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Original Article

ORIGINAL ARTICLE

Risks and outcomes of critical limb ischemia in hemodialysis patients: a prospective cohort study

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ABSTRACT

Background. Peripheral arterial disease (PAD) is more common in patients receiving maintenance hemodialysis than in the general population. Critical limb ischemia (CLI), the most severe form of PAD, is associated with high amputation and mortality risk. However, few prospective studies are available evaluating this disease's presentation, risk factors and outcomes for patients receiving hemodialysis.

Methods. The Hsinchu VA study, a prospective multicentre study, investigated the impact of clinical factors on cardiovascular outcomes of patients receiving maintenance hemodialysis from January 2008 until December 2021. We evaluated the presentations and outcomes of patients with newly diagnosed PAD and the correlations of clinical variables with newly diagnosed CLI.

Results. Of 1136 study participants, 1038 had no PAD on enrolment. After a median follow-up period of 3.3 years, 128 had newly diagnosed PAD. Of these, 65 presented with CLI, and 25 underwent amputation or died from PAD. Patients presenting with CLI had more below-the-knee (52%) and multi-level (41%) disease, and completely occluded segments (41%), and higher risk for amputation or PAD-related death compared with patients without CLI (27.7% vs 9.5%, $P = .01$). After multivariate adjustment, disability, diabetes mellitus, current smoking and atrial fibrillation were significantly associated with newly diagnosed CLI.

Conclusions. Patients undergoing hemodialysis had higher rates of newly diagnosed CLI than the general population. Those with disabilities, diabetes mellitus, smoking and atrial fibrillation may require careful examination for PAD.

Trial registration: Hsinchu VA study, ClinicalTrials.gov identifier: NCT04692636.

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LAY SUMMARY

Critical limb ischemia (CLI) is the most severe form of peripheral arterial disease (PAD), associated with high amputation and mortality risk. In the general population, most atherosclerotic risk factors are associated with PAD. However, there is limited understanding of the factors influencing PAD development in hemodialysis patients. Therefore, this study aimed to evaluate the presentation, risk factors and outcomes of incident CLI patients receiving maintenance hemodialysis. To the best of our knowledge, this is the first prospective cohort study to focus on the incidence, risk factors and outcomes of CLI in patients undergoing hemodialysis.

Keywords: critical limb ischemia, disability, hemodialysis, peripheral artery disease

INTRODUCTION

Peripheral arterial disease (PAD) is more common in patients with end-stage renal disease (ESRD) than in the general population [1, 2]. PAD increases risk for ischemic ulceration, gangrene, amputation and death in patients with ESRD [3, 4]. Its most severe manifestation is critical limb ischemia (CLI), defined as ischemic rest pain, lower-limb ulceration or gangrene lasting >2 weeks [5].

The factors influencing PAD development in hemodialysis patients are poorly understood. Previous studies have focused on prevalence, using registries or cross-sectional studies [6–10]. PAD was diagnosed using questionnaires and billing, procedure or hospital coding data. Findings have varied significantly regarding traditional and dialysis risk factors for PAD [7, 8]. No prospective study has directly examined risk factors and outcomes for CLI in patients receiving hemodialysis.

The prospective multicentre Hsinchu VA study investigated the impact of blood pressure (BP) variability and clinical factors on cardiovascular and vascular access outcomes in patients receiving maintenance hemodialysis [11]. Data were collected prospectively from January 2008 until December 2021 regarding PAD and CLI incidence; we evaluated the presentation, risk factors and outcomes of incident CLI in these patients.

MATERIALS AND METHODS

Participants and design

This prospective multicentre study investigated clinical factors related to vascular access and cardiovascular events in patients receiving maintenance hemodialysis (Hsinchu VA study, ClinicalTrials.gov identifier: NCT04692636) [11]. Participants were recruited from 12 hemodialysis centres in Taiwan's Hsinchu District from January 2018 until December 2021. Four centers are hospital-based and eight private dialysis clinics. Inclusion criteria were: age 18–90 years; maintenance dialysis for >6 months; and no hospitalizations within 3 months. The common dialysis settings were 4-h per session, thrice weekly, using 1.8 m^2 surface area biocompatible dialyzers, with bicarbonate-based dialysate (Ca^{2+} 3.0 mEq/L, K^+ 2.0 mEq/L, Na^+ 140 mEq/L, HCO_3^- 39 mEq/L) at 37°C and ultrapure water. All patients provided written informed consent. This study was approved by the Institutional Review Board of National Taiwan University Hospital, Hsinchu Branch (approval number: HCH-109-089-E).

Data collection

Data regarding demographics, comorbidities, dialysis-related parameters, medications, functional status, and laboratory investigations were collected from the medical records at enrolment. Trained coordinators at each site updated information every 3 months. Body mass index (kg/m^2) was categorized as underweight (<18.5 kg/m^2), average (18.5–24 kg/m^2), overweight (24–27 kg/m^2) and obese (>27 kg/m^2) [12, 13]. The patient's primary nephrologist ascertained comorbidities. Atrial fibrillation (AF), either paroxysmal or permanent, was defined by the recorded medical record diagnosis. The Charlson Comorbidity Index (CCI) was applied, with higher values indicating greater burden. A CCI >4 was considered "high," according to previous studies involving patients with ESRD [14]. The Katz Index of Independence in Activities of Daily Living (ADLs) was measured at enrolment [15], with questions regarding bathing, dressing, getting in and out of a chair, or walking around their home. Required assistance for any of these was considered an ADL disability.

