Influence of Severe Chronic Kidney Disease on Outcomes of Endovascular Therapy for Peripheral Artery Disease

Kayo Sugiyama*, Toshiya Nishibe and Hitoshi Ogino

1Department of Cardiac Surgery, Aichi Medical University Hospital, Aichi, Japan
2Department of Cardiovascular Surgery, Tokyo Medical University Hospital, Tokyo, Japan

Abstract

Background: The influence of hemodialysis (HD) on limb salvage and survival in patients with peripheral artery disease (PAD) has been reported. However, whether severe chronic kidney disease (CKD) may increase the risk of outcomes in patients with PAD undergoing endovascular revascularization is unknown. In this present study, we evaluated the influence of CKD grade on outcomes, including amputation-free survival (AFS) and major adverse limb events (MALEs) + 30-day perioperative death (POD), after endovascular treatment (EVT) in patients with PAD.

Methods: Only patients with primary intervention were included. The eGFR was calculated automatic for each patient and patients were then stratified into two groups for comparative analysis: those with severe CKD (classes 4 and 5; eGFR <30) vs. those with lesser degrees of low-grade CKD (eGFR ≥ 30).

Results: Severe CKD was associated with a significantly higher proportion incidence of diabetes mellitus, HD, critical limb ischemia (CLI), and infrapopliteal lesions. AFS and MALEs+POD were significantly better in low-grade CKD than in severe CKD. In multivariate analysis, showed that HD and CLI were found to negatively impact affects AFS. In multivariate analysis, only CLI was found to negatively affect MALEs+POD.

Conclusions: The presence of severe CKD did not independently influence AFS and MALEs+POD. Appropriate revascularization should be considered in CKD patients before developing irreversible renal insufficiency.

Keywords: Hemodialysis; Chronic kidney disease; Peripheral arterial disease; Critical limb ischemia; Endovascular treatment; Major adverse limb events; Amputation free survival; Estimated glomerular filtration rate

Abbreviations: HD: Hemodialysis; CKD: Chronic Kidney Disease; PAD: Peripheral Arterial Disease; CLI: Critical Limb Ischemia; EVT: Endovascular Treatment; MALE: Major Adverse Limb Events; AFS: Amputation Free Survival; eGFR: Estimated Glomerular Filtration Rate

Introduction

The influence of hemodialysis (HD) on limb salvage and survival in patients with peripheral artery disease (PAD) has been reported in many studies. However, whether severe chronic kidney disease (CKD) increases the risk of outcomes in patients with PAD undergoing endovascular revascularization is unknown. Willenberg et al. found that the presence of CKD is an independent predictor of higher mortality in patients with critical limb ischemia (CLI) undergoing endovascular treatment (EVT), although major amputation is not influenced by renal function [1]. By contrast, Patel et al. reported that severe CKD increases the risk of late mortality, amputation, and death or amputation, without increasing the risk of late reinterventions or major adverse limb events (MALEs) in patients undergoing infrapopliteal EVT [2].

The objective of the present study was to evaluate the influence of CKD grade on outcomes, including amputation-free survival (AFS) and MALEs+30-day perioperative death (POD), after EVT in patients with PAD. CKD was stratified according to estimated glomerular filtration rate (eGFR; ml/min/1.73 m²) that was calculated for each patient by using the modified diet in renal disease equation [186.3 × Cr−1.104 age−0.203 × 0.742 (if female)] [2].

Materials and Methods

Study design

This was a retrospective cohort study of patients who underwent EVT for PAD at Tokyo Medical University Hospital from January 2011 to December 2014. The primary endpoint was defined as amputation-free survival (AFS), and the secondary endpoint was defined as MALEs+30-day POD. Limb salvage was defined as the absence of ipsilateral major amputation proximal to the ankle. AFS was a composite endpoint defined as freedom from ipsilateral major amputation proximal to the ankle and freedom from all-cause mortality. MALE was a composite of either major amputation or major reintervention. Major reinterventions included the creation of a new surgical bypass graft, use of thrombectomy or thrombolysis, or a major surgical graft revision, such as a jump graft or an interposition graft. Minor reintervention included endovascular procedures (percutaneous transluminal angioplasty, atherectomy, stenting) without thrombectomy/thrombolysis, and minor surgical revisions (patch angioplasty) [3-5].

All procedures were performed in accordance with the Helsinki Declaration. All patients provided a written consent that their clinical data might be used for scientific presentations or publications when they consulted the hospitals for the first time.

*Corresponding author: Kayo Sugiyama, MD, Clinical Lecturer, Department of Cardiac Surgery, Aichi Medical University Hospital, 1-1, Yazakonokari-machi, Nagakute, Aichi, 480-1195 Japan, Tel: +81-561-62-3311; Fax: +81-561-63-6193; E-mail: kayotaro3@gmail.com

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Study population

Only patients with primary intervention were included. Patients with prior EVT or surgical bypass of any locations in the aortoiliac, femoral, popliteal or distal arteries were excluded.

