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Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Hikaru Morooka [1], Akihito Tanaka [1], Daijo Inaguma [2], Shoichi Maruyama[3]

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[1]Departmnt of Nephrology, Nagoya University Hospital, Nagoya, Aichi, Japan
[2]Department of Nephrology, Fujita Health University, Toyoake, Aichi, Japan
[3]Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Correspondence to
Dr Akihito Tanaka;
tanaka17@med.nagoya-u.ac.jp

ABSTRACT

Objectives Patients with peripheral artery disease (PAD) are reported to have a poorer prognosis than those without PAD. PAD is sometimes found at dialysis initiation, but its influence on the prognosis in these patients has not been investigated. We aimed to compare the mortality rate between patients with PAD at the time of dialysis initiation and those without PAD.

Design We undertook an observational prospective multicenter study of patients starting dialysis treatment. Data were collected on patients' sex, age, presence of PAD, medication, medical history and clinical and laboratory data.

Setting Seventeen centers participated in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis.

Participants A total of 1524 patients with chronic kidney disease started dialysis from October 2011 to September 2013. The patients were followed-up until March 2015. During this time, there were two patients who lost the follow-up.

Primary and secondary outcome measures The primary outcome was defined as all-cause mortality. The secondary outcomes were defined as each cause of mortality.

Results This study included 1030 men and 492 women with a mean age of 67.50±13.10 years. Of these, 71 had PAD and 1451 did not have PAD. After a median follow-up of 814.5 days, 33.80% of the former group and 17.00% of the latter group had died in March 2015 (p=0.001). After adjusting for confounding factors, PAD at dialysis initiation remained an independent risk factor for mortality (p<0.01).

Conclusions Patients with PAD at the time of dialysis initiation had a poorer prognosis than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered for their monitoring and follow-up.

Strengths and limitations of this study

- ► This observational prospective multicenter study analysed data in patients at the beginning of dialysis for a median follow-up of 814.5 days.
- ► Our study had a high follow-up rate (only two patients were lost to follow-up) and a well-defined population with comprehensive data while starting the dialysis.
- ► The number of patients with peripheral artery disease at the initiation of dialysis was comparatively small, and not all of them underwent other tests, such as contrast-enhanced CT, magnetic resonance angiography and peripheral angiography to confirm the diagnosis.

INTRODUCTION

The number of patients receiving dialysis treatment is increasing every year, and these patients have a high mortality risk from various causes, particularly cardiovascular diseases (CVDs).[1 2] End-stage kidney disease (ESKD) represents a considerable risk of atherosclerosis, and patients on dialysis tend to have further risk factors contributing to the rapid deterioration of CVD.[3] While CVD, including stroke, and coronary artery disease have been reported in more detail in patients on dialysis,[4–6] the problem of peripheral artery disease (PAD) in patients undergoing dialysis treatment has been less frequently addressed. With both ageing and a growing number of patients with diabetes on dialysis, the prevalence of PAD among these patients is likely to increase every year.[7] PAD with distal lesions is more common in patients with ESKD, making the transarterial approach to the stenosis sometimes difficult.[8 9] Furthermore, a vascular stenosis can promote peripheral ischemic skin ulcers or gangrene, leading to an intractable pathology. Thus, patients with PAD on dialysis treatment have a worse prognosis than those without PAD.[10] Consequently, there is an urgent need to clarify the relationships between PAD and mortality in patients on dialysis. Furthermore, to improve the prognosis of dialysis patients, it is crucial to understand the characteristics of those with high mortality risk.

The classic atherosclerosis risk factors, such as age, smoking, diabetes, hypertension and hyperlipidemia, are common in patients with

ESKD, but their chronic kidney disease (CKD) condition adds unique risk factors that promote PAD (eg, chronic inflammation, hypoalbuminemia and a pro-calcific state). PAD in patients with ESKD markedly increases the possibility of myocardial ischemia and stroke, and is the main cause of limb loss and mortality, the rates of which are much higher than those in the general population.[10 11] Moreover, it has been pointed out that if patients with PAD develop critical limb ischemia, their overall survival is worse than those of patients with malignant tumours.[12] Hence, when considering the prognosis of patients receiving dialysis, the presence of PAD is important.