Follow-up and outcomes

Facility coordinators recorded events using an interval summary questionnaire collected every 3 months for all-cause and cardiovascular deaths, all-cause and cardiovascular event hospitalization (myocardial infarction, stroke, amputation or vascular intervention) and vascular disease imaging studies (duplex ultrasound, computed tomography, magnetic resonance imaging and angiography). The investigators confirmed events and consulted with primary physicians as needed. Patients were censored at death, kidney transplant or transfer to peritoneal dialysis or a non-study centre. The primary outcome of the original Hsinchu VA study was the time to first vascular access thrombotic event. PAD-related events including CLI, amputation and death were secondary outcomes.

PAD diagnosis

At enrolment, chart review determined PAD with previous diagnosis or with endovascular or surgical intervention (including amputation) for PAD. After enrolment, newly diagnosed PAD was reviewed using medical records and an interval questionnaire. Diagnosis was confirmed by two investigators (M.-Y.H. and C.-C.W.) using the following criteria (on record): imaging (abnormal duplex waveform or stenosis >50% on angiography); endovascular or surgical revascularization; or PAD-related amputation or death. CLI was defined as ischemic rest pain (Rutherford stage 4), ulcers or gangrene (Rutherford stages 5 or 6) attributable to verified PAD on medical records and confirmed on review by two investigators (M.-Y.H. and C.-C.W.).

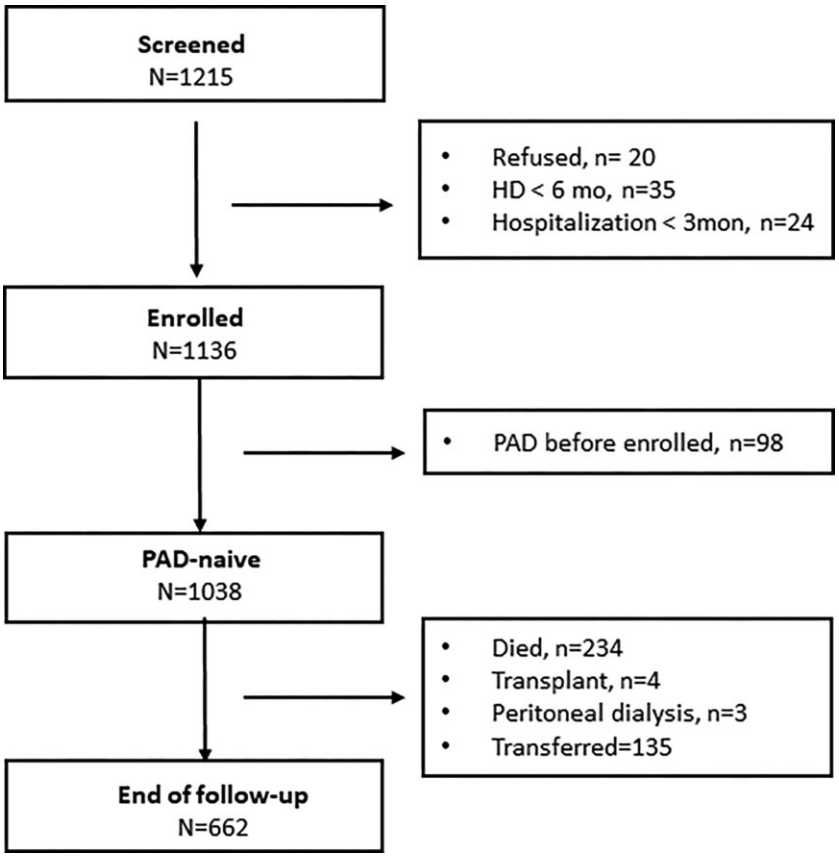

Figure 1: Flow diagram of the study participants. A total of 1215 patients were assessed for eligibility; 79 patients were excluded because they refused ($n = 20$), did not meet the criteria for inclusion ($n = 35$) or did meet the criteria for exclusion ($n = 24$). Of 1136 patients enrolled, 1038 patients were native for PAD.

Statistical analyses

The baseline characteristics were stratified according to PAD diagnosis, using analysis of variance for normally distributed continuous variables, the Kruskal–Wallis test for non-normally distributed continuous variables and the Chi-squared test for categorical variables. Incidence of PAD, CLI and amputation events were obtained using the Kaplan–Meier method and compared with log-rank tests. The proportionality assumption was checked graphically using a log-log plot and considered acceptable for the selected factors. Data were censored at death, kidney transplantation, transfer to peritoneal dialysis or loss-to-follow-up, unless there was a preceding event. Only baseline variables were used as exposures for incident PAD events. A Cox proportional hazard model was used to characterize cumulative major adverse limb events. Predictors on univariate regression analysis ($P < .20$) were included in a multivariate adjustment. P-value $<.05$ was statistically significant. Analyses were performed using the gtsummary package version 3.5.0 in R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Overall, 1136 participants were enrolled. After excluding 98 patients with baseline PAD, 1038 patients were analysed (Fig. 1). At baseline, mean patient age was 66 years (standard deviation 14 years), and 553 (53%) patients were men. The median dialysis vintage was 4.0 [interquartile range (IQR) 0.9–5.3] years and median CCI was 4 (IQR 3–5); 291 (28%) patients had ADL disability. Participants' baseline characteristics are presented in Table 1.

