The role of chronic kidney disease as a predictor of outcome after revascularisation of the ulcerated diabetic foot

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Abstract

Aims/hypothesis The aim of the study was to stratify the risk of diabetic patients with leg ulcer or gangrene undergoing infrainguinal revascularisation for critical limb ischaemia.

Methods The study cohort included 732 revascularisation procedures performed in 597 diabetic patients with ulcer or gangrene. Logistic regression and CART analysis were used for identification of predictors of 1-year outcome.

Results Logistic regression showed that chronic kidney disease (CKD) class (OR 1.38, 95% CI 1.16, 1.65) was an independent predictor of 1-year leg salvage (area under the receiver operating characteristic [ROC] curve 0.60, 95% CI 0.54, 0.65). The terminal nodes of the CART for 1-year leg salvage were CKD classes 4–5, the level (infrapopliteal vs femoropopliteal revascularisation), type of revascularisation (bypass surgery vs percutaneous transluminal angioplasty) and gangrene (area under the ROC curve 0.62, 95% CI 0.57, 0.68). Logistic regression showed that pulmonary disease (OR 1.76, 95% CI 1.11, 2.78), CKD class (OR 1.43, 95% CI 1.24, 1.65), foot gangrene (OR 1.76, 95% CI 1.21, 2.60) and patient age (OR 1.02, 95% CI 1.01, 1.04) were independent predictors of 1-year amputation-free survival (area under the ROC curve 0.65, 95% CI 0.60, 0.69). The terminal

nodes of the CART for 1-year amputation-free survival were CKD classes 3–5, patient's age of ≥ 75 years and foot gangrene (area under the ROC curve 0.64, 95% CI 0.60, 0.68). **Conclusions/interpretation** CKD is a formidable risk factor for poor intermediate outcome after infrainguinal revascularisation in diabetic patients with foot ulcer or gangrene. CART analysis indicates that foot gangrene is also a significant risk factor for adverse outcome.

Keywords Chronic kidney disease · Diabetic foot · Revascularisation · Ulcer

Abbreviations

CART Classification and regression tree
CKD Chronic kidney disease
CLI Critical limb ischaemia
ROC Receiver operating characteristic

Introduction

Peripheral arterial disease prevents healing of diabetic foot ulcers far more commonly than generally understood [1]. In two recent large studies, ischaemia was found in 60% to be a major aetiological component of diabetic foot complications with resulting ulcers and gangrene [1, 2]. Therefore diabetes is a determinant of poor outcome after revascularisation for critical lower limb ischaemia (CLI) [3]. It is associated with a significant number of postoperative systemic and lower limb adverse events [4], and, quite commonly, major limb amputation is required in diabetic patients despite a patent bypass graft [5] or patent endovascularly treated artery [6]. Estimation of the risk of adverse outcome in this high-risk patient population would enable clinicians to better understand the determinants of an

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unfavourable course of events after lower limb revascularisation, to direct resources to those patients with a potentially favourable outcome, and to focus research on those with poor prognosis. These risk estimates are usually based on conventional regression methods, but such prognostic information is not easy to use in routine clinical practice. During the last two decades, classification tree analysis methods have been developed to provide more ‘clinician-friendly’ data [7], and they are increasingly used in clinical research [8–10]. These methods may detect relevant interactions between variables and allow the identification of patients with a similar combination of clinical characteristics and prognosis.

The aim of this study was to develop classification trees to estimate the probability of adverse outcome 1 year after lower limb revascularisation for CLI in diabetic patients with a leg ulcer or gangrene.

Methods

From January 2000 to December 2006, 1,575 unilateral, infrainguinal revascularisation procedures were performed to treat CLI at the Department of Vascular Surgery, Helsinki University Central Hospital, Finland. Of these, 874 procedures were performed in 711 diabetic patients. In this series, at 1-year follow-up, diabetic patients had significantly lower amputation-free survival (65.3% vs 75.2%, logrank test, $p<0.0001$), leg salvage (84.0% vs 89.5%, logrank test, $p<0.0001$) and survival (74.1% vs 80.3%, logrank test, $p<0.0001$) rates than non-diabetic patients. Diabetic patients with rest pain, an ulcer or gangrene had significantly different 1-year leg salvage (rest pain, 90.3%; ulcer, 84.1%; gangrene, 74.8%; logrank test $p=0.005$), survival (rest pain, 81.0%; ulcer, 75.7%; gangrene, 62.9%; logrank test $p<0.0001$) and amputation-free survival (rest pain, 74.6%; ulcer, 66.4%; gangrene, 51.7%; logrank test $p<0.0001$) rates. Because of their significantly poorer intermediate outcome, our aim in the present analysis was to evaluate the outcome after 732 revascularisation procedures performed on 597 diabetic patients with a foot ulcer or gangrene, with a follow-up of at least 1 year. CLI in these patients was defined as a tissue lesion that had not healed with conservative treatment and haemodynamically significant atherosclerosis determined arteriographically supported with transcutaneous oxygen pressure, ankle and toe pressure when available.

