Impact of cardiovascular risk factors on severity of peripheral artery disease

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ABSTRACT

Objective: The development of peripheral artery disease is affected by the presence of cardiovascular risk factors. It is unclear, whether particular risk factors are leading to different clinical stages of peripheral artery disease. The aim of this retrospective cross-sectional study was to assess the association of cardiovascular risk factors with the presence of critical limb ischemia.

Methods: The study cohort was derived from a consecutive registry of patients undergoing endovascular therapy in a tertiary referral centre between January 2000 and April 2014. Patients undergoing first-time endovascular intervention for chronic peripheral artery disease of the lower extremities were included. Univariate and multivariate logistic regression models were used to assess the association of age, sex, diabetes mellitus, hypertension, dyslipidaemia, smoking, and renal insufficiency with critical limb ischaemia vs. intermittent claudication.

Results: A total of 3406 patients were included in the study (mean age 71.7±11.8 years, 2075 [61%] male). There was a significant association of age (OR 1.67, 95%-CI 1.53-1.82, $p < 0.001$), male gender (OR 1.23, 95%-CI 1.04-1.47, $p = 0.016$), diabetes (OR 1.99, 95%-CI 1.68-2.36, $p < 0.001$) and renal insufficiency (OR 1.62, 95%-CI 1.35-1.96, $p < 0.001$) with the likelihood of critical limb ischaemia. Smoking was associated with intermittent claudication rather than critical limb ischaemia (OR 0.78, 95%-CI 0.65-0.94, $p = 0.010$), while hypertension and dyslipidaemia did not show an association with critical limb ischaemia.

Conclusions: In peripheral artery disease patients undergoing first-time endovascular treatment, age, male gender, diabetes, and renal insufficiency were the strongest predictors for the presence of critical limb ischaemia.

KEY WORDS

Peripheral artery disease, diabetic vascular disease, age, diabetes mellitus, renal insufficiency

INTRODUCTION

Cardiovascular risk factors affect development, progression and anatomic distribution of peripheral artery disease (PAD).(1-5) Its prevalence is associated with the number of risk factors.(6) It has also been shown that risk factor control is worse in patients with PAD compared to coronary artery disease and cerebrovascular disease.(7) Additionally, the extent of symptomatic PAD has a substantial influence on outcome: claudicants have a considerably better prognosis compared to patients with critical limb ischaemia.(8,9) The latter is a severe disease and the consequences can be dire - amputation, disability and death.(10-12) Repeated hospitalisations and interventions are causing a high economic burden.(13) Optimal control of arterial hypertension, diabetes mellitus, dyslipidaemia, and smoking is essential and current guidelines on management of PAD have addressed this issue. Unfortunately, sufficient risk factor control is often missing in patients presenting with critical limb ischaemia.(11) Cardiovascular risk factors may independently influence the degree of the clinical stage and therefore disease outcome. Risk tailored patient management depends on reliable risk stratification models. (14) It is unclear, however, whether different risk profiles lead to different stages of PAD. Better understanding of the association of risk factors and clinical presentation may support the clinician in sound decision-making regarding timing and indication of treatment or follow-up visits to improve outcome. High-risk patients may benefit from closer surveillance schemes and earlier revascularization to avoid disease progression.

The aim of this study was to assess the association of cardiovascular risk factors with the presence of critical limb ischemia in patients undergoing endovascular treatment for the first time. Our hypothesis was that patients differ regarding their cardiovascular risk profile.

METHODS

The local ethics committee approved this analysis and waived the need for individual patient consent (approval number 302/2014). This is a retrospective cross-sectional study originating from a consecutive registry of patients undergoing endovascular therapy in a tertiary referral centre between January 2000 and April 2014. We explored primary interventions in patients with chronic PAD of the lower extremities of atherosclerotic origin. In case of multiple interventions at the same time, only the intervention for the highest clinical severity was retained. Patients with non-atherosclerotic lesions, interventions in bypasses and dissections, hypogastric arteries, or prior to endovascular aneurysm repair (coiling/embolisation), erectile dysfunction, all secondary interventions, and acute limb ischaemia were excluded. Critical limb ischaemia (corresponding to Fontaine stages III-IV and Rutherford categories 4-6, respectively) was defined as a chronic condition presenting with ischaemic rest pain, with an ankle pressure of <50 mmHg or toe pressure <30 mmHg, or ischaemic lesions/gangrene, with an ankle pressure of <70 mmHg or toe pressure <50 mmHg, respectively.(9) Risk factors included in the analysis were age, gender, diabetes mellitus, arterial hypertension, dyslipidaemia, smoking, and renal insufficiency. Diabetes mellitus was defined as a fasting plasma glucose level ≥7.0 mmol/l or glycated haemoglobin >6.0 %, or assumed if the patient was on hypoglycaemic drugs.(3) Arterial hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, or assumed if the patient was on antihypertensive drugs.(3) Dyslipidaemia was claimed in the presence of a total cholesterol level >5 mmol/L, or high-density lipoprotein cholesterol level <1 mmol/L, or triglyceride level >2 mmol/L, or assumed if the patient was on lipid-lowering drugs.(3) Patients were classified as smokers (current or former; ≥ 1 pack-year of tobacco use) or non-smokers based on patient interview or chart documentation.(3) Renal function was grouped according to estimated glomerular filtration rates using the Modification of Diet in Renal Disease method.(15) Moderate to severe renal insufficiency was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2, corresponding to chronic kidney disease stages ≥ 3.(16)