Demographics (age, sex, body mass index; BMI), comorbidities (hypertension, diabetes mellitus; DM, dyslipidemia), indications for intervention (intermittent claudication, critical limb ischemia; CLI), and noninvasive vascular laboratory data (ankle brachial pressure index; ABI) were recorded. Critical limb ischemia (CLI) was defined as rest pain or tissue loss (ulcer or gangrene).

The eGFR was calculated automatically for each patient by using the following equation: eGFR=186.3 × Cr−1.154 × age−0.203 × 0.742 (if female). Patients were assigned to standard CKD classes based on eGFR values: CKD1, GFR >90; CKD2 (mild), GFR of 60 to 89; CKD3 (moderate), GFR of 30 to 59; CKD4 (severe), GFR of 15 to 29; and CKD5 (kidney failure), GFR <15. Based on preliminary analysis, patients were then stratified, based on preliminary analysis, into two groups for comparative analysis: those with severe CKD (classes 4 and 5; eGFR <30) vs those with low-grade CKD (eGFR ≥ 30).

EVT procedure

All interventions were performed by or under the supervision of one certified vascular surgeon in an angiographic suite or an operating room with a portable imaging system [6,7]. Under local anesthesia, percutaneous access to the iliac, femoropopliteal, and tibial arteries was obtained from an ipsilateral, antegrade common femoral artery approach using a 6 or 7-F sheath. Lesions were crossed with a 0.035-inch, angle or straight, hydrophilic guidewire with or without a supporting 4-F straight catheter. Iliac artery lesions were treated with primary stenting, femoropopliteal artery lesions with primary stenting/balloon angioplasty with selective stenting (provisional stenting), and tibial artery lesions with plain old balloon angioplasty. Concomitant athrectomy was not generally performed. Typically, 70 units/kg of heparin sodium was administered intravenously during EVT, and 500 units/h of heparin sodium administration was continued for 48 hours after EVT. Aspirin (100 mg/day) and/or clopidogrel (75 mg/day) as well as cilostazol (100 to 200 mg/day) and/or beraprost sodium (60 to 120 μg/day) were orally administered after EVT, and were continued as long as adverse effects did not occur.

Data analysis and statistical methods

Data are shown as means ± standard deviation for continuous variables. The statistical software package JMP (SAS institute, NC, USA) was used for statistical analysis. Clinical outcomes of AFS and MALEs+POD were analyzed using the Kaplan-Meier method. Factors affecting AFS were assessed using univariate and multivariate analyses. For continuous data, the normality of the distribution was examined by the Kolmogorov-Smirnov test. Intergroup comparison was performed with the Student’s t test for normally distributed data, and with the Mann-Whitney U test for other data. Categorical data were analyzed using the Fisher exact test or Pearson χ2 test. The univariate predictors with a p<0.05 were selected with the stepwise method and entered into the multivariate analysis.

Clinically prescribed predictors, including age ≥ 75 years, male sex, BMI, ambulatory disturbance, ABI <0.7, CLI, smoking history, hypertension, dyslipidemia, DM, history of cerebrovascular disease, history of ischemic heart disease, infrapopliteal lesions, HD, severe CKD, and unsuccessful procedure, were included in the analyses. Hypertension was defined as a casual blood pressure of 149/90 mmHg and/or ongoing antihypertensive treatment. Diabetes was defined as an HbA1c level of 6.5% and/or ongoing antidiabetic medication. Dyslipidemia was defined as a serum low-density lipoprotein cholesterol level of 140 mg/dL, serum high-density lipoprotein cholesterol level of <40 mg/dL, or the prescription of lipid-lowering agents.

Results

We identified 175 patients (74%, 129 males), aged 73 ± 9 years old. Severe CKD (class 4 or 5) was found in 48 patients (27%), of which 12 had class 4 CKD (7%) and 36 had class 5 (20%); 35 patients were on HD, which was 20% of the total patients. The low-grade CKD group (classes 1-3) comprised 127 patients (73%), of which 12 had class 1 disease, 59 had class 2, and 56 had class 3.

Baseline characteristics of patients with severe CKD and low-grade CKD are presented in Table 1. Severe CKD was associated with a significantly (p <0.05) higher incidence of DM, HD, CLI, and infragingual lesions (p=0.0014, <0.0001, <0.0001 and 0.004). No significant differences were found in terms of age ≥ 75 years, sex, BMI <18.5, ambulatory disturbance, ABI <0.7, antplatelet therapy use, smoking history, hypertension, dyslipidemia, history of cerebrovascular disease, or history of ischemic heart disease between severe CKD and low-grade CKD groups.

