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Research Paper

Patients following lower limb amputation: A retrospective cohort study showing how to improve survival and rehabilitation outcomes

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ABSTRACT

Background: Increasing number of people are undergoing lower limb amputation as a result of complications of diabetes and peripheral vascular disease. Prosthetic rehabilitation is in these group of people is important in order to reduce dependency and maximize their function in society. Successful prosthetic outcome is dependent on associated comorbidities, which also affects survival.
Objective: To assess the survival rates in patients with lower limb amputation.
Study design: Retrospective analytic study of dysvascular lower limb amputation patients of age above 21 years discharged from rehabilitation facility in Singapore between March 2008 to November 2016.
Results: Seventy patients were followed up, of which 45 (64%) were men and 25 (36%) were women, with mean age of 62.7 (35–88) years. These patients were diagnosed with diabetes mellitus (DM), hypertension (HTN), ischaemic heart disease (IHD), or peripheral vascular disease (PVD), and had vascular interventions. At the time of amputation, patients have either normal renal function, chronic kidney disease (CKD), acute kidney injury, or end-stage renal failure (ESRF), of which some were on haemodialysis (HD). Significant comorbidities associated with mortality were IHD 4.44 (95%CI- 1.61–12.27, p value-0.003), CKD 8.31 (1.74, 39.75); p = 0.003, ESRF/HD, HR = 5.6 (0.65, 28.24); p = 0.083, combined CKD (stage 3,4) and ESRF/HD 10.49 (2.75, 40.1); p = 0.001.
Conclusion: From our study, lower limb amputation survival rate at 1 year was 84.13% and at 5 years was 48.6%. Mortality was significantly associated with ischaemic heart disease, CKD and those with ESRF with haemodialysis. This may indicate complications related to IHD and CKD rather than amputation itself.
Clinical relevance statement: Proactive management of ischaemic heart disease and chronic kidney disease is very important in dysvascular lower limb amputation as this affects the prosthetic rehabilitation outcomes. A multidisciplinary approach should be considered in patients with these comorbidities to improve survival and functional outcomes following prosthesis.

1. Background

Lower-limb amputee rehabilitation is a major component of multidisciplinary rehabilitation units. As the life expectancy is increasing, a higher number of elderly people with multiple comorbidities also undergo lower limb amputations. As a result, the survival rates in this group of patients vary. Revascularisation surgeries along with pre- and postoperative wound care may also affect the outcome in these patients.

Various comorbidities associated in patients with amputation have been shown to have significant effects on survival [1–7]. Majority of these patients undergo rehabilitation program with the aim of prosthesis fitting in the long term. Prosthetic rehabilitation outcomes in regard to functional use are better for those with fewer comorbidities. Rehabilitation in these patients should be goal oriented based on the individual need and functional status [8].

Knowing the survival outcomes of these patients with various co-morbidities may help allocate resources and save cost for the patients.

This study aimed to analyse survival outcome in patients with dysvascular lower limb amputation and identify relationship with

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existing comorbidities, i.e. diabetes mellitus (DM), peripheral vascular disease (PVD), ischaemic heart disease (IHD), estimated glomerular filtration rate (e-GFR), and chronic kidney disease (CKD). We also analysed the length of hospital stay, linear relationship with duration of DM, and vascular interventions.

2. Material and methods

2.1. Design

This is retrospective analytic study. This is a part of prognostication of various outcomes of patients admitted at secondary care government restructured hospital, rehabilitation medicine department. All patients' database is kept in paper and up-to-date electronic format, including all inpatient and outpatient document entries, recurrent admissions, investigations, and interventions. Death is recorded on electronic documents.

Patient: due to retrospective nature of the study, a waiver of consent was obtained from CIRB (2015/3112). The work has been reported in line with the STROCSS criteria [9].

This study registered with Research registry: research registry5005.

Subjects were patients with lower limb amputation consecutively admitted to the rehabilitation facility of a secondary care district general hospital and met the selection criteria of the study from March 2008 to November 2016. All the patients above age of 21 years, were included if they were admitted for rehabilitation following amputation, with minimum follow-up of 1 year during the study period.

We excluded those patients with traumatic amputation, those without follow-up records or lost follow-ups, and incomplete data. Follow-up records were reviewed from 1 to 8 years (January 2008 to November 2016).

2.2. Setting

The rehabilitation department is equipped with the most modern facilities for patients with stroke, acquired brain injury, spinal cord injury, post-amputation, and those with complex neurological problems. Hospital referrals include a mixture of population including all ethnicity and age groups. The post-amputation rehabilitation referrals are admitted under a rehabilitation team with long-term follow-up in combination with vascular surgery and diabetic services.

