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Risk of Retinal Artery Occlusion in Patients With End-Stage Renal Disease

A Retrospective Large-Scale Cohort Study

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Abstract: There is globally increasing prevalence and incidence in end-stage renal disease (ESRD). These patients are frequently reported to have retinal abnormalities and both diseases share some systemic risk factors. Hence, it is clinically relevant to determine whether ESRD is a predictor of retinal artery occlusion (RAO).

To investigate the risk of RAO in ESRD patients.

A retrospective, nationwide, matched cohort study. The study included 93,766 ESRD patients recruited between 2000 and 2009 from the Taiwan National Health Insurance Research Database. The same number control group included age- and sex-matched patients without ESRD selected from the Taiwan Longitudinal Health Insurance Database, 2000. Data for each patient were collected from the index date until December 2011.

The incidence and risk of RAO were compared between the 2 groups. The hazard ratio (HR) for RAO after adjustment for potential confounders was calculated using Cox proportional hazards regression. Kaplan–Meier analysis was used to calculate the cumulative RAO incidence rate.

In total, 237 ESRD patients and 73 controls exhibited RAO during follow-up; thus, the RAO incidence rate in ESRD patients was 4.49 times (95% confidence interval (CI), 3.45–5.83) that in the control patients. After adjustment for potential confounders, including diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and coronary artery disease, ESRD patients were 2.78 times (95% CI, 2.02–3.84) more likely to develop RAO in cohort for the total sample. Among patients with hypertension, the RAO incidence rate was significantly higher in the ESRD group, and hypertension significantly increased RAO risk even after adjustment for other confounders in the cohort.

ESRD increases the risk of RAO, particularly in ESRD patients with hypertension. Therefore, clinicians should educate ESRD patients about RAO and ensure appropriate blood pressure control.

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Abbreviations: CI = confidence interval, CIC = catastrophic illness certificate, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IRR = incidence rate ratio, NHI = National Health Insurance, NHIRD = Taiwan National Health Insurance Research Database, PY = patient-years, RAO = retinal artery occlusion, SD = standard deviation.

INTRODUCTION

End-stage renal disease (ESRD) is an important public health problem worldwide. Epidemiological studies conducted in both Western and Asian populations have shown that the prevalence and incidence of ESRD are increasing in developing and developed countries.[1–3] Compared with other countries, Taiwan has a remarkably high incidence and prevalence of ESRD.[4–6]

Retinal artery occlusion (RAO), classified into various types of central RAO (CRAO) and branch RAO (BRAO), is a common cause of severe visual impairment and requires emergency medical care.[7] The incidence rates of CRAO (IR = 1.64 per 100,000 person-years) and BRAO (IR = 4.99 per 100,000 person-years) are very low in the general population.[8] A definite diagnosis of CRAO or BRAO is based on the presence of the classical clinical findings. The diagnostic criteria for CRAO include sudden-onset of loss of vision in one eye, acute entire retinal ischemia, that is, retinal opacity with cherry red spot, and diffuse absence of retinal arterial circulation or marked stasis in fluorescein fundus angiography. The diagnostic criteria for BRAO include sudden monoocular visual deterioration, acute local retinal ischemia over the occluded branch retinal artery distribution area, and absence of local retinal arterial circulation or marked stasis in the involved branch retinal artery on fluorescein fundus angiography.[7] RAO in the eye is analogous to stroke in the brain. It is caused by acute occlusion of the retinal artery and results in acute, painless monocular visual impairment.[9] The retina is supplied by the central retinal artery, which originates from the ophthalmic artery, the first intracranial branch of the internal carotid artery.[10] The most common pathophysiology of RAO is embolism that typically arises from ulcerated atherosclerotic

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plaques or thrombi within carotid arteries or, less commonly, from cardiac valvular structures.[7] Furthermore, serotonin released by platelet aggregation on carotid atherosclerotic plaques may participate in occluding the retinal blood flow and contribute to RAO.[7,11]