There are few recent reports on PAD in patients with ESKD at the time of dialysis initiation. Several studies have investigated patients receiving maintenance dialysis. In these studies, descriptive data included the prognosis of 'only maintenance dialysis' patients.[10 13–15] According to them, PAD had an overall prevalence of 18.2 %, and the patient survival rate was 28.6% during 8.8 years in the PAD group. Moreover, since these studies focused on patients on maintenance dialysis, they mainly addressed PAD that occurred during dialysis. However, renal function in patients with CKD may decrease during the treatment of PAD. At other times, PAD is found when investigating the cause of renal function deterioration or when screening patients for their eligibility of a renal transplant. PAD at the time of dialysis initiation is a complex and clinically relevant problem.

In this study, we compared PAD and non-PAD patients who had started dialysis treatment in the Aichi prefecture to identify the mortality associated with PAD in patients with ESKD at the time of initiation of dialysis treatment.

PATIENTS AND METHODS

Patient registration and data collection

Data from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis[14 16] were used in this prospective multicenter study. Patients who started dialysis between October 2011 and September 2013 at 17 Japanese institutions were eligible for participation.

First, we screened all patients with ESKD for whom dialysis was initiated. Only patients who became stable and discharged or transferred from the hospital were included. Patients who were not discharged and died in the hospital were excluded (figure 1). Data regarding patients' demographics, medical history, comorbidities, medications and laboratory data during the period of dialysis initiation were collected. PAD was clinically diagnosed based on symptoms, physical findings and various examinations, but not all patients received angiography for diagnosis. After physician's careful evaluation of patients, we used the Fontaine classification for grading the severity.[17] The presence of PAD was defined as a Fontaine stage II or higher. Laboratory data were obtained immediately prior to the first dialysis session. Patients followed by survey slips were sent to the dialysis facilities until the end of March 2015.

Mortality

Patients were divided into one group with PAD and other group without PAD. The primary endpoint was all-cause mortality. Causes of death were recorded to a possible extent. The occurrence of death was investigated via survey slips sent to the dialysis facilities at the end of March 2015.

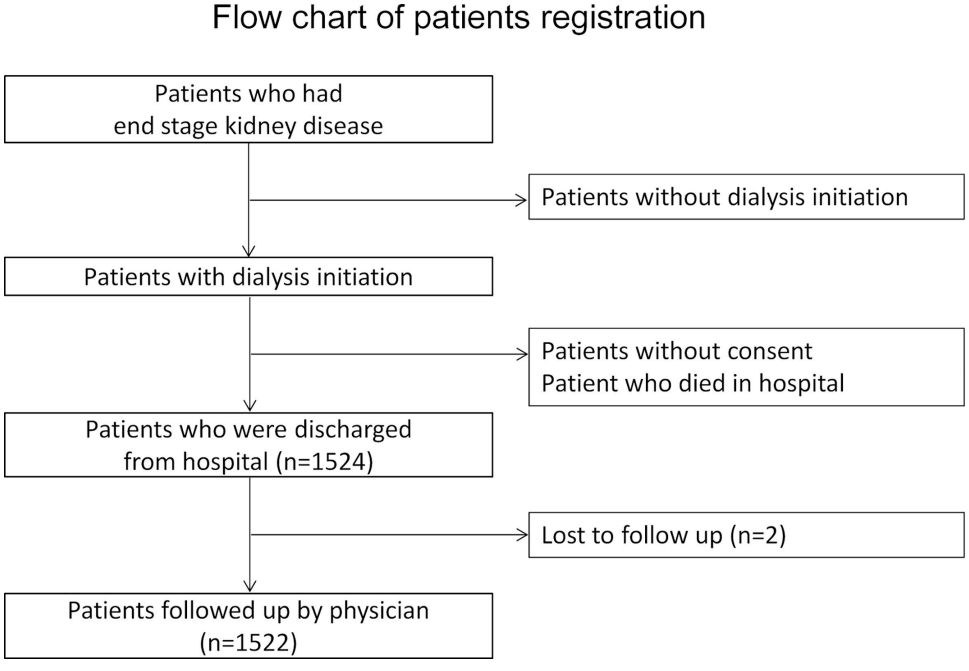

Figure 1 Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

Table 1 Baseline and clinical characteristics and outcomes of patients starting dialysis (n=1522) and propensity score-matched patients starting dialysis (n=284)