2.3. Data

Data collected were demographic details, cause and level of amputation, co-morbidities including DM, HTN, PVD, IHD, CCF (congestive cardiac failure), admission blood investigations including haemoglobin, albumin, renal function test, e-GFR, history of angioplasty, bypass grafting and number of days admitted during the postoperative period. Amputation levels were categorised as toe and forefoot amputation in one group, below-the-knee in second and above-the-knee amputation in third group with regard to the cause of amputation, clinical and biochemical evidence of DM, diabetic foot disease, and gangrene were categorised as DM alone. Clinical or radiological evidence of PVD was labelled as PVD. Clinical findings, biochemical parameters, electrocardiogram, Holter recording, and echocardiographic findings were reviewed and documented for evidence of IHD, cardiomyopathy, CCF, atrial fibrillation, and cardiac clots leading to acute embolism.

Left ventricular ejection fraction: of 50% and above was labelled as normal and 49% and below as impaired [10–12].

Admission, premorbid and subsequent eGFR were reviewed: The Kidney Disease: Improving Global Outcomes (KDIGO) staging was used as reference guide [13]. Those with normal renal function and those with CKD stage G1, G2, G3a were categorised into normal kidney function. Patients with CKD stages G3b, G4, G5 (are labelled as CKD). Acute kidney injury was labelled with transient impairment of eGFR which normalised subsequently. Patients on haemodialysis or peritoneal dialysis at the time of amputation were categorised separately.

Inpatient rehabilitation length of stay and post-discharge follow-up until death were reviewed and recorded.

2.4. Statistical methods

Categorical data are presented as frequency (percentage). Continuous data are presented as mean (standard deviation) for parametric distributions and median (interquartile range) for non-parametric distributions. Differences in characteristics were examined using chi-square tests for categorical variables and two-sample *t*-tests or Mann-Whitney U-tests for continuous variables, where appropriate. Odds ratios (OR) are presented along with 95% confidence intervals (CI). A two-tailed, p-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 19.0 (IBM Corp. Armonk, NY). Kaplan-Meier survival graphs were derived. Univariate and multivariate Cox proportional hazards regression was used for survival analysis and association with co-morbidities.

3. Results

A total of 70 patients were followed up, of which 45 (65%) were men and 28 (35%) women. The mean age was 62.7 (35–88) years. Of the patients, 69 (98%) had DM with median duration of 7 years, 62 (88%) had HTN, 37 (52%) had known IHD, 52 (74%) patients had PVD. Vascular interventions i.e. angioplasty or and bypass grafting was performed in 39 (55%) patients.

At the time of amputation, 35 (50%) had normal renal function, 18 (25.71%) had chronic kidney disease (CKD), 10 (14.28%) had AKI, and 8 (11.42%) had ESRF on haemodialysis at the time of amputation. Patient characteristics details (Table 1).

The results of the univariate analysis (Table 2).

These factors were assessed in a multivariable cox regression analysis to identify the optimal subset of independent predictors of mortality (Table 3).

The co-morbidities significantly associated with mortality were, underlying IHD, 4.44 (95%CI- 1.61 - 12.27, pvalue-0.003), (Fig. 1), CKD 8.31 (1.74, 39.75); $p = 0.003$, ESRF/HD, HR = 5.6 (0.65, 28.24); $p = 0.083$, combined CKD (stage 3,4) and ESRF/HD 10.49 (2.75, 40.1); $p = 0.001$ (Fig. 2).

However, analysis those without DM was not done, as there was only one patient in this category.

Of the 70 patients followed up for a minimum period of 12 months (maximum 112 months), 36 patients (51.4%) died. There was no statistically significant difference in survival between the above and below knee amputation groups ($p = 0.327$, HR = 0.545; 95% CI 0.162, 1.833) or below knee vs. toe and forefoot amputation. ($p = 0.378$, HR 0.514; 95% CI 0.117, 2.252), above knee vs. toe and forefoot amputation ($p = 946$, HR 0.943; CI 0.169, 5.248) and above knee vs. all other amputation (below knee, toe, forefoot) ($p = 0.416$, HR 1.63, CI 0.5–5.35). Other factors i.e. low haemoglobin, peripheral vascular disease, vascular interventions were not found to be significant associations with survival.

From our study, lower limb amputation survival rate at 1 year was 84.13% and at 5 years was 48.6%. The mean length of stay for lower amputation patients was 51.9 days (SD 28.6).

Table 1
Demographic details and significant comorbidities of patients.

