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Hemodialysis Is Associated With Increased Peripheral Artery Occlusive Disease Risk Among Patients With End-Stage Renal Disease

A Nationwide Population-Based Cohort Study

Chin-Sheng Lin, MD, PhD, Sy-Jou Chen, MD, Chih-Chien Sung, MD, Cheng-Li Lin, MSc, Shih-Hua Lin, MD, Shu-Meng Cheng, MD, PhD, I-Kuan Wang, MD, Wen-Sheng Huang, MD, and Chia-Hung Kao, MD

Abstract: To investigate the effect of different dialysis modalities on the incidence of peripheral artery occlusive disease (PAOD) among patients with end-stage renal disease (ESRD) in a large population-based cohort study.

The cohort study included 26,927 ESRD patients who underwent hemodialysis (17,737 patients, hemodialysis [HD] cohort) or peritoneal dialysis (PD, 9190 patients, PD cohort), and 107,588 matched controls between 2000 and 2010. A Cox proportional hazards model was to evaluate the risk of PAOD in the ESRD underwent HD or PD.

Based on a mean follow-up period of 2.92, 3.64, and 4.91 years in the PD, HD, and control cohorts, respectively, the incidences of PAOD were 18.1% and 8.10% higher in the HD and PD cohorts, respectively, compared with the control cohort (log-rank test $P < 0.001$). The patients who underwent HD or PD exhibited a higher risk of PAOD compared with the control cohort regardless of age, sex, and presence or absence of comorbidities. In addition, the incidence of PAOD in the PD cohort and the propensity score-matched HD cohort were 12.4 and 20.7 per 1000 person-years, respectively, with a hazard ratio of 1.92 (95% confidence interval = 1.62–2.28) in HD patients, compared with the PD cohort.

This nationwide population-based cohort study suggested a significantly increased risk of PAOD among ESRD patients. Moreover, the PD patients have a lower risk of developing PAOD compared with the HD cohort, indicating the beneficial roles of PD in reducing PAOD risk in ESRD patients.

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Abbreviations: AF = atrial fibrillation, CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, CRP = C-reactive protein, ESRD = end-stage renal disease, HD = hemodialysis, HDL = high-density lipoprotein, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IL = interleukin, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PAOD = peripheral artery occlusive disease, PBMC = peripheral blood mononuclear cell, PD = peritoneal dialysis, PTH = parathyroid hormone.

INTRODUCTION

Peripheral artery occlusive disease (PAOD) resulting from atherosclerosis refers to partial or complete obstruction of the lower limb arteries.[1] Patients with PAOD may be completely asymptomatic or present with atypical leg symptoms with an exercise limitation, classic intermittent claudication, or ischemic pain and ulceration.[2] Most patients with PAOD who are asymptomatic have a greatly reduced exercise capacity, leading to an impaired functional status and quality of life.[3] Similar to coronary artery disease (CAD), vascular inflammation plays a vital role in the initiation and progression of PAOD. The most critical risk factors for PAOD are diabetes mellitus, cigarette smoking, hypertension, advanced age, and hyperlipidemia.[1] Moreover, inflammatory mediators, such as homocysteine, C-reactive protein (CRP), and lipoprotein (a),

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From the Division of Cardiology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (C-SL, S-MC); Department of Emergency Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (S-JC); Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (C-CS, S-HL); Management Office for Health Data, China Medical University Hospital (C-LL); College of Medicine, China Medical University (C-LL); Graduate Institute of Clinical Medical Science and School of Medicine (I-KW, C-HK); Department of Internal Medicine, College of Medicine, China Medical University (I-KW); Division of Kidney Disease, China Medical University Hospital, Taichung (I-KW); Department of Nuclear Medicine, Changhua Christian Hospital, Changhua (W-SH); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).

Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der, Road, Taichung 404, Taiwan (e-mail: d10040@mail.cmuh.org.tw).