The technical success rates were 97% and 94% in total cases and severe CKD cases, respectively. The 30-day survival rates were 99.5% in total cases and 100% in severe CKD cases. No complications occurred due to local access, including no hematomas, pseudoaneurysms, dissections, or emboli. At a median follow-up of 27 ± 16 months, of all patients, 19 (11%) had died and 10 limbs (6%) required major amputation. Among patients with severe CKD, 11 (23%) had died; moreover, 7 limbs (15%) required major amputation. Among all patients, major adverse cardiovascular events occurred in 19 patients (11%), and major re-intervention was performed in 8 limbs (5%), including below-knee femoropopliteal bypass, distal bypass surgery, and reinfrapopliteal PTA. Among patients with CKD, major adverse cardiovascular events occurred in 16 cases (33%) and major re-intervention was performed in 3 limbs (6%).

Freedom from MALEs+POD and AFS was found in 79% and 69% of patients, respectively, at 12 months (Figures 1 and 2). The Kaplan-Meier curves showed that the AFS was significantly better in patients with severe CKD.
with low-grade CKD than in those with severe CKD (73% low-grade CKD vs. 27% severe CKD, p <0.0001; Figure 3). Kaplan-Meier curves showed that the MALEs+POD was significantly better in low-grade CKD than in severe CKD (78% cases of low-grade CKD vs. 27% cases of severe CKD, p<0.0001; Figure 4).

The results of the univariate and multivariate Cox proportional hazard regression analysis for AFS are shown in Table 2. In univariate analysis, diabetes mellitus, history of coronary artery disease, CLI, ankle brachial pressure index lower than 0.7, severe CKD and HD negatively impacted AFS. In multivariate analysis, HD and CLI were found to negatively impact AFS.

The results of the univariate and multivariate Cox proportional hazard regression analysis for AFS are shown in Table 3. In univariate analysis, CLI, infrainguinal lesions and HD negatively impacted
Discussion

HD is a recognized risk factor for atherosclerosis. It is also well known that HD is associated with poor long-term survival after percutaneous catheter intervention for coronary artery disease and EVT for PAD [1,2]. Moreover, HD is well known to be associated with poor limb salvage after EVT [8-10]. Kumada et al. reported that HD is a strongly predictive risk factor for amputation and all-cause death, but not for restenosis [11]. By contrast, Iida et al. found that the significant risk factors associated with MALEs are HD, heart failure, and Rutherford classification 6 [12]. Based on these reports, whether HD is significantly associated with adverse limb events is unclear. Moreover, whether CKD, not HD alone, increases the risk of outcomes after EVT is not clearly elucidated.

The importance of CKD grade in the outcomes of revascularization for PAD has been reported in a few studies. O’Hare reported that patients with mild-to-moderate renal insufficiency are at increased risk for adverse outcomes such as death and cardiovascular complications after both lower extremity revascularization and other surgeries [9]. Brosi et al. reported that the presence of renal insufficiency is associated with increased major adverse events, mortality, and restenosis as well as with lower technical success rates in patients undergoing percutaneous coronary artery intervention and below the knee endovascular interventions [13]. Owens et al. found that the presence of severe CKD, particularly in those with an eGFR <30 ml/min/1.73 m² (CKD 4 and 5), is a powerful independent prognostic factor for the risk of death and amputation in this patient population [11]. Puri et al. reported that severe CKD increases the risk of late mortality, amputation, and death or amputation, without increasing the risk of late reinterventions or MALEs [2]. By contrast, Willenberg et al. reported that functional lower limb outcomes are not affected by the presence of CKD [1]. Patel et al. reported that severe CKD increases the risk of late mortality, amputation, and death or amputation, without increasing the risk of late reinterventions or MALEs [2]. By contrast, Willenberg et al. reported that functional lower limb outcomes are not affected by the presence of CKD [1]. Furthermore, they found no differences in both hemodynamic improvement and limb amputation rates after 1 year among patients with normal renal function, moderate CKD, and severe CKD. Based on these reports, the association between renal function and adverse limb events in revascularization for PAD is controversial but most of them revealed that CKD, particularly severe CKD, is associated with outcomes in revascularization for PAD. However, the present report revealed that HD negatively affected AFS, but severe CKD did not. The present report also revealed that CKD, and even HD, did not affect MALEs+POD. Given these outcomes, the presence of CKD need not be considered as a risk factor for revascularization of patients with PAD.