Patient characteristics	% (no.)
Age (years); mean (range)	62.7 (21, 88)
Male	65% (45)
Length of hospital stay (days)	
median (range)	44.0 (8, 142)
Diabetes	96% (70)
Duration (years); median (range)	7 (1, 45)
Hypertension	64 (88%)
Ischaemic heart disease	63% (46)
SWMA	54% (36)
EF	
Normal	59% (39)
Mildly impaired	15% (10)
Severely impaired	26% (17)
Smoking	
No	73% (35)
Yes	21% (10)
Ex	6% (3)
Kidney function on admission	
Normal	44% (32)
CKD (stage3/4)	8% (6)
AKI	19% (14)
ESRF	29% (21)
Albumin; mean (range)	26.7 (11, 43)
Dialysis	11% (8)
Type of amputation	
Below knee	75% (53)
Above knee	25% (17)
Anaemia	
Normal (Hb $\geq$ 12)	12% (9)
Mild (Hb 8–<12)	81% (59)
Moderate (Hb 6–<8)	7% (5)
PVD	82% (60)
Angioplasty	55% (40)

Abbreviations: AKI, acute kidney disease; CKD, chronic kidney disease; ESRF, end-stage renal failure; Hb, haemoglobin; PVD, peripheral vascular disease; SWMA, segmental wall motion abnormalities.

Table 2
Relationship with survival (Cox proportional hazards regression).

Patient characteristics	Univariate analysis Unadjusted hazard ratio (95% CI)
Age (years)	1.025 (0.996, 1.054); p = 0.09
Male	1.44 (0.70, 2.98); p = 0.32
Length of hospital stay (days)	1.01 (0.996, 1.017); p = 0.24
Diabetes[a]	–
Duration[b] (years)	1.03 (0.98, 1.08); p = 0.23
Hypertension	1.17 (0.36, 3.85); p = 0.79
Ischaemic heart disease	2.34 (1.05, 5.20); p = 0.037
SWMA	2.12 (1.01, 4.46); p = 0.048
EF	
Normal	1
Mildly impaired	1.56 (0.60, 4.02); p = 0.36
Severely impaired	1.80 (0.84, 3.90); p = 0.13
EF	
Normal	1
Mildly/severely impaired	1.71 (0.86, 3.41); p = 0.12
Smoking	
No	1
Yes	1.90 (0.77, 4.70); p = 0.16
Ex	1.90 (0.24, 14.9); p = 0.54
Smoking	
No	1
Yes/Ex	1.90 (0.80, 4.55); p = 0.15
Kidney function on admission	
Normal	1
CKD (stage3/4)	1.53 (0.43, 5.42); p = 0.51
AKI	1.38 (0.52, 3.71); p = 0.52
ESRF	1.76 (0.79, 3.93); p = 0.16
Kidney function on admission	
Normal	1
Abnormal	1.60 (0.79, 3.27); p = 0.19
Albumin; mean (range)	1.024 (0.97, 1.08); p = 0.40
Haemodialysis	2.34 (0.96, 5.70); p = 0.06

Abbreviations: AKI, acute kidney disease; CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; ESRF, end-stage renal failure; Hb, haemoglobin; PVD, peripheral vascular disease; SWMA, segmental wall motion abnormalities. The number 1, indicated in front of the boxes of EF normal, smoking, and kidney function are the reference category for statistical analysis comparing with the next category below that parameter.

[a] Analysis not possible as only 3 patients without diabetes survived up to end of the study period.

[b] Analysis restricted to 69 patients with diabetes with data available on duration.

4. Discussion

Majority of patients undergoing amputation have DM and PVD as underlying causes.

In patients with PVD, significant and common factors associated are DM and smoking. With worsening of PVD, these patients are likely to have other co-morbidities, i.e. IHD, renal issues, and DM-related complications [1]. Moreover, poorer survival has been associated with age, level of amputation, and co-morbidities.

We studied the survival outcomes of patients who underwent a period of rehabilitation and correlated it with the level of amputation, revascularisation, underlying co-morbidities including DM, IHD, impaired renal function, and cardiac EF. Our survival analysis period covers from 6 months to 8 years.

Previous studies have described 30-day, 1-year and 5-year survival analysis in patients with limb amputation. We analysed the survival rates in patients with dysvascular lower limb amputation in the local population with various ethnicities and co-morbidities.

In a study of 299 subjects with amputations, Forthington et al. concluded that the median time to death was 20.3 months, and mortality was associated with cerebrovascular and renal diseases. For unilateral transtibial amputation, survival was 27.8 months and that of trans-femoral amputation was 10.6 months [2]. They also found high 30-day mortality (22%), which was attributed to amputation being done for pain relief as a part of end-of-life care. The authors did not find significant difference of mortality between patients with and without DM [2].