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are suggested to be associated with PAOD.[4–6] Because of the underlying atherosclerotic disease process and general poorly controlled PAOD-risk factors, patients with PAOD are associated with increased risks of subsequent all-cause mortality, cardiovascular mortality, CAD, and stroke.[2,7,8]

Epidemiological studies have revealed that PAOD is more prevalent among patients with end-stage renal disease (ESRD) than in the general population. This patient population is associated with an increased cardiovascular mortality, morbidity and hospitalization, and reduced health-related quality of life.[9,10] Hence, in addition to identifying PAOD in ESRD patients early, aggressive-risk factor reduction and interventional treatment are crucial for attenuating disease progress and improving prognoses.

To date, risk factors for PAOD among ESRD patients are not well understood but likely include both conventional and dialysis- or uremia-associated-risk factors.[9] A recent study of nondiabetic hemodialysis patients indicated that duration of dialysis is correlated with a decreased ankle-brachial index, which is a helpful index for diagnosing PAOD.[11] Similarly, O'Hare et al[12] indicated that PAOD is positively associated with the duration of dialysis. These results suggested the link between PAOD and dialysis process. We are therefore interested in whether different dialysis modalities, such as hemodialysis (HD) and peritoneal dialysis (PD), contribute to the incidence of PAOD.

In this study, we used the Taiwan National Health Insurance Research Database (NHIRD) for analysis and statistics and evaluated the risk of PAOD among patients who underwent HD or PD. We suggested that patients with ESRD who underwent HD are associated with a higher risk of developing PAOD compared with those who underwent PD, even when most conventional PAOD-risk factors are controlled. Our results indicated that PD could be a highly effective dialysis modality for reducing PAOD risk in patients with ESRD.

METHODS

Data Source

The data source of this retrospective cohort study was the NHIRD of the National Health Research Institutes (NHRI). The National Health Insurance (NHI) program began from 1995 to provide comprehensive health care to all inhabitants in Taiwan. The NHI program covers approximately 99.5% of the 23.74 million residents of Taiwan (http://www.nhi.gov.tw/english/index.aspx). The NHIRD offers a set of patient clinical information, including outpatient, inpatient, emergency, traditional Chinese medicine services, prescriptions, medical expenditures, and demographics, which was managed and publicly released by the NHRI from 1996 to 2011. Diseases in the NHIRD are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To protect the privacy of all people registered in the NHI program, the NHRI encrypts and converts the identification numbers of all NHIRD records before releasing them to researchers. The Research Ethics Committee of China Medical University Hospital approved this study (CMU-REC-101–012).

Sampled Patients

All ESRD (ICD-9-CM code 585) patients who underwent dialysis for 3 months or longer were identified from the Registry of Catastrophic Illness Database of the NHIRD from 2000 to 2010, and the first dialysis date served as the index date. In Taiwan, proof of ESRD is necessary to apply for an ESRD catastrophic illness certificate to obtain exemption from related medical costs such as hospital expenses. ESRD patients who died within 90 days after the first dialysis session, were younger than 20 years, underwent transplantation, had a history of PAOD (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9) before the index date, and had incomplete information were excluded. Dialysis modality was defined as the modality at day 90 after the first dialysis session. The ESRD patients were divided into HD and PD cohorts according to the dialysis modalities with different operation codes (HD, 3995; PD, 5498). Two HD patients for each PD were frequency matched according to age (every 5 year), sex, and year of the index date. For the control cohort, we randomly selected 4-fold to ESRD patients without a history of kidney disease (ICD-9-CM codes 580–589) or a history of PAOD and frequency matched with the dialysis patients according to age (in 5-year bands), sex, and year of the index date. Additional PD and HD cohorts were selected according to 1:1 matching based on a propensity score. The propensity score was calculated using logistic regression to estimate the probability of treatment assignment, based on the baseline variables including year of dialysis initiation, age, sex, and comorbidities of CAD (ICD-9-CM codes 410–413, 414.01–414.05, 414.8, and 414.9), diabetes (ICD-9-CM code 250), stroke (ICD-9-CM code 430–438), hyperlipidemia (ICD-9-CM code 272), atrial fibrillation (AF, ICD-9-CM code 427.31), hypertension (ICD-9-CM code 401–405), and congestive heart failure (CHF, ICD-9-CM codes 428, 398.91, and 402.x1).