Carotid atherosclerosis and plaque are common complications of ESRD. Several reports have demonstrated a close relationship between carotid atherosclerosis and plaque formation in dialysis patients.[12–14] Atherosclerotic plaques in the carotid artery are associated with both embolism and serotonin release, which are the leading causes of RAO. Meanwhile, Song et al[15] demonstrated that the mean carotid intima-media thickness and total plaque area are significantly greater in RAO patients than in the general population. Furthermore, microvascular disease, including a defective renal microcirculation, is a prominent pathological feature of ESRD. Retinal microvascular abnormalities are also frequently reported in ESRD patients.[16–18] Microvascular retinopathies such as focal or generalized arteriolar narrowing and arteriovenous nicking are more common in not only ESRD patients[19,20] but also RAO patients.[10,21] In addition to their common pathogenic mechanisms, ESRD and RAO share some systemic risk factors, including hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, and coronary artery disease. Therefore, it is clinically relevant to determine whether ESRD is a predictor of RAO. However, few previous studies have discussed this association, and the results of published studies are limited by the small number of patients or the absence of comparative control data. Therefore, we used a nationwide population-based dataset to design a cohort study for evaluating the association between ESRD and RAO in Taiwan.

METHODS

Database

After March 1, 1995, Taiwan launched a single-payer National Health Insurance (NHI) scheme, which provides extensive medical care coverage for all residents in Taiwan. As of 2007, 22.60 million individuals, comprising >98% of the total Taiwanese population of 22.96 million, were enrolled in this program. The data for our cohort study were obtained from the Taiwan National Health Insurance Research Database (NHIRD), which supplies enciphered patient identification numbers as well as information regarding patient gender, birth date, and admission and discharge dates. It also includes the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnoses and procedure codes, prescriptions details, and costs covered and paid by NHI. This study was granted exemption from review by the Institutional Review Board of Chi-Mei Medical Center. The requirement of informed consent was waived because analyzing datasets in a database is devoid of identifiable personal information.

Selection of Patients and Variables

This retrospective cohort study was conducted using 2 study groups: a new-onset ESRD group and a matched non-ESRD (control) group, both recruited during 2000 to 2009. ESRD patients who began dialysis treatment after December 31, 2000 and received a catastrophic illness certificate (CIC) with the code number 585 between January 1, 2000 and December 31, 2009 were included. Patients with unknown gender or missing data were excluded, as were patients diagnosed with RAO [ICD-9-CM codes 362.31 (CRAO) and 362.32 (BRAO)] before ESRD.

For each ESRD patients, one control without ESRD was randomly selected from the longitudinal Health Insurance Database, 2000 (LHID2000), which is a data subset of NHIRD that includes the overall claim data for 1 million beneficiaries (4.34% of the total population) randomly selected in 2000. There was no significant difference in age, gender, and health care costs between the sample group and all NHI enrollees. The controls were matched with the ESRD patients by gender, age, and index date. The index date for the ESRD patients was the date of first dialysis, while that for the controls was created by matching with the ESRD patient's index date. Controls diagnosed with RAO before the index date were excluded. Each patient was followed up to determine the incidence of RAO until the end of 2011 or death, whichever came earlier.

To distinguish patients who developed RAO after ESRD, we tracked every patient from his or her index outpatient visit or hospitalization through December 2011 and recorded their demographic data (eg, age and sex). Furthermore, we collected data for comorbidities, including diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM code 428), and coronary artery disease (ICD-9-CM code 410–414), because these conditions are critical risk factors for RAO.[7] In this study, the inclusion criterion for diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and coronary artery disease was as follows: documentation of the condition at least once in the inpatient setting or ≥3 times in the ambulatory setting within 1 year before the initial dialysis date. A flowchart illustrating how the study participants were selected and a table listing all ICD-9 codes for all variables are shown as appendix data.

Statistical Analysis

SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC) was used for statistical analyses. Demographic characteristics and comorbidities were compared between the ESRD and control groups using Pearson Chi-square tests. The incidence rate for RAO was calculated as the number of RAO patients identified during the follow-up period divided by the total number of person-years (PY) for each group by age, sex, and selected comorbidities. Poisson regression analysis was performed to calculate the incidence rate ratio (IRR), which represented a comparison of the RAO risk between the ESRD and control groups. Adjusted hazard ratios (HRs) for developing RAO were calculated using Cox proportional hazards regression. The cumulative incidence rates for RAO were calculated using Kaplan–Meier analyses, and differences in the cumulative incidence rate curves were analyzed using log-rank tests. Then, we subdivided the patients into 3 age subgroups for further analysis: <50 years, 50 to 64 years, and ≥65 years. Additionally, we subdivided the patients into 2 dialysis subgroups—hemodialysis (HD) and peritoneal dialysis (PD)—to evaluate whether ESRD patients on different modalities would have different risk of RAO. Data are presented as means [standard deviations (SDs)], and 95% confidence intervals (CIs) are provided where applicable. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographic Data

Between 2000 and 2009, 93,766 ESRD patients and 93,766 controls were recruited after excluding ineligible subjects.