Follow-up and events

Patients were observed through December 2021. Four participants received kidney transplants, three were transferred for peritoneal dialysis, 135 were transferred to non-study facilities and 234 died. The median follow-up duration was 3.3 (IQR 2.4–4.0) years. PAD was diagnosed in 128 and CLI in 65 patients; amputation or PAD-related death occurred in 25. The incidence of PAD was 4.1/100 person-years (PY), and of CLI, amputation or PAD-related death, and all-cause mortality was 2.4/100, 0.8/100 and 7.4/100 PY, respectively. Figure 2 shows Kaplan–Meier plots of incident PAD-related events. Of the 128 patients with newly diagnosed PAD, angiographic diagnosis was available for 73 and vascular duplex diagnosis for 107 patients. Two were classified according to surgical reports without image studies.

PAD event presentation

Of patients with newly diagnosed PAD, 65 (51%) had rest pain (16%), ulcers (20%) or gangrene (16%) at diagnosis. Half presented with CLI. Table 2 presents the anatomical characteristics. Among the 128 diagnosed patients, 26 (20%) had aortoiliac disease, 33 (26%) had common femoral lesions, 66 (52%) had superficial femoral artery stenosis or occlusion, 49 (38%) had popliteal

Table 1: Baseline characteristics of the study participants.

Characteristic	With PAD history, N = 98	Without PAD history, N = 1038
Demographics		
Age (years)	71 (12)	66 (14)
Male	39 (40%)	553 (53%)
Dialysis vintage (years)	4.8 (3.5, 7.4)	3.7 (0.8, 5.1)
Body mass index (kg/m^2)	22.4 (3.8)	22.9 (4.2)
Socioeconomic factors		
Education level >9 years	44 (45%)	392 (38%)
Single or widowed	32 (33%)	237 (23%)
Unemployed	81 (83%)	740 (71%)
Disability of activity of daily livings	51 (52%)	291 (28%)
Risk factors		
Current smoking	17 (17%)	147 (14%)
Hypertension	82 (84%)	807 (78%)
DM	68 (69%)	479 (46%)
Hyperlipidemia	33 (34%)	188 (18%)
Comorbidities		
CAD	42 (43%)	219 (21%)
Heart failure	13 (13%)	100 (9.6%)
Cerebral infarction or hemorrhage	13 (13%)	53 (5.1%)
AF	21 (21%)	129 (12%)
Cancer	4 (4.1%)	84 (8.1%)
COPD	0 (0%)	20 (1.9%)
Laboratory data		
Haemoglobin (g/dL)	10.9 (1.2)	10.7 (1.4)
Cholesterol (mg/dL)	157 (32)	160 (30)
Albumin (g/dL)	3.8 (0.3)	3.3 (0.3)
Calcium (mg/dL)	9.5 (0.9)	9.3 (0.9)
Phosphate (mg/dL)	5.0 (1.2)	5.0 (1.4)
Ca × P (mg^2/dL^2)	47 (12)	46 (13)
Medications		
Antiplatelet[a]	52 (52%)	228 (22%)
Vitamin K antagonist	2 (2.0%)	9 (0.9%)
Statin	24 (24%)	141 (14%)
Beta-blocker	22 (22%)	173 (17%)

Values are expressed as mean (standard deviation), number (percentage) or median (interquartile range).
[a]Aspirin: 61%; cilostazol: 25%; clopidogrel: 14%.
COPD, chronic obstructive pulmonary disease.

artery lesions and 66 (52%) had infra-popliteal artery stenosis or occlusion; 53 (41%) patients had multi-level disease both below and above the knee. Total lower-limb artery occlusion at any segment occurred in 52 (41%) patients. Patients with CLI had more below-the-knee, bilateral and multi-level disease, and more entirely occluded segments.

Incident PAD factors

The univariate Cox proportional hazards regression model associated these factors with incident PAD: age, unemployment, ADL disability, BP (systolic, diastolic and pulse pressure), cigarette smoking, diabetes mellitus (DM), hypertension, hyperlipidaemia, history of coronary artery disease, stroke, heart failure, AF, chronic obstructive pulmonary disease, hemoglobin level, and antiplatelet agent or statin use (Table 3). After multivariate adjustment, age [hazard ratio (HR) 1.21; 95% confidence interval (CI) 1.01–1.44; $P = .041$], ADL disability (HR 2.88; 95% CI 1.93–4.29; $P < .001$), cigarette smoking (HR 2.60; 95% CI 1.71–3.94; $P < .001$), DM (HR 1.85; 95% CI 1.19–2.88; $P = .006$), AF (HR 2.17; 95% CI 1.41–3.35; $P < .001$), hemoglobin (1.24; 95% CI 1.08–1.42; $P = .002$) and antiplatelet agent use (HR 1.88; 95% CI 1.24–2.84; $P = .003$) remained significantly associated with incident PAD.