Outcome

All of the patients were followed up until PAOD diagnosis, loss to follow-up, renal transplantation, withdrawal from insurance, or the end of 2011, whichever date came first.

Statistical Analysis

Baseline distributions for demographic and clinical characteristics were compared among the PD, HD, and control cohorts as well as between the PD and HD subgroups and were examined using a *t*-test or Chi-square test as appropriate. The incidence of PAOD per 1000 person-years was computed for each cohort. We further used a similar approach to measure the corresponding incidences of PAOD according to age, sex, and comorbidity for all cohorts. The Cox proportional hazards model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for PAOD and PAOD-associated-risk factor for the HD and PD cohorts compared with the control cohort. In addition, the age-, sex-, and comorbidity-specific risks in the ESRD, PD, and HD cohorts compared with the control cohort were assessed. The risks of PAOD in the PD cohort compared with the propensity score-matched HD cohort were evaluated. The cumulative incidence of PAOD in the 3 cohorts was plotted using the Kaplan–Meier method, and the difference was presented according to the log-rank test. All data processing and statistical analyses were performed using the SAS software Version 9.3 (SAS Institute, Inc., Cary, NC). A 2-tailed P value of <0.05 was statistically significant.

RESULTS

The demographic characteristics and comorbidities of both age- and sex-matched cohorts and the propensity score-matched cohorts are shown in Table 1. We identified 26,927 ESRD patients (including 9190 PD patients and 17,737 HD patients) and 107,588 patients for the control cohort. Both the ESRD and control cohorts comprised patients younger than 50 years

TABLE 1. Distributions of Demographic and Clinical Comorbid Status in the Study Cohorts With and Without Propensity Score Matching

	Age and Sex Frequency Matched								Propensity Score Matched						
	Controls $N = 107,588$		Total ESRD $N = 26,927$		HD $N = 17,737$		PD $N = 9190$		ESRD vs Controls	HD vs PD	HD $N = 9190$		PD $N = 9190$		HD vs PD
	n	%	N	%	N	%	N	%	*P* Value		n	%	N	%	*P* Valve
Age, year									0.99	0.01					0.13
<50	43,827	40.7	10,960	40.7	7093	40.0	3867	42.1			4012	43.7	3867	42.1	
50–59	28,222	26.2	7060	26.2	4708	26.5	2352	25.6			2326	25.3	2352	25.6	
60–69	19,540	18.2	4889	18.2	3259	18.4	1630	17.7			1589	17.3	1630	17.7	
70+	15,999	14.9	4018	14.9	2677	15.1	1341	14.6			1263	13.7	1341	14.6	
Mean ± SD*	53.7	14.7	53.8	14.6	54.2	14.4	53.2	15.0	0.10	<0.001	53.2	14.4	53.2	15.0	0.94
Sex									0.96	0.15					0.84
Women	57,468	53.4	14,389	53.4	9422	53.1	4967	54.1			4953	53.9	4967	54.1	
Men	50,120	46.6	12,538	46.6	8315	46.9	4223	46.0			4237	46.1	4223	46.0	
Comorbidity															
CAD	13,997	13.0	8920	33.1	6230	35.1	2690	29.3	<0.001	<0.001	2721	29.6	2690	29.3	0.62
Diabetes	8849	8.22	11,643	43.2	8494	47.9	3149	34.3	<0.001	<0.001	3107	33.8	3149	34.3	0.51
Stroke	3498	3.25	3490	13.0	2623	14.8	867	9.43	<0.001	<0.001	878	9.55	867	9.43	0.78
Hyperlipidemia	19,790	18.4	12,260	45.5	8210	46.3	4050	44.1	<0.001	<0.001	3986	43.4	4050	44.1	0.34
AF	813	0.76	418	1.55	266	1.50	152	1.65	<0.001	0.33	126	1.37	152	1.65	0.12
Hypertension	315,82	29.4	26,927	89.4	15,850	89.4	8217	89.4	<0.001	0.89	8266	90.0	8217	89.4	0.23
CHF	3064	2.85	6170	22.9	4587	25.9	1583	17.2	<0.001	<0.001	1613	17.6	1583	17.2	0.56