In univariate and multivariate logistic regression models using two sided Wald tests the association of age, sex, diabetes mellitus, hypertension, dyslipidaemia, smoking, and renal insufficiency with the clinical severity of PAD (critical limb ischaemia vs. intermittent claudication) was assessed. Crude estimates are from logistic regression models containing only the specified risk factor while adjusted values are from models including all risk factors. Odds ratios >1 represent that patients were more

likely to suffer from critical limb ischaemia vs. intermittent claudication. The odds ratio for age represents increase in odds per decade increase of age. Missing data was accounted for using multiple imputation with age, sex, diabetes mellitus, hypertension, dyslipidaemia, creatinine, smoking, and the severity of PAD in the model to create 25 imputed datasets. A sensitivity analysis was carried out using only those patients with complete information on covariates. Additionally, we performed an analysis stratified for diabetes to assess whether associations of hypertension, dyslipidaemia, smoking, and renal insufficiency differed between diabetics and non-diabetics. A $p < 0.05$ was considered statistically significant. All analyses were performed using Stata version 13.1 (Stata Corporation, College Station, Texas).

RESULTS

Overall, there were 8875 procedures entered as primary interventions conducted on 4175 patients. The severity level was not recorded for 1899 interventions. Patients received up to 14 interventions, but only the first procedure for a given patient was retained in the analysis (excluding 787 interventions). In the case of multiple interventions at the same time, only the intervention for the highest severity was retained (excluding 2744 interventions). Furthermore, only interventions addressing Fontaine severity stages IIa, IIb, III and IV (corresponding to Rutherford categories 1-6) were retained (excluding a further 39 patients). This resulted in a final sample size of 3406 patients. Demographic data and pre-interventional characteristics (including missing values) of the patients at the time of the first intervention are shown in Table 1. Table 2 shows the association of each factor with the stage at which the patient received the first treatment.

All seven risk factors were significantly associated with disease stage using univariate logistic regression models. Hypertension and dyslipidaemia were no longer significantly associated in multivariate models. There were significant associations of age (OR 1.67, 95%-CI 1.53-1.82, p <0.001), male gender (OR 1.23, 95%-CI 1.04-1.47, p = 0.016), diabetes (OR 1.99, 95%-CI 1.68-2.36, p <0.001), renal insufficiency (OR 1.62, 95%-CI 1.35-1.96, p <0.001), and smoking (OR 0.78, 95%-CI 0.65-0.94, p = 0.010). Age, male gender, diabetes mellitus, and renal insufficiency increased the likelihood of critical limb ischaemia, while smoking reduced the likelihood. Results were broadly similar when restricted to cases with complete data (1985 [58.3%] patients, Table 3); although smoking (OR 0.83, 95%-CI 0.65-1.06, p = 0.134) was no longer associated after adjustment for other variables. Analyses stratified by diabetes status (Table 4) revealed that the effect of hypertension, dyslipidaemia, smoking or renal insufficiency on clinical severity did not differ between patients with and without diabetes (P for all interactions > 0.1).

DISCUSSION

We explored differences in cardiovascular risk profiles between patients with critical limb ischaemia versus intermittent claudication in a cross-sectional study of 3406 patients undergoing endovascular treatment for the first time. Older people, men, diabetics, and patients with impaired renal function were more likely to suffer from critical limb ischaemia. There was no significant association of arterial hypertension and dyslipidaemia after adjusting for the other risk factors. When the analysis was restricted to the 1985 patients with complete data, smoking was no longer significant. This large dataset identifies a group of cardiovascular risk factors that may independently influence the clinical severity and therefore disease outcome.