One-year mortality rates have been documented between 30 and 50% [2–7]. Age, level of amputation, vascular intervention, cerebrovascular accident, and renal or cardiac diseases have been associated with higher mortality [2].

Compared with other studies, our survival at 1 year was 84.13%. In previous studies, 5-year mortality was recorded between 56 and 70%, and risk of death was 5.4 times higher patients with renal disease [2,6,14,15]. Furthermore, we found subsequent survival of

Table 3
Relationship with survival (Cox proportional hazards regression).

Patient characteristics	Univariate analysis Unadjusted hazard ratio (95% CI)
Type of amputation	
Below knee	0.73 (0.29, 1.84); p = 0.51
Above knee	0.78 (0.17, 2.24); p = 0.64
Anaemia	
Normal (Hb $\geq$ 12)	1
Mild (Hb 8–<12)	1.28 (0.39, 4.22); p = 0.69
Moderate (Hb 6–<8)	1.44 (0.29, 7.20); p = 0.65
Anaemia	
Normal (Hb $\geq$ 12)	1
Mild/moderate (Hb 6–<12)	1.29 (0.39, 4.24); p = 0.67
PVD	1.33 (0.46, 3.80); p = 0.59
Angioplasty	2.33 (1.08, 5.02); p = 0.031

Abbreviations: CI, confidence interval; Hb, haemoglobin; PVD, peripheral vascular disease.
Number indicated as 1, in front of anaemia, is the reference category for statistical analysis to compare with those with low haemoglobin(anaemia).

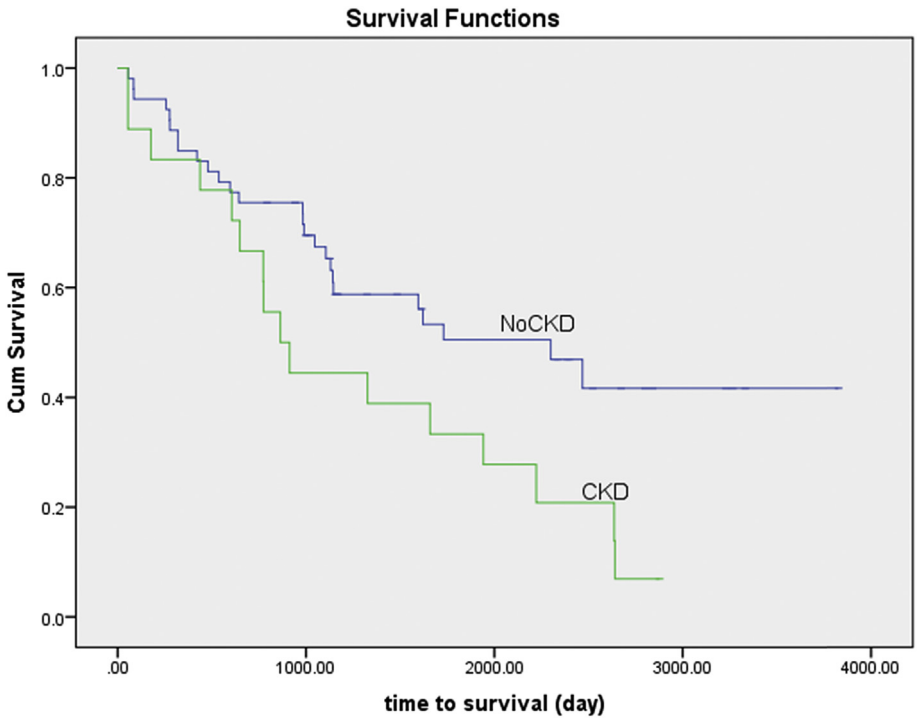

Fig. 1. Survival K-M curve comparing time to survival between patients with CKD and without CKD. There was significant difference in time to survival between two groups (p-value = 0.02).

48.6% at 5 years. In our study; we did not find significant difference in survival between above and below knee and toe/forefoot amputations, this could be attributed to relatively small sample size and associated co-morbidities.