AF = atrial fibrillation, CAD = coronary artery disease, CHF = congestive heart failure, ESRD = end-stage renal disease, HD = hemodialysis, PD = peritoneal dialysis.

*Chi-square test

†*t*-test.

(40.7%) and consisted predominantly of women (53.4%). The average ages of the ESRD, PD, and HD patients were 53.8, 54.2, and 53.2 years (SD = 14.6, 14.4, and 15.0), respectively. Comorbidities were more prevalent in the ESRD cohort than in the control cohort (all $P < 0.001$). Compared with the patients in the PD cohort, the HD patients had more CAD, diabetes, stroke, hyperlipidemia, and CHF. Conversely, the propensity score-matched PD and HD cohorts ($N = 9190$ patients each) exhibited similar baseline demographic characteristics and comorbidities. The median follow-up periods for the age- and sex-matched PD, HD, and control cohorts were 2.92, 3.64, and 4.91 years, respectively (data not shown). The cumulative incidence of PAOD was presented according to the Kaplan–Meier analysis after 12 years of follow-up (Figure 1). Compared with the control cohort, the risk of developing PAOD was 18.1% higher in the HD cohort and 8.10% higher in the PD cohort (log-rank test $P < 0.001$). The overall incidences of PAOD were 2.73, 24.2, 12.4, and 20.7 per 1000 person-years in the control, HD, PD, and all ESRD cohorts, respectively (Table 2). In addition, the rate of lower extremities amputation (ICD-9-CM code 84.1) among patients with PAOD is 0.69% (10/1443), 11.2% (175/1564), and 16.3% (54/277) in control, HD, and PD cohorts, respectively.

After age and comorbidities of CAD, diabetes, stroke, hyperlipidemia, AF, hypertension, and CHF were adjusted, the HD, PD, and ESRD cohorts exhibited a higher risk of PAOD compared with the control cohort (HR = 4.40, 95% CI = 4.01–4.82 for HD; HR = 2.78, 95% CI = 2.44–3.17 for PD, and HR = 3.94, 95% CI = 3.60–4.30 for all ESRD, respectively). The incidence of PAOD increased with age and among

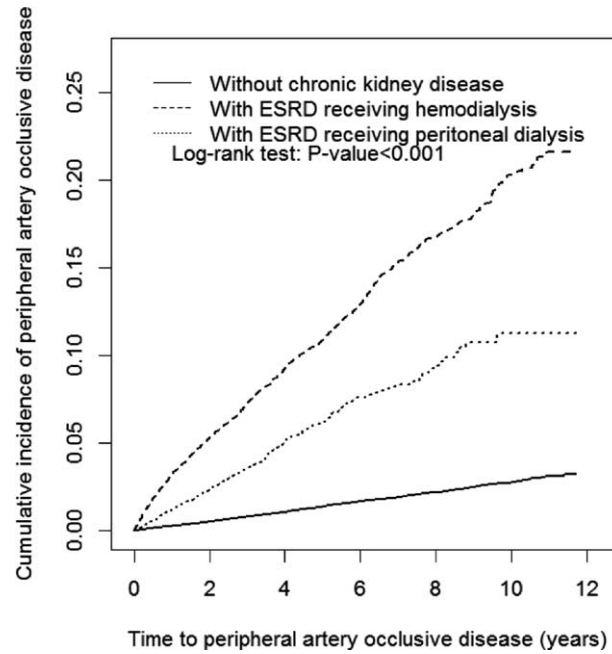

FIGURE 1. Cumulative incidence of PAOD in the patients with ESRD who received different dialysis modalities compared with those without chronic kidney disease. ESRD = end-stage renal disease, PAOD = peripheral artery occlusive disease.