	Without propensity-score matched (n=1522)			With propensity-score matched (n=284)		
	Patients without PAD (n=1451)	Patients with PAD (n=71)	P value	Patients without PAD (n=213)	Patients with PAD (n=71)	P value
Female (%)	33.10	16.90	0.007	15.00	16.90	0.850
Age (years) [mean (SD)]	67.40 (13.10)	69.90 (12.10)	0.106	69.10 (12.20)	69.90 (12.10)	0.607
History						
Diabetes (%)	50.20	67.60	0.006	67.10	67.60	1.000
CAD (%)	15.90	36.60	<0.001	40.40	36.60	0.674
PCI (%)	9.60	21.10	0.003	26.80	21.10	0.431
CABG (%)	3.80	14.10	<0.001	9.90	14.10	0.442
Aortic dissection (%)	5.00	15.50	<0.001	7.00	15.50	0.057
Admission of HF (%)	19.40	42.30	<0.001	29.10	42.30	0.057
Stroke (%)	9.10	7.00	0.704	14.10	7.00	0.175
Cause of CKD			0.294			0.091
Diabetes (%)	42.50	59.20		58.70	59.20	
Nephrosclerosis (%)	25.30	25.40		25.40	25.40	
CGN (%)	15.60	4.20		8.50	4.20	
Others, unknown (%)	4.30	4.20		2.30	4.20	
Vital data						
Pre-dialysis SBP (mmHg) [mean (SD)]	151.10 (25.90)	151.70 (29.50)	0.843	151.80 (28.30)	151.70 (29.50)	0.977
Cardiac ultrasonography						
EF (%) (mean (SD))	60.90 (12.20)	55.80 (13.70)	0.001	59.80 (13.80)	55.80 (13.70)	0.049
Chest X-ray						
CTR (%) (mean (SD))	55.20 (7.20)	55.20 (7.10)	0.973	55.30 (6.80)	55.20 (7.10)	0.885
Administration						
ARB or ACEI (%)	60.60	56.30	0.554	59.20	56.30	0.781
BB (%)	34.00	47.90	0.024	49.30	47.90	0.945
Statin (%)	39.40	53.50	0.024	58.70	53.50	0.533
VDRA (%)	26.90	29.60	0.726	27.20	29.60	0.819
Antiplatelets (%)	28.90	56.30	<0.001	58.20	56.30	0.890
ESA (%)	85.80	87.30	0.861	89.70	87.30	0.742
Laboratory data						
WBC ($\times 10^9$/L) (mean (SD))	6.73 (3.13)	7.21 (3.58)	0.214	6.70 (2.72)	7.21 (3.58)	0.217
Hb (g/L) (mean (SD))	93.70 (15.50)	94.00 (14.50)	0.887	96.20 (14.30)	94.00 (14.50)	0.275
Plt ($\times 10^9$/L) (mean (SD))	182.40 (76.20)	181.70 (81.90)	0.943	179.00 (73.90)	181.70 (81.90)	0.796
Alb (g/dL) (mean (SD))	3.21 (0.59)	3.02 (0.62)	0.010	3.20 (0.60)	3.02 (0.62)	0.032
BUN (mg/dL) (mean (SD))	92.02 (30.69)	86.68 (24.84)	0.149	87.14 (27.58)	86.68 (24.84)	0.901
Cr (mg/dL) (mean (SD))	9.03 (3.24)	7.74 (2.22)	0.001	8.47 (2.82)	7.74 (2.22)	0.049
eGFR (mL/min/1.73 m^2) (mean (SD))	5.40 (2.23)	6.34 (1.83)	0.001	6.05 (2.47)	6.34 (1.83)	0.368
Na (mEq/L) (mean (SD))	137.88 (4.41)	137.93 (3.91)	0.933	138.36 (4.56)	137.93 (3.91)	0.475
K (mEq/L) (mean (SD))	4.56 (0.84)	4.43 (0.81)	0.194	4.51 (0.83)	4.43 (0.81)	0.492
Adjusted Ca (mg/dL) (mean (SD))	8.59 (1.06)	9.06 (0.93)	<0.001	8.71 (0.96)	9.06 (0.93)	0.007
P (mg/dL) (mean (SD))	6.40 (1.89)	5.76 (1.56)	0.005	5.96 (1.63)	5.76 (1.56)	0.372
Mg (mg/dL) (mean (SD))	2.15 (0.49)	2.17 (0.44)	0.826	2.22 (0.46)	2.17 (0.44)	0.497
UA (mg/dL) (mean (SD))	8.80 (2.44)	8.64 (2.27)	0.582	8.75 (2.49)	8.64 (2.27)	0.731
LDL C (mg/dL) (mean (SD))	89.97 (34.25)	87.08 (37.14)	0.525	87.07 (32.01)	87.08 (37.14)	0.999