A high prevalence of PAD has been reported in the primary care population and routine ankle brachial index measurement to detect subclinical PAD has been proposed.(17,18) According to our results, older patients, men, patients with diabetes mellitus or patients with renal insufficiency have a higher risk to present with critical limb ischaemia. Health professionals should be aware of the causes leading to such a highly compromised situation. Therefore, early detection, best medical treatment and timely revascularisation to slow progression and evade complications, e.g. major amputation and death, are necessary. Additionally, a suitable follow-up scheme for high-risk patients and efforts to intensively control modifiable risk factors should be stimulated. Patients at lower risk could rather be managed conservatively; including supervised walking exercise to improve functional status.

Advanced disease can be expected at older age since there is a natural progression over the years.(1) We observed that age increases the risk of being treated with a critical limb ischaemia. Conversely, younger patients seem to be treated when moderately affected. This can be explained by higher demands, concerning physical function, and an increased life expectancy of younger patients, suggesting invasive interventions are performed already in less impaired individuals.

Several studies have previously confirmed the role of diabetes mellitus as a firm risk factor in cardiovascular disease.(5,19,20) In our analysis diabetes demonstrated the strongest association. Hence, diabetes not only causes the disease but also predisposes patients to an intervention at a higher stage. Diabetic peripheral neuropathy is common and can present as insensate feet and trigger ulceration. A fast disease progression with patient management (including referral to a specialised

department) lagging behind could support this finding as well. Obviously, rigorous serum glucose level control is very important in the prevention of complications.

Moderate to severe renal dysfunction (estimated glomerular filtration rate <60 ml/min per 1.73 m^2) was present in over one third of the patients in this series. Chronic kidney disease is a strong predictor for PAD.(21,22) We identified a significant difference when renal insufficiency existed, increasing the odds to present with critical limb ischaemia. At this stage, it is also a predictor for higher mortality.(23)

Smoking is a potent risk factor for lower limb atherosclerosis.(5,20,24,25) Interestingly, in this series smoking lowered the risk to undergo intervention with critical limb ischaemia. The reason for this relationship is not fully understood. Maybe it is influenced by higher alertness when it comes to patients who smoke, especially if they are younger, and endovascular treatment is performed at an earlier clinical stage. Additionally, our presented data cannot consider the effect of patients who went straight to surgery, e.g. revascularization or amputation, without prior endovascular intervention. In proportion, rate of primary amputation is less than 2% and surgical revascularization accounts for a quarter of patients. At our institution, smoking cessation is not mandatory for patients in order to undergo an endovascular intervention or surgery. However, after restriction of the analysis to only patients with complete data, smoking was no longer significant. A better understanding of this inconsistent behaviour is required.

Population-based studies show a female predominance in the burden of PAD in older age groups and the prevalence increases for both men and women with age.(26) Our adjusted analyses found a gender-link between endovascular treatment and clinical severity of PAD. Male gender increased the chance to present with critical limb ischaemia.

After taking into account other risk factors, arterial hypertension and dyslipidaemia were not significantly associated with critical limb ischaemia. These factors traditionally have a weaker effect on PAD evolution and progression than smoking and diabetes.(20) Furthermore, we could speculate that medical treatment of hypertension and dyslipidaemia as well as patient compliance is superior to diabetes. Another reason could be earlier referral for treatment.

Study Limitations. The following limitations of this study have to be addressed. Missing data can under- or overestimate the rate of events and change the odds ratio as seen with gender and smoking. Another limitation could be due to the selection of patients: only patients with PAD who

received a first endovascular intervention were included, whereas patients who did not receive an intervention or went straight to surgery were excluded. Furthermore, existing risk factors together with PAD severity might have played a role in the general practitioner's decision to refer the patient and our decision to intervene. Thus, selection bias might be an explanation for the lower risk observed for patients with tobacco use. We examined the presence of cardiovascular risk factors according to the definitions stated in the methods section. Since medication is also prescribed for secondary prevention, the true presence of a risk factor can be misrepresented. Secondly, patients might or might not be taking medication to control the risk factors. Thus, we do not know whether patients are a mix of controlled (e.g. treated) and uncontrolled risk factors. Taking medication could be a moderator here. Our patient registry only stored dichotomous answers for the presence/absence of risk factors and therefore does not allow for retrospective examination of actual continuous laboratory parameters.

CONCLUSION

In PAD patients undergoing first-time endovascular treatment, age, male gender, diabetes, and renal insufficiency were the strongest predictors for the presence of critical limb ischaemia.

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