TABLE 2. The Incidence (per 1000 Person-Year) and Risk Factors for PAOD With Age and Sex Frequency Matching

Variable	Event	Person-Year	IR	cHR (95% CI)	aHR† (95% CI)
ESRD					
None	1443	528,165	2.73	1.00	1.00
HD	1564	64,632	24.2	8.78(8.17, 9.43)***	4.40(4.01, 4.82)***
PD	331	26,812	12.4	4.44(3.94, 5.01)***	2.78(2.44, 3.17)***
All	1895	91,444	20.7	7.53(7.03, 8.07)***	3.94(3.60, 4.30)***
Age, year					
<50	820	288,006	2.85	1.00	1.00
50–59	917	156,573	5.86	2.04(1.85, 2.24)***	1.50(1.36, 1.65)***
60–69	839	104,454	8.03	2.79(2.53, 3.07)***	1.82(1.64, 2.02)***
70+	762	70,576	10.8	3.70(3.35, 4.09)***	2.40(2.15, 2.69)***
Sex					
Women	1904	346,272	5.50	1.00	1.00
Men	1434	273,338	5.25	0.94(0.88, 1.01)	0.97(0.91, 1.04)
Comorbidity					
CAD					
No	2010	535,208	3.76	1.00	1.00
Yes	1328	84,401	15.7	4.12(3.85, 4.42)***	1.34(1.24, 1.46)***
Diabetes					
No	1826	553,796	3.30	1.00	1.00
Yes	1512	65,813	23.0	6.95(6.48, 7.45)***	2.18(2.01, 2.97)***
Stroke					
No	2911	598,596	4.86	1.00	1.00
Yes	427	21,013	20.3	4.03(3.64, 4.47)***	1.17(1.05, 1.30)**
Hyperlipidemia					
No	1779	500,134	3.56	1.00	1.00
Yes	1559	119,476	13.1	3.61(3.38, 3.87)***	1.22(1.13, 1.32)***
AF					
No	3263	615,911	5.30	1.00	1.00
Yes	75	3699	20.3	3.66(2.91, 4.60)***	1.31(1.04, 1.66)*
Hypertension					
No	732	405,143	1.81	1.00	1.00
Yes	2606	214,467	12.2	6.68(6.16, 7.26)***	1.81(1.63, 2.01)***
CHF					
No	2593	591,226	4.39	1.00	1.00
Yes	745	28,382	26.3	5.83(5.37, 6.33)***	1.28(1.17, 1.41)***

aHR = adjusted hazard ratio, cHR = crude hazard ratio, CI = confidence interval, ESRD = end-stage renal disease, HD = hemodialysis, PD = peritoneal dialysis, PAOD = peripheral artery occlusive disease.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

† Multivariable analysis including age, CAD, diabetes, stroke, hyperlipidemia, AF, hypertension, and CHF.