Table 2: Univariate and multivariate analysis for AFS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate p Value</th>
<th>Multivariate p Value</th>
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<tr>
<td>Age &gt;75 years</td>
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<td>Male, sex</td>
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<tr>
<td>Body mass index &lt;18.5</td>
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<td>History of smoking</td>
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<td>Hypertension</td>
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<td>Severe CKD</td>
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<tr>
<td>Hemodialysis</td>
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<td>History of cerebrovascular disease</td>
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<tr>
<td>Antiplatelet therapy</td>
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<tr>
<td>Ankle brachial pressure index &lt;0.7</td>
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<tr>
<td>Ambulatory disturbance</td>
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<tr>
<td>Critical limb ischemia</td>
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<tr>
<td>Infragenual lesions</td>
<td>0.0083</td>
<td>0.13</td>
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</table>

Table 3: Univariate and multivariate analysis for MALEs+POD.

MALE+POD although severe CKD didn’t. In multivariate analysis, CLI was found to negatively impact MALE+POD.
However, HD is significantly associated with AFS. Thus, appropriate revascularization in patients with CKD should be considered before developing irreversible renal insufficiency.

The etiology of atherosclerosis in severe CKD is as follows. One of the major reasons of atherosclerosis is the peculiar atherosclerotic changes of HD, namely, hyperphosphatemia and calcification. Greater degree of vascular peripheral calcification results in greater the risk of mortality [14,15]. Another reason of atherosclerotic changes in CKD is related to Mönckeberg atherosclerotic change [16]. Mönckeberg sclerosis is well known as a degenerative and apparently noninflammatory disease in which the media of small- and medium-sized muscular arteries become calcified independently. Since its first description in 1903, the cause of medial calcinosis remains unclear, although Mönckeberg sclerosis has been related to media calcification of small-to-medium-sized arteries. Uncontrolled lifestyle-related diseases are evidently associated with kidney function worsening. Meanwhile, the phenomenon comes from CKD like proteinuria and insulin resistance can worsen lifestyle-related diseases. Thus, severe atherosclerosis can be associated with worsening of CKD, and CKD, especially HD, can be related to progression of atherosclerosis. Severe CKD should be considered as a risk factor for revascularization in PAD, and revascularization should be done in patients before they develop irreversible renal insufficiency.

The choice of strategy for severe CKD patients is either open bypass surgery or intervention therapy. Brosi et al. showed the clinical efficacy of infrapopliteal angioplasty in patients on HD in spite of the severely diseased pedal arteries [13]. However, achieving technical success along with hemodynamic success is difficult, particularly in patients with diffuse atherosclerotic disease and highly calcified lesions, as they often occur in patients on HD. Kumada et al. also reported that EVT is a useful therapeutic strategy in patients on HD with PAD, however, EVT for TASC C+D lesions remains controversial [11]. In patients on HD, TASC C+D lesions are independent predictors of restenosis and amputation. Nakano et al. found that isolated infrapopliteal balloon angioplasty is an effective treatment choice for CLI in patients on HD although these patients have a high repeated revascularization rate [17]. In the present study, although patients with PAD with severe CKD were more likely to present with CLI and undergo infrainfungal interventions, the outcomes after EVT may be acceptable for revascularization. However, mortality, major amputation, major adverse cardiovascular events and major reintervention in severe CKD patients occur more frequently than those in other patients. Guntani et al. reported that blood flow to the foot is not sufficiently improved in CLI patients with DM who are on HD, despite paramealleolar bypass [18]. In patients on HD, because the host artery of the foot may be severely calcified and tissue healing after bypass surgery may be delayed, limb amputation may become necessary whereas the bypass remains patent. Based on these results, the appropriate strategy for PAD in patients with severe CKD, especially in those on HD, remains controversial. We concluded that EVT is the first choice for patients with PAD with CKD because EVT is less invasive than bypass surgery. Moreover, EVT can be performed repeatedly, and its technique has improved dramatically.

**Limitation**

This study has two main limitations. First, its design is retrospective. Second, data were obtained only from a single institution. Therefore, the study results might not reflect the general features of patients with PAD who are on HD. Further studies regarding prognosis are warranted to determine the appropriate treatment strategy for PAD in patients on HD.

**Conclusion**

MALEs+30-day POD was not affected by being on HD and presence of severe CKD. Renal function did not independently influence MALEs+30 POD. Furthermore, AFS was not affected by severe CKD although HD negatively affected AFS. Accurate and appropriate revascularization should be considered in severe CKD patients before they develop irreversible renal insufficiency.

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**Patient Consent**

The patient has provided permission to publish the features of his case. The identity of the patient has been protected.

**Conflicts of Interest**

The authors declare that they have no competing interests.

**Authorship and Contributorship**

All the authors equally took part in the conception of the case study; acquisition, analysis, or interpretation of data; drafting and revising of the paper; final approval of the paper; and agreement to be accountable for the integrity of the case report. All authors read and approved the final manuscript.

**References**