Tentolouris et al. compared patients with and without DM with amputees, and the mortality rates were 61% and 54.3% at 5.2 and 5.3 years, respectively. In our study, only one patient without DM survived until the end of the study. Our data for 5-year mortality are similar to those of previous studies at 48.6% [16] Furthermore, they concluded that in patients with DM, DM duration, stroke history, and creatinine level were significantly associated with mortality, but stroke, creatinine, and higher WBC counts in patients without

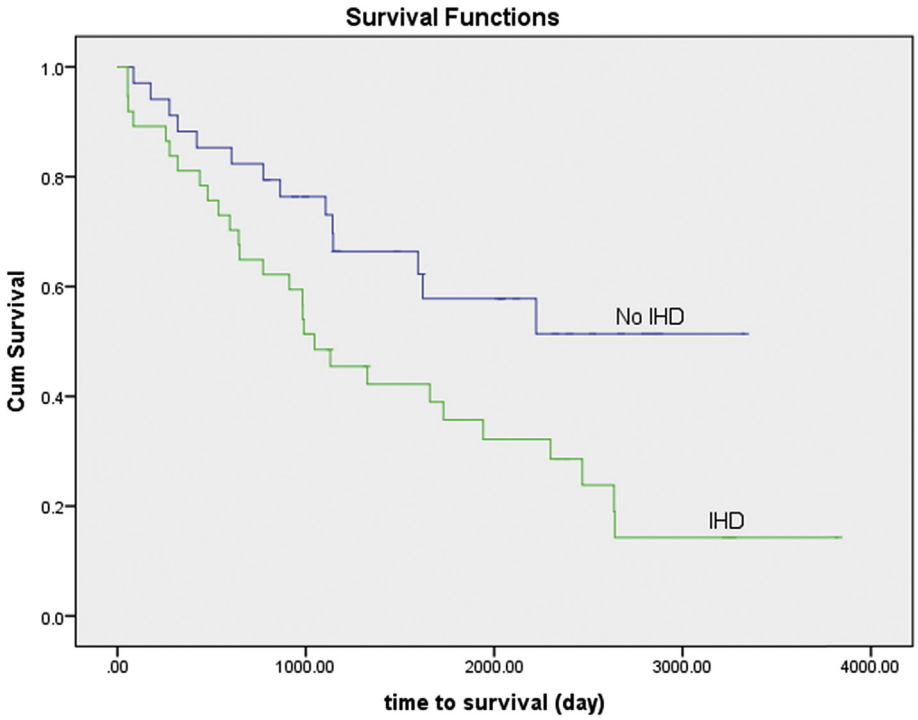

Fig. 2. Survival K-M curve comparing time to survival between patients with IHD and without IHD. There was significant difference in time to survival between two groups (p-value = 0.14).

DM. Nephropathy was the only modifiable risk factor found to improve survival [16]. In our study, of all the 70 patients, 35 (50%) had normal kidney function, 18 (25.71%) had CKD, 10 (14.28%) had AKI, and 8 (11.42%) had ESRF with HD.

Although survival was not associated with previous revascularisation from the present study, Faglia et al. [17] concluded that revascularisation allowed postponing the amputation only with better survival compared with the non-revascularised group [18]. From our study, 39 (55.71%) patients underwent vascular interventions without any relationship with mortality.

Limitation of the study:

1. Single centre and retrospective nature of the study.
2. Only patients studied which underwent rehabilitation program.
3. Immediate perioperative mortality might have influenced our results.

5. Conclusion

Our 1- and 5-year dysvascular lower limb amputation survival rates are 84.13% and at 5 years was 48.6%. We concluded that CKD and ESRD with HD had significant independent relationship with mortality. Similarly, higher mortality in subjects with CKD and ESRD could imply long-term complications associated with deteriorating renal function and HD itself, reducing survival rates in patients with amputation.

Improved perioperative medical management of underlying cardiac risk factors should be considered for better post amputation survival.

Conservative approach may be considered for patients with severe renal dysfunction and those on HD, and amputation can be offered as a life saving measure.

Prosthetic prescription should be carefully chosen, as it may worsen the underlying cardiovascular status.

We aim to analyse survival rates from all the postoperative lower amputation patients in our future study along with prosthesis usage and functional outcomes.

Ethical approval

The data collection was done with SingHealth IRB approval. 2015/3112.

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Author contribution

All the authors have contributed towards this study.
Study conception: S D Pande.
Data collection: Aliah Kamal, Eimon Zaw.
Statistical analysis: Aung Soe Tin.
Investigation: S D Pande, Aliah Kamal, Eimon Zaw.
Writing: S D Pande.

Conflict of interest statement

None of the authors in the study has any conflict of interest to declare.

Guarantor

I Shrikant D Pande, as first and corresponding author will accept full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

Research registration number

Name of the registry: Research registry.
Unique Identifying number or registration ID: researchregistry5005.
Hyperlink to the registration (must be publicly accessible): Post-amputation Survival Following Rehabilitation Medium and Long-term Follow up Study, a Retrospective Analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2019.08.003.

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