patients with comorbidities. In a multivariate model, the risk of PAOD increased with age from 1.51 to 2.40, and the patients with CAD, diabetes, stroke, hyperlipidemia, AF, hypertension, or CHF had a 1.34-, 2.18-, 1.17-, 1.22-, 1.31-, 1.81-, or 1.28-fold risk of PAOD, respectively. Table 3 shows the incidence and HRs of PAOD for the age- and sex-matched cohorts stratified according to age, sex, and comorbidities. An age-specific analysis revealed that the ESRD patients had a higher risk of PAOD compared with the control cohort in all age groups. The sex-specific analysis showed that the patients with ESRD, compared with the control cohort, exhibited a higher risk of PAOD for both the women and men. The HR for PAOD in the ESRD patients without or with comorbidities was 7.39 (95% CI = 5.75–9.49) or 5.26 (95% CI = 4.85–5.71), respectively, compared with the control cohort. Similar results were observed in the HD and PD patients who had a higher risk of PAOD compared with the control cohort in all age groups, sex, and with or without comorbidities. The PAOD incidences in the PD cohort and the propensity score-matched HD cohort were 12.4 and 20.7 per 1000 person-years, respectively, with an HR of 1.92 (95% CI = 1.62–2.28) for PAOD in the HD patients compared with the PD cohort (Table 4).

DISCUSSION

In this nationwide population-based retrospective cohort study, we observed a significant increase in cardiovascular comorbidities and PAOD risk among the ESRD patients, including both the HD and PD groups, compared with the control group, which is consistent with previous reports.[9,12] Moreover, we suggested that, in patients with ESRD, the HD cohort exhibited a higher risk of developing PAOD compared with the PD cohort, irrespective of age, sex, and baseline comorbidities such as hypertension, diabetes, stroke, hyperlipidemia, CAD, CHF, and AF (Table 4). These results indicated

TABLE 3. Incidence (per 1000 Person-Year) and HR for PAOD in Patients With ESRD Receiving Different Dialysis Modalities Compared With Those Without Any Kidney Disease and Frequency Matching According to Age and Sex

	Control		Total ESRD		HD		PD		aHR† (95% CI)		
	Case	Rate	Case	Rate	Case	Rate	Case	Rate	ESRD vs Control	HD vs Control	PD vs Control
Age, year											
<50	232	0.95	588	13.1	508	16.2	80	5.93	5.42(4.28, 6.86)***	6.35(5.00, 8.06)***	3.10(2.27, 4.22)***
50–59	346	2.60	571	24.4	458	27.7	113	16.4	3.86(3.23, 4.62)***	4.16(3.45, 5.02)***	3.18(2.50, 4.04)***
60–69	419	4.65	420	29.1	342	33.0	78	19.2	3.78(3.20, 4.47)***	4.09(3.43, 4.89)***	2.99(2.31, 3.87)***
70+	446	7.21	316	36.1	256	40.1	60	25.4	3.05(2.58, 3.60)***	3.37(2.82, 4.01)***	2.19(1.65, 2.91)***
Sex											
Women	854	2.90	1050	20.4	883	24.6	167	10.7	3.94(3.51, 4.42)***	4.50(3.99, 5.08)***	2.56(2.14, 3.06)***
Men	589	2.52	845	21.1	681	23.7	164	14.6	3.87(3.38, 4.44)***	4.21(3.66, 4.85)***	3.00(2.48, 3.64)***
Comorbidity											
No	427	1.24	73	7.81	64	9.70	9	3.27	7.39(5.75, 9.49)***	9.10(6.99, 11.9)***	3.14(1.62, 6.09)***
Yes	1016	5.56	1822	22.2	1500	25.9	322	13.4	5.26(4.85, 5.71)***	6.01(5.53, 6.53)***	3.23(2.84, 3.68)***

aHR = adjusted hazard ratio, cHR = crude hazard ratio, CI = confidence interval, ESRD = end-stage renal disease, HD = hemodialysis, PD = peritoneal dialysis, PAOD = peripheral artery occlusive disease.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$

† Multivariable analysis including age, CAD, diabetes, stroke, hyperlipidemia, AF, hypertension, and CHF.

the beneficial roles of PD in reducing PAOD risk in patients with ESRD.