Continued

Table 1 Continued

	Without propensity-score matched (n=1522)			With propensity-score matched (n=284)		
	Patients without PAD (n=1451)	Patients with PAD (n=71)	P value	Patients without PAD (n=213)	Patients with PAD (n=71)	P value
CRP (mg/dL) (mean (SD))	1.82 (4.14)	2.39 (4.68)	0.271	1.61 (3.30)	2.39 (4.68)	0.137
β2MG (ng/dL) (mean (SD))	19.32 (5.78)	17.33 (5.05)	0.027	17.95 (5.04)	17.33 (5.05)	0.497
TSAT (%) (mean (SD))	27.16 (16.60)	25.44 (17.95)	0.438	25.41 (14.74)	25.44 (17.95)	0.992
Ferritin (ng/dL) (mean (SD))	222.28 (1009.80)	226.65 (395.74)	0.972	171.44 (208.99)	226.65 (395.74)	0.153
Outcome						
Infection-related death (%)	3.40	8.50	0.062	3.80	8.50	0.206
CVD-related death (%)	6.60	11.60	0.167	8.20	11.60	0.537
All-cause death (%)	17.00	33.80	0.001	21.60	33.80	0.056

ACEI, ACE inhibitor; Adjusted Ca, adjusted calcium; Alb, albumin; ARB, angiotensin receptor blocker; BB, beta blocker; BUN, blood urea nitrogen; Ca, calcium; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CGN, chronic glomerulonephritis; CKD, chronic kidney disease; Cr, creatinine; CRP, C reactive protein; CTR, cardiothoracic ratio; CVD, cardiovascular disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; hb, haemoglobin; HF, heart failure; K, potassium; LDL-C, low-density lipoprotein cholesterol; β2MG, beta-2 microglobulin; Mg, magnesium; Na, sodium; P, phosphate; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Plt, platelet; SBP, systolic blood pressure; TSAT, transferrin saturation; UA, uric acid; VDRA, vitamin D receptor agonist; WBC, white blood cells.

We compared the outcomes, HRs and logistic regression model between the two groups.

Statistics

Baseline characteristics were presented descriptively and compared between the two groups using the Student's t-test or χ^2-test. Survival was presented graphically using the Kaplan-Meier method and analysed using univariate and multivariate Cox regression and univariate and multivariate logistic regression model. HRs were calculated and presented graphically using forest plots. ORs were calculated and presented on a table. We used propensity score matching to account for differences in baseline characteristics between the two groups. The propensity score was calculated based on age, sex, presence of diabetes, medication (use of statins, ACE inhibitors, angiotensin-receptor blockers, beta blockers and antiplatelets), laboratory data (levels of phosphorus, haemoglobin and estimated glomerular filtration rate) and history of coronary artery disease.

P values of <0.05 were considered to be statistically significant. We used the R software (V.4.0.0, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/) for all statistical analysis. For the propensity score matching, the R-package MatchIt (1:3 matching with the nearest neighbour) was used.[18] Missing data were not complemented, however the characteristics used for propensity score matching were not missing. Moreover, we conducted the marginal structural Cox model between two groups after propensity score matching.

Patient and public involvement

Patients were not involved at any stage of the research for this study.