The study protocol was approved by the Institutional Review Board of Helsinki University Central Hospital (Department of Surgery).

Clinical characteristics as well as operative and immediate postoperative outcome data of these patients were collected prospectively in our institutional database and scrutinised case

by case retrospectively. Later, dates of death were retrieved from the Finnish national registry, Statistics Finland. Data on any major lower limb amputation and re-interventions were completed retrospectively from the files of the National Research and Development Centre for Welfare and Health, an institution that stores the information on all surgical procedures in a national database. Major amputations included all amputations above ankle level. Leg salvage was defined as freedom from major amputation of the revascularised leg.

Preoperative GFR was estimated using the modified Modification of Diet in Renal Disease Study equation [11, 12]. Renal failure severity was classified according to the chronic kidney disease (CKD) classification [13].

Angiographic status of runoff arteries Preoperative angiographs were reviewed retrospectively, and the angiographic status of leg and foot arteries was quantified according to the following criteria: 0, normal or <20% stenosis; 1, 20–49% stenosis; 2, 50–99% stenosis; 3, less than half of the artery occluded; 4, half or more of the artery occluded. The angiographic status of the revascularisation target artery was estimated by the site of the percutaneous transluminal angioplasty/distal anastomosis downward, as advised in the Ad Hoc Committee’s reporting standards [14]. Furthermore, angiographic runoff was categorised in terms of target vessel patency, also known as in-line open continuation, down to the pedal arteries. If only the peroneal artery was patent below the knee, it was rated as no in-line continuation to the pedal arteries.

Outcome end points Since poor early outcome characterises the course of treatment for a large number of patients, we chose 1-year major lower limb amputation and amputation-free survival as the main outcome measures for the identification of adverse risk factors and for the comparison of logistic regression and classification and regression tree (CART) analyses. Indeed, an analysis of 1-year outcome facilitates the identification of those patients who are not likely to gain any significant benefit from revascularisation attempts. Because of this, only patients with a follow-up of at least 1 year or who experienced a lower limb amputation and/or died within 1 year after revascularisation were included in the present analysis.

Statistical analysis Statistical analysis was performed using SPSS statistical software (SPSS v. 15.0; SPSS, Chicago, IL, USA). Continuous variables are reported as the mean±SE. Pearson’s χ^2 test, Fisher’s exact test and the Mann–Whitney test were used for univariate analysis. Logistic regression with backward selection was performed to identify predictors of major lower limb amputation and/or all-cause mortality 1 year after revascularisation. Hosmer–Leme-

show's test was applied to assess the regression model fit. Only variables listed in Table 1 with a p value <0.2 at univariate analysis were included in the regression model. The angiographic status of the target vessel was included in the analyses instead of the angiographic runoff score, as the latter has been estimated for different levels of revascularisation and, by definition, differs according to the level of revascularisation.

CART analysis was performed to identify independent risk factors for 1-year outcome. CART analysis is a non-parametric decision tree methodology that has the ability to efficiently segment populations into meaningful subgroups. This allows clinicians to identify subgroups of a study population that have most or least risk of an adverse event. Because CART analysis is intended to identify distinct population subgroups, its hierarchical nature does not allow the estimation of net effects of a single independent variable. Thus it must be viewed as an additional tool to identify risk factors for adverse outcome. Validation of the classification tree procedure was assessed by means of cross-validation through 25-folds. The minimum number of patients for the parent node was set to 100 and the minimum for the child node was 50 in the CART analysis of 1-year leg salvage and 1-year amputation-free survival. The maximum classification tree depth was 5. Gini's method was used to measure impurity, which is the extent to which a node does not represent a homogeneous subset of cases. Minimum change in improvement was set at 0.0001. Bar charts of model importance by independent variable were developed. CART estimated the most appropriate cut-off value of CKD classes and patient age for predicting each outcome end point. Once such cut-off values were identified, the variable was dichotomised to simplify the CART analysis. Receiver operating characteristic (ROC) curve analysis was used to estimate the area under the curve of probabilities values estimated by the logistic regression and CART analysis models in predicting adverse outcome events. Long-term outcome was assessed by means of the Kaplan–Meier and Cox regression methods. $p<0.05$ was considered significant.