CLI outcomes and risk factors

Patients with CLI had higher amputation or PAD-related death risk than those without (27.7% vs 9.5%, $P = .01$; Fig. 3). Cox proportional hazards regression analysis showed that age, disability, current smoking, DM, hyperlipidaemia, CAD and AF were associated with CLI. After multivariate adjustment, only ADL disability (HR 3.03; 95% CI 1.82–5.05; $P < .001$), DM (HR 2.51; 95% CI 1.37–4.61; $P = .003$), current smoking (HR 2.00; 95% CI 1.14–3.51; $P = .02$) and AF (HR 1.90; 95% CI 1.10–3.28; $P = .02$) remained significantly associated with CLI (Table 4). When BP and cardiovascular risk factors were excluded from the multivariate analysis, CAD remained a significant predictor of PAD (HR 1.52; 95% CI 1.03–2.25; $P = 0.04$). In subgroup analysis, disability remained a significant predictor of CLI, even in patients without cardiovascular disease (CVD) or diabetes (Fig. 4).

DISCUSSION

Main findings

To our knowledge, this is the first prospective cohort study on incidence, risk factors and outcomes of CLI in patients undergoing

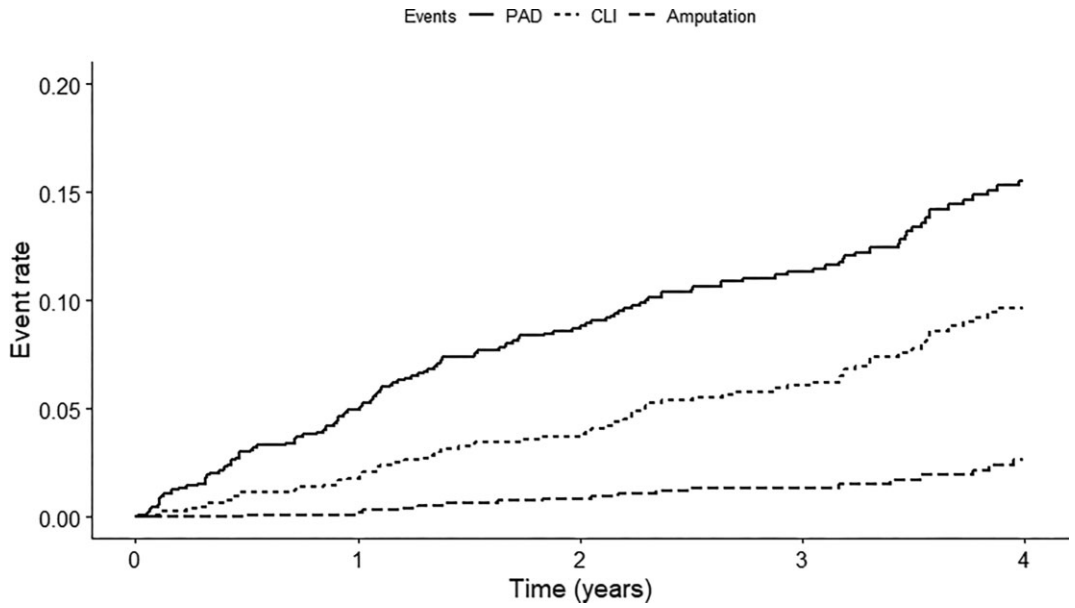

Figure 2: Kaplan–Meier curve of incident lower-extremity peripheral artery–related events. The incidence rate of PAD was 4.1/100 PY, CLI 2.4/100 PY, amputation or PAD-related death 0.8/100 PY, and all-cause mortality rate 7.4/100 PY.

Table 2: Characteristics of lesions at initial diagnosis of PAD stratified by the clinical presentation.

Characteristic	Overall, $N = 128$[a]	Presented with CLI, $N = 65$[a]	Presented without CLI, $N = 63$[a]	P-value[b]
Locations				
Aorto-iliac disease	26 (20)	18 (28)	8 (13)	0.035
Common femoral artery disease	33 (26)	17 (26)	16 (25)	0.99
Superficial femoral artery disease	66 (52)	41 (63)	25 (40)	0.008
Popliteal artery disease	49 (38)	28 (43)	21 (33)	0.3
Infrapopliteal disease	66 (52)	44 (68)	22 (35)	<0.001
Sides				
Left side	65 (51)	40 (62)	25 (40)	0.013
Right side	84 (66)	48 (74)	36 (57)	0.05
Both sides	56 (44)	34 (52)	22 (35)	0.05
Levels				
Below the knee	66 (52)	44 (68)	22 (35)	<0.001
Above the knee	85 (66)	48 (74)	37 (59)	0.07
Multi-level disease	53 (41)	33 (51)	20 (32)	0.029
Completely occluded[c]	52 (41)	38 (58)	14 (22)	<0.001

[a]n (%).
[b]Fisher's exact test; Pearson's Chi-squared test.
[c]At any segment.

hemodialysis. Half of the patients with PAD presented with CLI at initial diagnosis. Patients with CLI had more infra-popliteal and totally occluded lesions than those with less severe PAD presentations. Disability, DM, current smoking and AF were the most significant CLI risk factors. The risk for amputation or PAD-related death was three times higher in patients with CLI than in those with less severe forms of PAD.