RESULTS

Baseline characteristics

Patients' baseline characteristics are shown in table 1. The initial population included 1524 participants, of which 1032 were men and 492 were women. Two patients were untraceable and lost to follow-up. The mean age was 67.50±13.10 years. Of the remaining 1522 patients, 71 (4.70%) had PAD and 1451 did not have PAD. There were significant differences between patients with and without PAD with regard to comorbidities and drug use. Antiplatelet administration was significantly more frequent in those with PAD than in those without PAD. This may be because the treatment for PAD includes antiplatelets. However, since other causes, such as myocardial infarction, can be the reason why these patients were on the antiplaltelet therapy. The prevalence of diabetes mellitus, coronary artery disease and aortic dissection was significantly higher in those with PAD than in those without PAD. Patients with PAD had significantly lower ejection fractions than patients without PAD. The use of both beta-blockers and statins was significantly higher in patients with PAD than in those without PAD (beta-blockers: 34.00% and 47.90%, respectively, p=0.024; statins: 39.40% and 53.50%, respectively, p=0.024). The estimated glomerular filtration rate[19] was significantly higher in patients with PAD than in those without PAD (6.34±1.83 mL/min/1.7 m^2 and 5.40±2.23 mL/min/1.7 m^2, respectively, p=0.001). The median follow-up was 814.5 days (IQR 645–1037).

Mortality

During the follow-up period, 271 patients died from various causes, including cardiovascular events (102 patients, 37.6 %), infectious disease (56 patients, 20.7 %), cancer (45 patients, 16.6 %) and other causes. The

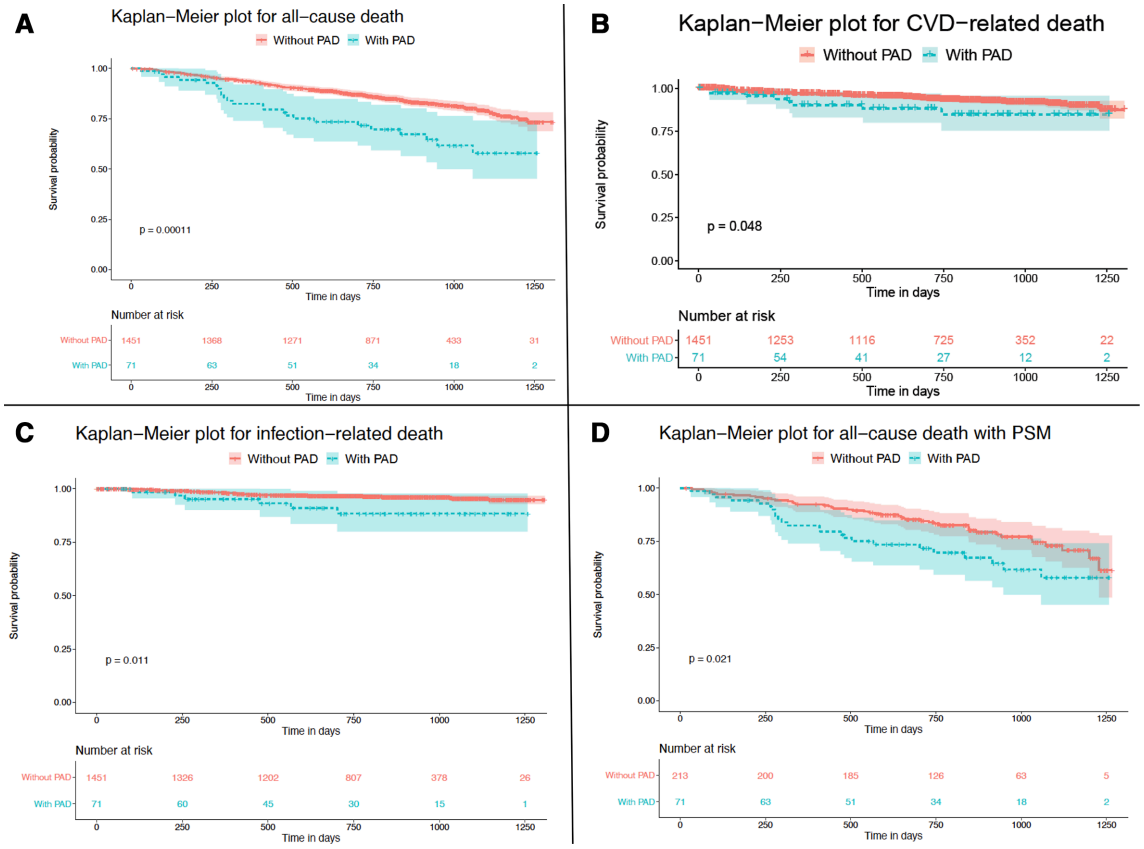

Figure 2 Kaplan-Meier plots. (A) All-cause mortality in patients (n=1522) who started dialysis. (B) CVD-related death in patients (n=1522) who started dialysis. (C) Infection-related death in patients (n=1522) who started dialysis. (D) All-cause mortality in propensity score-matched patients (n=284) with and without PAD who started dialysis. CVD, cardiovascular disease; PAD, peripheral artery disease; PSM, propensity score matching.