Results

The baseline clinical characteristics and operative data of the study population are summarised in Table 1. The mean length of follow-up was 2.8 ± 2.2 years. The Kaplan–Meier estimate of survival, leg salvage and amputation-free survival are summarised in Table 2. As reported below, CKD class was an independent predictor of 1-year outcome (1-year leg salvage: class 1=88.3%, class 2=86.1%, class 3=86.3%, class 4=75.4%, class 5=70.1%, $p<0.0001$; 1-year

amputation-free survival: class 1=79.3%, class 2=67.1%, class 3=59.8%, class 4=52.5%, class 5=47.8%, $p<0.0001$). Patients with gangrene had significantly poorer 1-year leg salvage (78.8% vs 85.5%, logrank $p=0.044$) and amputation-free survival (51.7% vs 66.4%, log rank $p=0.001$) rates.

One-year major lower limb amputation Predictors of 1-year major lower limb amputation at univariate analysis are summarised in Table 1. Logistic regression (Hosmer–Lemeshow: $p=0.31$) showed that only CKD class ($p<0.0001$, OR 1.38, 95% CI 1.16, 1.65) was an independent predictor of 1-year major lower limb amputation. The area under the ROC curve for this model was 0.60 (95% CI 0.54, 0.65, $p=0.001$).

CART analysis was performed including CKD class, level of revascularisation (infrapopliteal vs femoropopliteal revascularisation), foot gangrene and type of revascularisation (bypass surgery versus percutaneous transluminal angioplasty). Figure 1 shows the CART for prediction of 1-year major lower limb amputation. Terminal nodes of the CART were CKD classes 4–5, level (infrapopliteal vs femoropopliteal revascularisation) and type (bypass surgery vs percutaneous transluminal angioplasty) of revascularisation as well as gangrene. This model had an area under the ROC curve of 0.62 (95% CI 0.57, 0.68; $p<0.0001$).

Cox regression analysis revealed that the probabilities for 1-year leg salvage rate as estimated with both the logistic regression ($p<0.0001$) and the CART procedure ($p<0.0001$) were also predictive of late outcome.

One-year amputation-free survival Predictors of 1-year amputation-free survival at univariate analysis are summarised in Table 1. Logistic regression (Hosmer–Lemeshow: $p=0.07$) showed that pulmonary disease ($p=0.02$, OR 1.76, 95% CI 1.11, 2.78), CKD class ($p<0.0001$, OR 1.43, 95% CI 1.24, 1.65), foot gangrene ($p=0.003$, OR 1.76, 95% CI 1.21, 2.60) and patient age ($p=0.004$, OR 1.02, 95% CI 1.01, 1.04) were independent predictors of 1-year amputation-free survival. The area under the ROC curve for this model was 0.65 (95% CI 0.60, 0.69; $p<0.0001$).

CART analysis was performed including CKD class, foot gangrene, pulmonary disease, coronary artery disease and patient age. A preliminary CART analysis identified a cut-off value for age of 77, and a cut-off point of 75 was used to simplify the final CART analysis.

In CART analysis, coronary artery and pulmonary disease had low predictive importance. When the minimum number of patients for the parent node was set to 100 and the minimum for the child node was 50 in the CART, pulmonary disease and coronary artery disease were not included in the tree (Fig. 2). The terminal nodes of the CART for the prediction of 1-year amputation-free survival were CKD classes 3–5, patient age of ≥ 75 years and

Table 1 Baseline characteristics and operative data on 732 isolated infrainguinal revascularisation procedures performed on diabetic patients with critical leg ischaemia and a leg ulcer or gangrene