PAD presentation

Our study demonstrated that the stenosis pattern in patients receiving hemodialysis was diffuse and multi-level, involving multiple vessels. Approximately half of the stenoses were below-the-knee, and half of the patients had completely occluded lesions at diagnosis. Few studies have examined the initial manifestations of PAD in patients undergoing hemodialysis. In this study, half of the patients with newly diagnosed PAD initially presented with CLI events. Similar to previous studies, 70% of CLI events observed were either ischemic ulcers or gangrene; only 30% were rest pain [3]. The clinical presentations were partially explained by the lesion patterns seen on imaging. Half of the lesions were in small vessels below the knees, and half were completely occluded at diagnosis. This was comparable to the findings of previous retrospective studies of patients with renal insufficiency [16, 17]. Infra-popliteal lesions were more common in patients with CLI (68%) than without (35%). Our results highlight that CLI progression in PAD is variable and unpredictable in patients receiving hemodialysis and can circumvent the

Table 3: Cox proportional hazard regression analysis of variables associated with a newly diagnosed PAD.

	Univariable			Multivariable		
Variables, unit of increase	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Demographics						
Age, 10 years	1.34	1.17–1.53	<.001	1.21	1.01–1.44	.041
Female	0.84	0.59–1.19	.33			
Dialysis vintage, 1 year	0.97	0.93–1.00	.08			
Socioeconomic factors						
Education level >9 years	1.20	0.85–1.71	.30			
Single or widowed	1.33	0.90–1.96	.15			
Unemployed	1.81	1.17–2.79	.008	0.84	0.50–1.40	.5
ADL disability	3.14	2.22–4.45	<.001	2.88	1.93–4.29	<.001
BMI, 10 kg/m^2	0.84	0.55–1.28	.42			
Blood pressure						
SBP, 10 mmHg	1.14	1.06–1.22	<.001	1.35	0.91–2.01	.14
DBP, 10 mmHg	0.79	0.69–0.91	.001	0.66	0.44–1.01	.054
PP, 10 mmHg	1.31	1.20–1.43	<.001	0.93	0.63–1.39	.7
Risk factors						
Smoking	2.20	1.49–3.26	<.001	2.60	1.71–3.94	<.001
DM	3.12	2.14–4.57	<.001	1.85	1.19–2.88	.006
HTN	1.99	1.18–3.36	.010	1.01	0.56–1.79	.99
Hyperlipidemia	2.85	2.00–4.07	<.001	1.51	0.97–2.34	.07
Comorbidities						
CAD	2.41	1.69–3.44	<.001	0.95	0.62–1.46	.8
CVA or ICH	1.94	1.05–3.61	.035	0.98	0.51–1.89	.99
Heart failure	1.97	1.23–3.15	.005	1.09	0.66–1.78	.7
AF	2.33	1.55–3.48	<.001	2.17	1.41–3.35	<.001
Cancer	0.58	0.25–1.31	.19			
COPD	2.27	0.93–5.56	.07	2.16	0.83–5.63	.11
Laboratory data						
Cholesterol, 1 mg/dL	1.00	0.99–1.00	.12			
Albumin, 1 g/dL	0.98	0.58–1.68	.95			
Calcium, 1 mg/dL	1.22	0.99–1.49	.06	1.13	0.92–1.38	.3
Phosphate, 1 mg/dL	0.94	0.83–1.07	.35			
Ca × P, 1 mg^2/dL^2	1.00	0.98–1.01	.64			
KT/V, 1	0.52	0.24–1.15	.11	0.96	0.42–2.23	.99
Hb, 1 g/dL	1.27	1.12–1.44	<.001	1.24	1.08–1.42	.002
Medication						
Antiplatelet	2.96	2.09–4.19	<.001	1.88	1.24–2.84	.003
VKA	1.58	0.39–6.38	.52			
Statin	2.34	1.58–3.48	<.001	1.50	0.95–2.38	.09
Beta-blocker	1.12	0.72–1.75	.62			

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; Hb, hemoglobin; HR, hazard ratio; HTN, hypertension; ICH, intracranial hemorrhage; PP, pulse pressure; SBP, systolic blood pressure.

traditionally understood progression from claudication to CLI. CLI is the most severe form of PAD, with a significantly higher risk of limb loss or death [5]. In this study, patients with CLI had three times the risk of PAD-related amputation or death than those without CLI (27.7% vs 9.5%). Therefore, it is critical to identify patients at risk of CLI to prevent devastating complications of PAD.

CLI risk factors

Smoking, AF, DM and disability were the most important predictors of CLI. The highest risk estimate was for the association between disability and CLI, even after adjusting for possible confounders. This association is biologically plausible from various perspectives. Patients with disability may have severe PAD disease that is asymptomatic because of their inability to walk enough to provoke symptoms [18–20]. In a study of 460 patients with PAD, one-third of asymptomatic patients were unable to walk more than six blocks [21]. Another possibility is confounding by common CVDs associated with CLI and disability. We assessed the potential confounding bias from underlying vascular comorbidities in two ways. On multivariate analyses, risk estimates between disability and CLI decreased but remained the highest of all variables. When subjects with CVD were excluded, risk estimates were even higher than those of the original cohort, suggesting that confounding factors alone do not fully account for the relationship.