PAD group had a significantly higher mortality rate of 33.80% than the group without PAD with 17.00% (p=0.001; table 1). Figure 2A shows the Kaplan-Meier plot for all-cause mortality in patients with and without PAD. Figure 2B shows the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group (p=0.048). Figure 2C shows the Kaplan-Meier plot for infection-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group (p=0.011). Figure 3 shows the forest plot for the HRs of PAD for all-cause death with adjustment for confounding factors. PAD was an independent risk factor for death (HR, 1.76; 95% CI, 1.15–2.69; p=0.009). As sensitivity analyses, we conducted the same analyses on patients, who survived longer than 3 months after the observation beginning. The results resembled the former ones (online supplemental figure S1–S3), except the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD (p=0.094; online supplemental figure S4).

Propensity score-matched comparison between patients with and without PAD

The baseline and clinical characteristics in table 1 showed significant differences between patients in the group with and without PAD, suggesting that there was a possibility of bias. Table 1 shows the baseline characteristics of the propensity score-matched patients with (n=71) and without PAD (n=213).

Figure 2D shows the Kaplan-Meier plot for all-cause mortality in matched patients with and without PAD. Patients with PAD showed a significantly worse prognosis than those without. For CVD-related and infection-related death, respectively, in matched patients with and without PAD with no significant differences between the groups (p=0.300, p=0.069). In logistic regression analysis including propensity score into multivariable factors, patients with PAD had significantly worse prognosis than patients without PAD (table 2). Online supplemental table S1 shows results of the marginal structural Cox model. In all models, PAD was an independent risk factor even after propensity score matching (HRs>2.20, p<0.01).

DISCUSSION

Our study showed that patients with PAD at the time of dialysis initiation had a significantly higher mortality rate than patients without PAD. This higher risk should be considered in the treatment and monitoring of these patients.

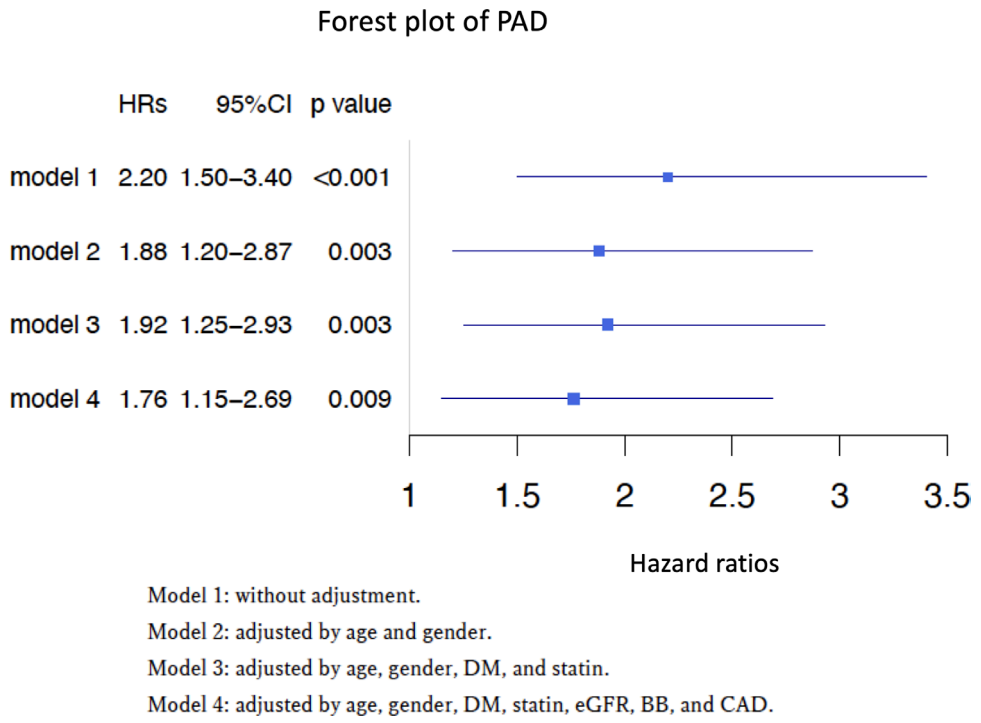

Figure 3 HR of PAD for all-cause mortality. BB, beta-blocker; CAD, coronary artery disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PAD, peripheral artery disease.