Characteristic	Mean±SE or <i>n</i> (%)	1-Year leg salvage		1-Year major amputation-free survival	
		Univariate analysis (<i>p</i> value)	Logistic regression: <i>p</i> value, OR (95% CI)	Univariate analysis (<i>p</i> value)	Logistic regression: <i>p</i> value, OR (95% CI)
Age (years)	71.7±11.5	0.24		0.003	0.004, 1.02 (1.01, 1.04)
Female	313 (42.8)	0.78		0.24	
Pulmonary disease	91 (12.4)	0.27		0.024	0.02, 1.76 (1.11, 2.78)
Hypertension	570 (77.9)	0.68		0.67	
Coronary artery disease	489 (66.8)	0.31		0.013	
Cerebrovascular disease	152 (20.8)	0.59		0.49	
Previous lower limb revascularisation	70 (9.6)	0.23		0.49	
Previous revascularisation on the same segment	37 (5.1)	0.25		0.37	
Serum creatinine (μmol/l)	154±150	0.003		<0.0001	
eGFR (ml/min/1.73 m ²)	59±32	0.013		<0.0001	
CKD class ^a		0.003	<0.0001, 1.39 (1.16, 1.65)	<0.0001	<0.0001, 1.43 (1.24, 1.65)
1	111 (15.2)				
2	237 (32.4)				
3	256 (35.0)				
4	61 (8.3)				
5	67 (9.2)				
Indication for revascularisation		0.044		0.001	0.003, 1.76 (1.21, 2.60)
Ulcer	581 (79.4)				
Gangrene	151 (20.6)				
Angiographic score	6.8±1.9	0.11		0.18	
Target vessel patent down to the pedal arteries	241 (32.9)	0.22		0.79	
Target level		0.10		0.65	
Femoropopliteal segment	303 (41.4)				
Infrapopliteal arteries	429 (58.6)				
Treatment method					
PTA	377 (51.5)	0.17		0.44	
Surgery	355 (48.5)				

Results of univariate and multivariate analysis are for 1-year leg salvage and 1-year amputation-free survival

^a CKD class, chronic kidney disease class according to estimated GFR (eGFR; ml min⁻¹ 1.73 m⁻²): class 1 (normal), eGFR ≥90; class 2 (mild), eGFR 60–89; class 3 (moderate), eGFR 30–59; class 4 (severe), eGFR 15–29; class 5 (kidney failure), eGFR <15

PTA, percutaneous transluminal angioplasty

gangrene. The area under the ROC curve for this model was 0.64 (95% CI 0.60, 0.68; *p*<0.0001).

Cox regression analysis showed that the risk of 1-year amputation-free survival as estimated with both the logistic

Table 2 Kaplan–Meier estimates of outcome after isolated, infrainguinal revascularisation procedures for critical limb ischaemia in diabetic patients with a leg ulcer or gangrene

Outcome	30-day	1-year	2-year	3-year	4-year	5-year
Survival, % (<i>n</i>)	95.6 (700)	73.1 (535)	63.4 (381)	52.4 (287)	45.0 (213)	41.3 (144)
Leg salvage, % (<i>n</i>)	95.5 (672)	82.3 (464)	78.9 (327)	78.1 (237)	75.8 (177)	74.1 (116)
Amputation-free survival, % (<i>n</i>)	91.8 (672)	63.4 (464)	54.6 (327)	44.1 (237)	37.0 (177)	33.5 (116)

Number of patients entering intervals is reported in parentheses

Fig. 1 CART summarising independent predictors of 1-year leg salvage. The improvement values are reported at the splitting of the parent node. rev., revascularisation

regression ($p < 0.0001$) and the CART procedure ($p < 0.0001$) was also predictive of late outcome.

Discussion

Diabetes is the most significant risk factor for CLI and amputation. Patients with diabetic foot have several additional risk factors for developing a limb-threatening tissue lesion compared with non-diabetic patients, with the most important being neuropathy, tendency to infection, foot deformities and renal insufficiency. Indeed, after bypass for CLI, diabetic patients may have an amputation with a patent bypass graft more often than non-diabetic

patients within 30 days of the procedure [4]. Also, the nature of peripheral artery disease is different in diabetic compared with non-diabetic patients, the former more often having arterial lesions in infrapopliteal arteries [15]. Treatment of diabetic neuroischaemic foot forms a significant workload in vascular surgery. Despite the different nature of peripheral artery disease in diabetic patients, studies on diabetic patients only are not common. Because of this, we decided to study factors predicting the outcome of CLI with tissue lesion in this group of patients. The main finding of our study is that, in diabetic patients, with ulcer or gangrene due to CLI, CKD is a significant predictor of both leg salvage and amputation-free survival. In previous studies, renal failure has been

Fig. 2 CART summarising independent predictors of 1-year amputation-free survival. The improvement values are reported at the splitting of the parent node

reported to be associated with less efficient wound healing and major amputations in such patients [2, 16]. Also, the outcome is associated with the level of kidney disease: the risk of amputation increases with worsening kidney function [2]. In patients with end stage renal disease, primary amputation rates have been reported to be as high as 40% [17].

In our hospital, we have a very active revascularisation policy, and kidney disease has not usually had an effect on the revascularisation decision. Only bedridden or severely demented patients, patients with a large tissue lesion in the calcaneal area with no opportunity for microvascular flap reconstruction, patients with short life expectancy, and those with no technical revascularisation possibilities assessed from the angiogram have been left without revascularisation. In this study, amputation-free survival in patients in CKD classes 3–5 was 41%. This suggests that there should be more careful patient selection in this patient group.