AF was an independent risk factor for CLI, even after adjusting for conventional risk factors and comorbid CVDs. In non-dialysis populations, lower-extremity arteries were the most frequent location of extra-cerebral thromboembolisms [22]. Several studies have confirmed that the heart is the primary source of embolic material. In the general population, patients with AF have an additional incidence rate of aortoiliac and

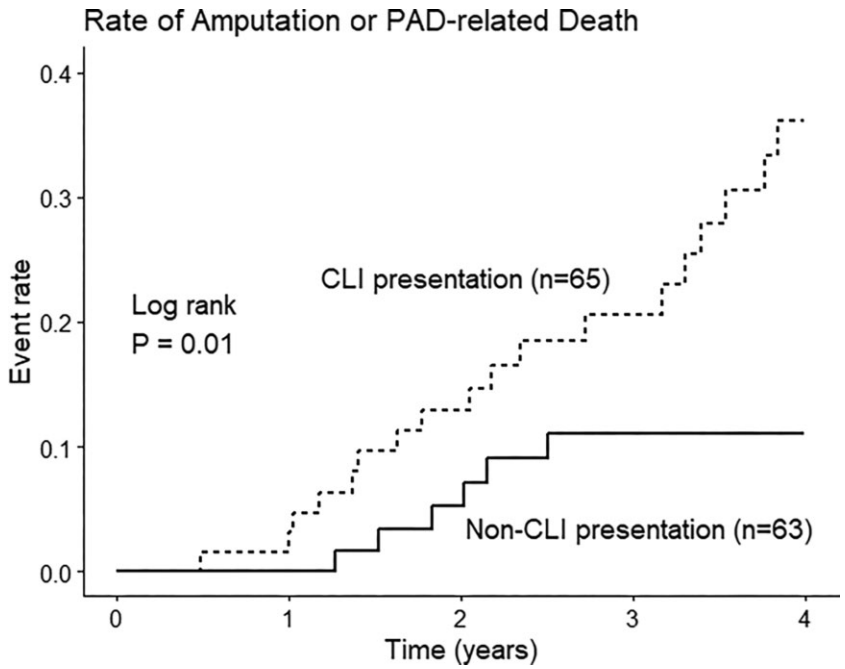

Figure 3: Kaplan–Meier curve of incident PAD-related amputation or death. Patients presented with CLI had higher risk of amputation or PAD-related death than patients not presented with CLI (27.7% vs 9.5%, P = .01).

lower-extremity arterial thromboembolism of 0.4% per year [22]. AF is associated with increased risk of both acute and CLI [23, 24]. Thromboembolism risk might be even higher in patients with ESRD because anti-coagulation therapy is rarely used. Furthermore, lower-extremity embolization may be unrecognized because of high prevalence of neuropathy and small-vessel disease in patients on dialysis [19]. Use of vitamin K antagonists (VKAs) in AF patients may be associated with vascular calcification which precipitates PAD, and calcific uremic arteriolopathy (CUA) which mimic CLI presentation [19, 25, 26]. In our cohort, however, VKAs were used by only 11 patients and not associated with CLI.

In patients with diabetes, classic PAD presentation is frequently absent, and up to 50% of patients have no history of intermittent claudication [27, 28]. This could be due to peripheral neuropathy [19, 20, 29]. As such, patients receiving diabetic hemodialysis may be unaware that they have PAD until it has progressed to the tissue loss stage. This explains our finding that diabetes and CLI were more strongly associated than diabetes and less severe forms of PAD. Diabetes is known to preferentially affect small distal vessels that are less amenable to revascularization, further predisposing to CLI [30, 31]. Furthermore, our study confirms that smoking is an independent risk factor for CLI, regardless of renal insufficiency. Cigarette smoke has been implicated in inflammatory processes driving the development of atherosclerotic lesions and platelet instability [32]. As such, smoking drives CLI development via mechanistic pathways independent of disability or diabetes.

PAD incidence

The diagnostic criteria for PAD used in previous epidemiologic studies included prior diagnosis, amputation, revascularization, claudication, gangrene and decreased pulses [8]. Some studies have used non-invasive diagnostic testing, such as segmental pressure index or impedance plethysmography, to measure PAD prevalence among patients with ESRD [8, 10, 33]. However, very few studies have used imaging to confirm PAD diagnosis. In patients on dialysis, the association between claudication and PAD was not ideal because neuromuscular, venous and other origins may account for nearly half of typical claudication reports [34]. Increased arterial stiffness might interfere with ankle-brachial index (ABI) measurement, which is reportedly unsuitable for detecting PAD in patients receiving dialysis [35, 36]. The use of imaging to ascertain PAD is a study strength. The strict criteria we used should theoretically reduce misclassification errors when exploring causal relationships. Based on imaging or revascularization procedures, PAD prevalence was 8.9% at enrolment and incidence was 4.1/100 PY over the 3.5-year follow-up, much higher than reported in the general population (0.2/100 PY in men aged over 65 years) [37, 38]. Significant geographic variations in PAD prevalence have been reported in previous international observational studies. For example, the Dialysis Outcomes and Practice Patterns Study found PAD in 17.5%–37.8% of patients in Europe, but only in 11.5% of patients in Japan [6]. Therefore, the lower prevalence of PAD in this study compared to previous Western cohorts may be due to differences in diagnostic methods or ethnic backgrounds.