The NHIRD employed in this investigation is an effective database for providing population-based studies with age- and sex-matched groups. Because participation in the NHI program is mandatory and all residents in Taiwan can have access to medical care with low copayments, loss to follow-up is low. Proof of ESRD and dialysis modalities are necessary to apply for an ESRD catastrophic illness certificate to obtain exemption from related medical costs such as hospital expenses. Moreover, PAOD were diagnosed and coded (ICD-9 codes) by the specialists according to the standard diagnosed criteria including typical symptoms and signs, laboratory data, and imaging findings. Because the database used in this study is managed by the Bureau of NHI for reimbursement purposes, these data are valid and the diagnoses of PAOD, ESRD, and dialysis modalities are highly reliable.

Consistent with our findings (Tables 2 and 3), increasing evidence has suggested that uremia promotes PAOD disease initiation and progression.[11–13] The substantially increased risk of atherosclerosis and PAOD in patients with ESRD is likely related to uremia-associated inflammation and immune dysfunction, high-density lipoprotein (HDL) dysfunction, and uremic vasculopathy.[14,15] Patients with ESRD have increased numbers of specific proinflammatory subsets of T cells and monocytes, which are commonly observed in healthy aged patients and may contribute to inflammation and destabilization of atherosclerotic plaques, suggesting the presence of premature immunological aging in these patients.[14,16,17] Regarding HDL dysfunction in patients with ESRD, several studies have shown that HDL alters antioxidant and antiinflammatory effects in a chronic uremic state, either by a reduction in its antioxidant enzymes or by an impairment of their activity.[15,18,19] In addition, vascular smooth muscle cell hypertrophy, proliferation, and calcification have been reported to play a pivotal role in uremic vasculopathy.[20–22] Thus, vascular calcification caused by alterations in the metabolism of calcium, phosphorous, and parathyroid hormone (PTH) has been proposed as a potential risk factor for PAOD.[9,23] London et al[24] indicated that PAOD is associated with low bone turnover and low bone formation with pronounced osteoblast resistance to PTH in prevalent nondiabetic patients with ESRD, which clarifies the role of PTH in the pathogenesis of uremia-related PAOD. All of these factors lead to patients with ESRD becoming prone to atherogenesis and predisposed to developing PAOD.

TABLE 4. Overall Incidence (per 1000 Person-Year) and HR for PAOD With Propensity Score Matching

	Propensity Score Matched	
	HD ($N = 9190$)	PD ($N = 9190$)
Person-year	34,723	26,812
Peripheral artery disease		
Overall		
No. of event	717	331
Incidence rate	20.7	12.4
HR (95% CI)	1.92 (1.62, 2.28)***	1 (Reference)

CI = confidence interval, HD = hemodialysis, HR = hazard ratio, PD = peritoneal dialysis, PAOD = peripheral artery occlusive disease.

*** $p < 0.001$

The current study suggested that HD was associated with a higher risk of developing PAOD among the patients with ESRD, compared with PD, which is consistent with previous study from a single-center patient population (Table 4, Figure 1).[25] The underlying mechanism still needs to be explored. Although Lee et al[25] suggested these results may be caused by younger age and lower prevalence of diabetes in PD group, our study suggested HD independently associated with PAOD risk compared with PD group, irrespective of age, sex, and underlying comorbidities, including diabetes (Tables 2 and 3). Possible explanations for these results may be different

inflammatory reactions caused by an HD or PD procedure per se. Conventional PD fluids with glucose as the osmotic agent and glucose degradation products have been shown to induce peritoneal inflammation and oxidative stress.[26,27] Moreover, factors associated with peritonitis, exposure to endotoxin from dialysate, PD catheter-related infections, and the use of bioincompatible PD solutions may cause inflammation in PD patients.[28] In contrast to a relatively local inflammatory reaction caused by a PD procedure per se, numerous systemic inflammatory signals were found to be associated with an HD procedure. An in-vivo examination of human peripheral blood mononuclear cells (PBMCs) revealed that gene expression of interleukin (IL)-1 was increased in PBMCs leaving the dialyzer, but was not increased in PBMCs reentering the dialyzer from the systemic circulation, suggesting that the systemic inflammatory process was induced during the HD process.[29] Memoli et al[30] indicated a significant association between dialysis membrane bioincompatibility and circulating levels of CRP, IL-6, and albumin. Furthermore, small bacterial DNA fragments have been detected in conventional dialysis fluid and can pass through dialyzer membranes.[31] Changing from conventional to ultrapure dialysate substantially reduced circulating levels of CRP and IL-6.[32] These results indicated the additional systemic inflammatory process related to an HD procedure per se, which may partially explain why the patients who underwent HD exhibited a higher risk of developing PAOD compared with the PD cohort.