This study shows that CART analysis can provide clinicians with a clear and easy-to-use map of risk factors that threaten the intermediate outcome of diabetic patients with CLI and leg ulcer or gangrene requiring lower limb revascularisation. In addition to its intuitive nature and easy-to-understand graphic explanatory trees, this method allows the identification of the relatively small number of patients who are reasonably homogeneous with regard to the outcome. In contrast with the traditional regression method, which computes the prognostic index as a weighted average of patients' characteristics, CART analysis provides subgroups based directly on patient characteristics and demonstrates the association between different variables and their direct effect on patients' outcome.

Herein, logistic regression and CART analysis produced somewhat different results. Foot gangrene and the level and type of revascularisation were significant predictors of poor leg salvage in CART analysis, but not in logistic regression. Pulmonary disease was an independent predictor of poor 1-year amputation-free survival rate in logistic regression. However, pulmonary disease as well as coronary artery disease had only marginal predictive value in CART analysis. This may be due to differences in the methods of analysis between CART and logistic regression, as well as possible differences in classification methods. In fact, CART is only one (but the most commonly used) of the classification tree procedures, the results of which can be affected by several methodological issues. In the present analysis, we attempted to develop classification trees of reduced size and possibly of more clinical relevance. The inclusion of more variables in classification trees with a rather large minimum number of patients in the parent and child nodes probably resulted in the exclusion of a few

variables that would have had some predictive value in subgroups of small size, although they would not necessarily have been of clinical relevance. This was the case with, for example, coronary artery disease in the CART analysis for the prediction of 1-year amputation-free survival. Decreasing the minimum number of patients in the parent and child nodes resulted in a much larger CART, in which coronary artery disease was shown to be associated with poorer 1-year amputation-free survival rates in each terminal node (data not shown). This links the observation of a major clinical impact of coronary artery disease in patients with CLI [3]. However, the analysis in these terminal nodes was necessarily restricted to a rather small number of patients and is thus possibly not so reliable. It is worth noting that 'enlargement' of the CART in any way failed to reveal any significant effect of pulmonary disease on 1-year amputation-free survival. We believe that an estimation of the predictive importance of these variables effectively guided us in the development of clinically sound and valuable classification trees.

It is worth noting that, herein, we did not achieve optimal areas under the ROC curve for the prediction of poor intermediate outcome with either logistic regression or CART. We had previously encountered the same problem in a study dealing with a large series of infrainguinal revascularisation procedures from the nationwide registry, Finnvasc [3]. This is probably due to the wide heterogeneity of the degrees of lower limb ischaemia [18], the lack of data on biochemical variables such as C-reactive protein to stratify the severity of lower limb ischaemia-related infections [5, 19], a lack of data on wound characteristics [20], possible heterogeneity in the methods and techniques of revascularisation, and, in this setting, the severity of diabetes and its related complications as well as the regimen of blood glucose level control [21]. As the last, but not least, influencing factor, the functional status of the patient with CLI may affect the outcome of lower limb revascularisation [22] and is not adequately depicted by the usually recorded clinical variables.

As the present study is based on registry data examined retrospectively, it has certain limitations. The vascular registry in our hospital has very good coverage, because missing data are checked annually against the anaesthesia records. Patient selection was also necessarily dependent on the use of TASCII criteria for peripheral artery disease [23], but these are accepted as having limited relevance to a population with diabetes. In a registry-based study, the patient population is heterogeneous and predisposed to several confounding factors. The data are derived only from patients who underwent revascularisation and do not include patients turned down for revascularisation. The selected population was also potentially subjected to

unquantifiable factors that determine referral to our particular specialist unit, even though we believe it to be representative. On the other hand, the advantage of a registry-based study is that all the patients are included in the analysis, avoiding selection bias as far as possible. The choice of outcomes was also determined by the limitations imposed by data stored on the registry and was restricted to amputation and death.

In conclusion, CKD was found in this study to be a formidable risk factor for poor intermediate outcome after infrainguinal revascularisation in diabetic patients with foot ulcer or gangrene. CART analysis indicates that foot gangrene is also a significant risk factor for adverse outcome.

CART analysis, as shown herein, may enable clinicians to investigate multilevel interactions between risk factors and therefore to make a detailed estimation of the risk of poor intermediate outcome after revascularisation for CLI. This method may be useful in investigating the associations between clinical variables that are not evident with other conventional regression methods.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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