PAD risk factors

To date, risk factors for PAD in patients with ESRD have mostly been examined in cross-sectional studies. This study's prospective nature helped re-examine the relationships between risk factors and incident PAD and CLI events in an appropriate temporal series. Similar to previous cross-sectional studies, we found that advanced age, cigarette smoking and DM were significantly associated with incident PAD [7, 39]. Systolic BP was positively associated and diastolic BP was negatively associated with PAD, but only on univariate analyses, similar to the HEMO

Table 4: Cox proportional hazard regression analysis of association with a newly diagnosed CLI.

	Univariable			Multivariable		
Variables, unit of increase	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Demographics						
Age, 10 years	1.31	1.10–1.56	.002	1.07	0.84–1.36	.6
Female	0.89	0.56–1.41	.62			
Dialysis vintage (years)	0.98	0.93–1.02	.31			
Socioeconomic factors						
Education level >9 years	1.24	0.79–1.97	.35			
Single or widowed	1.30	0.78–2.17	.32			
Unemployed	2.85	1.46–5.55	.002	1.35	0.64–2.87	.4
ADL disability	4.27	2.69–6.76	<.001	3.03	1.82–5.05	<.001
BMI, 10 kg/m^2	1.12	0.66–1.93	.67			
Blood pressure						
SBP, 10 mmHg	1.12	1.01–1.23	.027	0.74	0.44–1.23	.2
DBP, 10 mmHg	0.76	0.63–0.92	.004	1.14	0.67–1.94	.6
PP, 10 mmHg	1.31	1.18–1.47	<.001	1.65	0.99–2.77	.06
Risk factors						
Smoking	1.84	1.08–3.14	.024	2.00	1.14–3.51	.02
DM	4.09	2.40–6.96	<.001	2.51	1.37–4.61	.003
HTN	2.28	1.09–4.75	.028	0.89	0.40–2.02	.8
Hyperlipidemia	2.28	1.41–3.67	<.001	1.17	0.67–2.05	.6
Comorbidities						
CAD	2.82	1.78–4.47	<.001	1.37	0.81–2.31	.2
CVA or ICH	3.02	1.50–6.08	.002	1.45	0.69–3.03	.3
Heart failure	0.95	0.43–2.06	.89			
AF	2.43	1.44–4.10	<.001	1.90	1.10–3.28	.02
Cancer	0.69	0.25–1.90	.48			
COPD	2.14	0.67–6.79	.20			
Laboratory data						
Cholesterol, 1 mg/dL	1.00	0.99–1.01	.99			
Albumin, 1 g/dL	0.73	0.36–1.45	.37			
Calcium, 1 mg/dL	1.32	1.02–1.72	.036	1.22	0.94–1.58	.1
Phosphate, 1 mg/dL	0.92	0.77–1.09	.32			
Ca × P, 1 mg^2/dL^2	1.00	0.98–1.01	.71			
KT/V, 1	0.36	0.13–1.03	.057	0.56	0.19–1.67	.3
Hb, 1 g/dL	1.21	1.02–1.42	.024	1.10	0.92–1.32	.3
Medication						
Antiplatelet	2.52	1.59–4.01	<.001	1.47	0.86–2.52	.2
VKA	1.28	0.18–9.24	.80			
Statin	1.61	0.91–2.83	.10	0.91	0.48–1.74	.8
Beta-blocker	0.84	0.44–1.59	.59			

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; Hb, hemoglobin; HR, hazard ratio; HTN, hypertension; ICH, intracranial hemorrhage; PP, pulse pressure; SBP, systolic blood pressure.

study [7]. CAD and stroke were associated with PAD in univariate but not multivariate analyses, suggesting a common link through conventional cardiovascular risk factors. No association existed between PAD and dialysis-related factors, such as dialysis vintage, urea clearance, serum calcium, phosphate and albumin levels, except for a positive association with hemoglobin level. Previous cross-sectional studies also demonstrated various relationships between dialysis factors and PAD [6, 7, 39]. Further prospective studies with adequate patient numbers and time-varying analyses may be needed for clarification. The association of antiplatelet agent use with PAD may be due to reverse causality, because these agents may be a proxy for CVD. Few studies have investigated roles of socioeconomic and performance status in incident PAD. We found that unemployment, disability and impaired performance status were associated with incident PAD, consistent with previous observations that physical activity is associated with atherosclerotic CVDs in the general population [40]. The correlation is biologically plausible because of the well-known beneficial effects of physical activity on cardiovascular risk factors, endothelial function, vascular inflammation, platelet aggregation and vascular oxidative stress. Patients with asymptomatic PAD have significantly increased risk for impaired ADLs than non-PAD patients [41]. Failure to identify asymptomatic patients at baseline may also confound the association between disability and incident PAD.

