of this into routine clinical practice at present[16,17]. Given that these studies have not examined VTE incidence at later dates post-amputation, the optimal timing for screening remains unclear.

There is also no consensus in the literature regarding optimal VTE prophylaxis amongst this patient group. A recent Cochrane review[8] concluded that there is insufficient evidence regarding VTE prophylaxis in lower limb amputees as only two studies (Lastoria 2006, Williams 1978) met their inclusion criteria for analysis. Of these, Lastoria et al found no significant difference in DVT rates in those undergoing major lower limb amputation treated with low-molecular weight heparin as opposed to those treated with unfractioned heparin[16]. Williams et al, however, found no significant difference in VTE incidence in those treated with unfractioned heparin compared with placebo[18]. The patients in our cohort did not routinely receive VTE prophylaxis upon discharge from the Vascular Surgery Unit as per policy within the Unit within 2014 and 2015. The effects of a change in local policy whereby patients being discharged following amputation and deemed to be at increased risk of VTE receive a 30-day course of prophylactic-dose low molecular weight heparin remain to be seen.

Limitations of our study include the single-centre data and small cohort size. We also relied upon documentation on NIECR and in medical charts, which may not always be accurate. Formal review of autopsy/ coroner documentation was not undertaken. We also have not explored the effect of pre-amputation vascular intervention and the potential impact of undergoing ipsilateral/contralateral amputation before, during or after follow-up. Additionally, the effect of further hospital admissions during the study period was not analysed, which may alter VTE risk.

CONCLUSION

This study adds to the evidence that vascular amputation is associated with significant mortality in patients with poor baseline health status. No significant association between level of amputation, diabetic status or presence of heart failure, CKD or COPD and mortality was found, although a non-significant trend was observed in the case of CKD.

Although lower than demonstrated in other studies, 30-day all-cause mortality was 8% and three-year all-cause mortality was 44%. Further work should be undertaken to identify those who are most at risk and to establish methods to reduce mortality.

Several patients also experienced VTE events; therefore, we suggest that further work be conducted to establish optimal practice regarding VTE detection and prevention. The impact on mortality of the change in local policy regarding VTE prophylaxis upon discharge wherein patients receive 30-days prophylactic-dose enoxaparin post-procedure remains to be seen.

Sources of financial support: None.

Declarations of interest: None

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