A previous study suggested that the prevalence of PAD in patients with ESKD reached almost 20%.[15] In our cohort, the prevalence of PAD was much lower, most likely because our patients started dialysis, whereas the patients in the literature were on maintenance dialysis. This might reflect a deterioration of peripheral atherosclerosis with longer duration of dialysis. Another study suggested that the chronic uremic state is associated with systemic inflammation in dialysis patients, leading to hypoalbuminemia and an increased risk of PAD.[20] Hence, our results are remarkable because we showed the prevalence of PAD at the time of dialysis initiation, while previous studies reported on PAD during maintenance dialysis. Furthermore, patients with PAD in our study more frequently had a decreased ejection fraction and decreased albumin and increased adjusted calcium levels than those without PAD, even after propensity score matching. We cannot exclude the possibility of other factors associated with PAD that were not corrected even after our propensity score matching. This implies that PAD is one symptom of a systemic atherosclerotic disease that affects not only the peripheral but also coronary arteries. When seeing patients with myocardial infarction or low cardiac systolic function, it is recommended to suspect that they have PAD.[7]

Table 2 ORs of the mortality of the patients (n=1522)

	OR	95% CI	P value
Model 1	2.49	1.49 to 4.15	<0.001
Model 2	2.00	1.18 to 3.38	0.010
Model 3	2.12	1.24 to 3.61	0.006
Model 4	1.93	1.12 to 3.30	0.017

Model 1: PAD.
Model 2: PAD + propensity score.
Model 3: PAD + propensity score + pre SBP.
Model 4: PAD + propensity score + pre SBP + adjusted calcium.
PAD, peripheral artery disease; SBP, systolic blood pressure.

In this study, patients with PAD at the time of dialysis initiation had a worse prognosis than patients without PAD. Patients with PAD suffered more frequently from CVD and infectious diseases. After propensity score matching, all-cause mortality still indicated a similar result. As our propensity score included a history of coronary artery disease, we could not show a significant difference between patients with and without PAD regarding this aspect. We assume that the number of patients with PAD was too small to demonstrate a significant difference in infection-related deaths between patients with and without PAD. However, these results support that atherosclerosis is likely to occur not only in the coronary but also in the peripheral arteries in patients with ESKD. PAD is a systemic disease, which can negatively affect patients' prognosis. Based on our findings, it is critical to detect patients with PAD at the time of dialysis initiation.

Our results should be interpreted within the limitations of our study. First, as this was an observational study, there is an inevitable selection bias in our patients with ESKD and PAD. Second, the number of patients with PAD was small, and the number of patients who received Ankle Brachial Index (ABI) is not available. As we did not examine ABI for all patients, we were not able to diagnose

asymptomatic patients or those who did not describe their symptoms seen in PAD. ABI is a frequently used examination for PAD diagnosis and the lack of this result is important. Furthermore, how many patients underwent other diagnostic tests, such as contrast-enhanced CT, magnetic resonance angiography and peripheral angiography, and the results of these tests were unavailable. Hence, the statistical power of our results may be low. Furthermore, we did not include patients with Fontaine stage I into the PAD group. However, our study included a well-defined population as a strength.

CONCLUSION

Patients with PAD at the time of dialysis initiation showed higher rates of mortality than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered for their monitoring and follow-up.

Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

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Contributors DI conceived and designed the study. DI developed the bespoke dataset. AT accessed the dataset, contributed to data analysis and interpretation, and provided feedback on the article. HM performed the data analysis and interpretation, wrote the first draft of the article and subsequent revisions. SM contributed to study design, provided feedback on the article and approved the submitted version. All authors have approved the final version for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Ethics Committee of the Institutional Review Board in Nagoya University (Approval number 1335), and all patients provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs
Hikaru Morooka http://orcid.org/0000-0003-0758-4988
Akihito Tanaka http://orcid.org/0000-0001-8866-5901
Daijo Inaguma http://orcid.org/0000-0002-3977-5933

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