Strengths and limitations

Strengths of our study included the large prospective cohort, use of confirmatory imaging or revascularization procedures and multiple variable adjustment. To reduce bias arising from outcome misclassification, we used medical records containing information on imaging and consulted with the treating physicians as required. This ensured that cases were

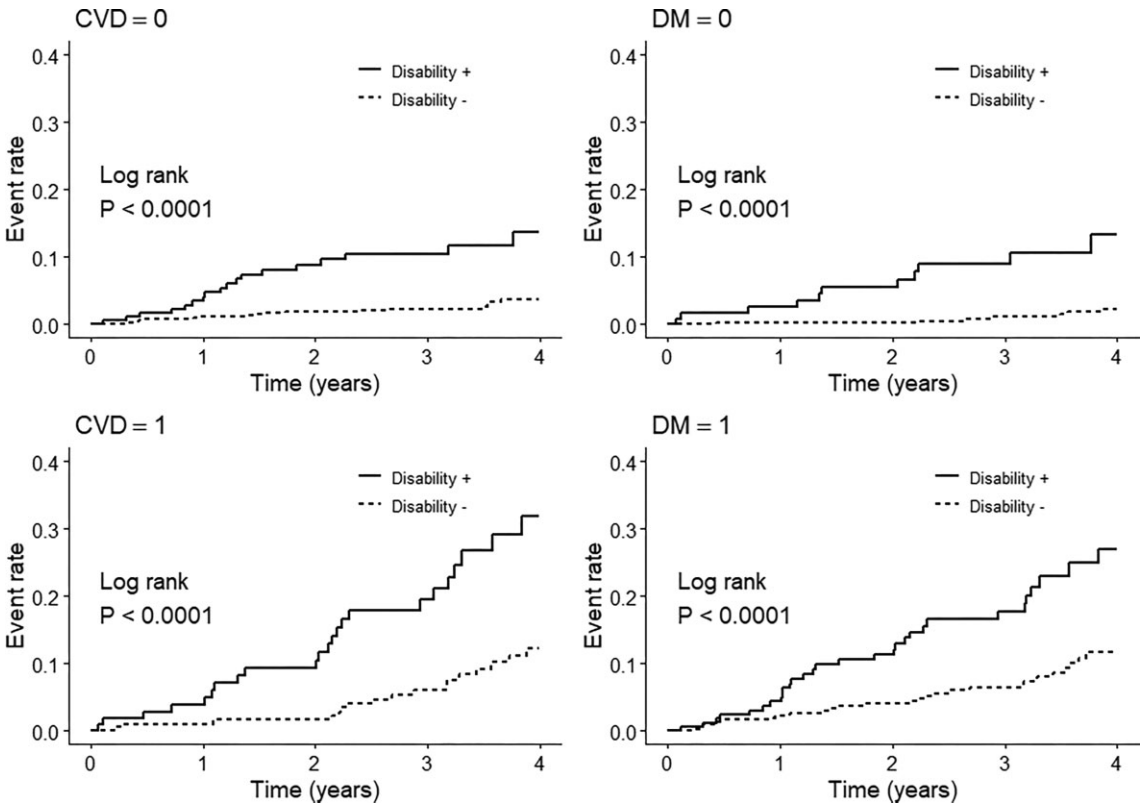

Figure 4: Subgroup analysis of the effect of disability on critical limb ischemia by Kaplan–Meier curve. In subgroup analysis, disability remained a significant predictor for CLI, even in the group of patients without diabetes or CVD. CVD was defined by the presence of either coronary artery disease, stroke or heart failure.

comprehensively and appropriately identified. These approaches reduced potential recall bias or reverse causation, enabling us to determine a temporal sequence in the associations between risk factors and outcomes and to separately examine effects of other confounding factors. However, our study was imperfect. One important limitation was the lack of systematic evaluation of PAD, potentially leading to underdiagnosis [42]. Functional status, laboratory data and risk factors were assessed at baseline; adjustments were not made for subsequent changes. Second, although we adjusted for potential confounders, other unmeasured factors are possible. Third, the study was exploratory and included an ethnically uniform population. Further validation in other dialysis populations is needed for greater generalizability. Finally, we could not exclude the possibility that skin lesions could be from co-existing CUA without CLI. Nonetheless, the risk of misclassification should be minimal; imaging was predominantly used to confirm CLI, and VKA use was rare.

Clinical relevance

CLI is more common in patients receiving hemodialysis than in the general population. The CVD guidelines for dialysis patients recommend PAD evaluation for all on initiation [43]. Given the ever-increasing healthcare system demands, regular surveillance for PAD has not been suggested. Based on our findings, a strategy of regular surveillance should be developed for patients at high CLI risk. Early PAD identification may allow initiation of integrated care, such as regular surveillance, foot care, pharmacotherapy, revascularization and exercise rehabilitation, which may help prevent devastating PAD complications.

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AUTHORS' CONTRIBUTIONS

Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author (C.C.W.).

CONFLICT OF INTEREST STATEMENT

None declared.

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