Although PD is considered a particularly suitable dialysis modality for ESRD patients with few comorbidities,[33] the cause of PAOD in this study might have been these comorbidities instead of a dialysis procedure per se. However, propensity score matching between the ESRD and control groups as well as the HD and PD groups was performed (Table 1). Therefore, the risk factors for PAOD have been well investigated, and the 2 groups (ie, the HD and PD groups) share the same risk factors ($P > 0.05$) (Table 1). Moreover, the HRs for PAOD in the ESRD patients without comorbidities and who underwent HD or PD were 9.10 (95% CI = 6.99–11.9) and 3.14 (95% CI = 1.62–6.09), respectively, compared with the control cohort (Table 3), implying that the HD cohort had a higher risk of developing PAOD compared with the PD cohort even without comorbidities. These results revealed that the higher risk of developing PAOD in the HD patients, compared with the PD patients, may not be due to their underlying comorbidities.

Several limitations should be considered before the findings are interpreted. First, the NHIRD does not provide detailed information on the lifestyle or health-related factors of patients, such as smoking, nutrition status, body mass index, socioeconomic status, functional status, and a family history of PAOD, which may increase the risk of PAOD. Moreover, some potential-confounding factors, including genotypes, severity of PAOD including claudication, ischemic rest pain, and wound necrosis or ulcers, heterogeneous clinical manifestations, and certain laboratory parameters such as PTH, homocysteine, CRP, lipoprotein (a) and levels of blood urea nitrogen (BUN), and creatinine, were not available in this study. Second, evidence from a cohort study is generally considered to have a lower methodological quality than that from randomized trials. Third, the risk of PAOD was evaluated by ICD-9 codes instead of a screening program. Patients with asymptomatic PAOD might not seek health care until they experience significant discomfort, leading to the underestimation for the risk of PAOD among patients with end-stage renal disease (ESRD) or the matched controls. Forth, although PAOD diagnosis was strictly monitored by certified medical reimbursement specialists, we did not use additional procedure codes to verify the PAOD population. An additional limitation is that, although a considerably small population, the HD patients with arteriovenous shunt occlusion or graft failure (ICD-9-CM code 99673) might have been miscoded as PAOD by inexperienced clinicians, which would have overestimated the risk of PAOD in patients with HD. Finally, despite the meticulous study design to control the confounding factors, the potential bias resulting from possible unmeasured or unknown confounders was a key limitation of this study. However, even with these limitations, this study provided worthwhile information on the effects of HD and PD on the risk of PAOD.

Collectively, the strength of this study was the use of a nationwide population-based cohort longitudinal analysis of the risk of PAOD among Asian ESRD patients undergoing HD or PD. We demonstrated that HD is associated with an increased risk of PAOD compared with PD among patients with ESRD. Additional prospective randomized studies with effective control of potential confounding factors, such as smoking and serum levels of PTH, homocysteine, CRP, and lipoprotein (a), are necessary to verify the effects of different dialysis modalities on the development of PAOD and to elucidate its possible underlying mechanisms. Together with previous evidence suggesting the beneficial role of PD in the reduction of PAOD among patients with ESRD,[25] we recommended ESRD patients with PAOD-risk factors, such as diabetes, CAD, and hyperlipidemia, should consider PD as their choice of dialysis modality.

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