TABLE 1. Demographic Characteristics and Comorbid Disorders in the ESRD and Control Groups*

	ESRD (N = 93,766), n (%)	Controls (N = 93,766), n (%)	*P*
Age at index date (y; mean ± SD)	62.22 ± 14.65	62.22 ± 14.65	1.0000
Age at index date (y)			
<50	18,214 (19.42)	18214 (19.42)	1.0000
50–64	29,971 (31.96)	29971 (31.96)	
≥65	45,581 (48.61)	45581 (48.61)	
Gender			
Male	46,552 (49.65)	46552 (49.65)	1.0000
Female	47,214 (50.35)	47214 (50.35)	
Baseline comorbidities			
DM	49,442 (52.73)	10244 (10.93)	<0.0001
HTN	77,124 (82.25)	23590 (25.16)	<0.0001
HPL	18,602 (19.84)	7099 (7.57)	<0.0001
CHF	21,818 (23.27)	1688 (1.80)	<0.0001
CAD	23,892 (25.48)	7297 (7.78)	<0.0001
Dialysis type			
HD	83,532 (89.09)		
PD	10,234 (10.91)		

CAD = coronary artery disease, CHF = congestive heart failure, DM = diabetes mellitus, ESRD = end-stage renal disease, HD = hemodialysis, HPL = hyperlipidemia, HTN = hypertension, PD = peritoneal dialysis, SD = standard deviation.
*Two groups were compared using Pearson Chi-square tests.

Table 1 provides the demographic data for the ESRD patients and age- and sex-matched controls. Data for the evaluated comorbidities are also presented in Table 1. The mean age of the ESRD and control patients was 62.22 (SD, 14.65) years. Of the 93,766 ESRD patients, 46,552 (49.65%) were men and 47,214 (50.35%) were women, with 18,214 (19.42%) aged < 50 years, 29,971 (31.96%) 50 to 64 years, and 45,581 (48.61%) ≥65 years. With regard to the comorbidities, the ESRD patients exhibited a significantly higher prevalence compared with the controls. We have classified the ESRD patients into the HD and PD groups based on the different treatment modalities, and we found that of the 93,766 ESRD patients, 85,532 (89.09%) were under HD and 10,234 (10.91%) were under PD (Table 1). The mean age of the HD and PD groups were significantly different ($P < 0.0001$), with 63.43 (SD, 13.93) years in the HD group and 52.33 (SD, 16.50) years in the PD group (data not shown).

Incidence Rates for RAO

During the follow-up period, 310 (310/187,532, 0.17%) patients developed RAO, with the proportion being significantly higher in the ESRD group (237/93,766, 0.25%) than in the control group (73/93,766, 0.08%; Table 2). In addition, there was a significant difference in the RAO incidence rate (ESRD, 5.37/10,000 PY; control, 1.20/10,000 PY) and IRR (4.49, 95% CI, 3.45–5.83, $P < 0.0001$; Table 2) between the 2 groups.

Next, we classified RAO into CRAO and BRAO. The majority of RAO cases in both groups were those of CRAO, including 136 of 237 (57.38%) and 46 of 73 RAO (63.01%) patients in the ESRD and control groups, respectively. There was a significant difference in the CRAO incidence (ESRD, 3.08/10,000 PY; control, 0.75/10,000 PY) and IRR (4.09; 95% CI, 2.92–5.71; $P < 0.0001$; Table 2) between the 2 groups. With regard to BRAO, there were 101 patients (42.62%) in the ESRD group and 27 (36.99%) in the control group (5.17; 95% CI, 3.38–7.90; $P < 0.0001$; Table 2).

With regard to the 3 age groups, ESRD patients aged 50 to 64 years exhibited the highest incidence rate for RAO (7.10/10,000 PY), followed by those aged < 50 years (4.98/1000 PY) and ≥65 years (4.14/1000 PY). The IRR values were significantly higher for the 3 ESRD age groups than for controls within the same age ranges (Table 2). In particular, the incidence was 13.08 times higher in ESRD patients aged < 50 years than in controls of the same age (IRR, 13.08; 95% CI, 5.24–32.64; $P < 0.0001$).

The incidence rate of RAO was 5.35/10,000 PY for the male ESRD patients and 1.25/10,000 PY for the male controls (IRR, 4.29; 95% CI, 2.96–6.21; $P < 0.0001$). A significant difference was also observed between the female ESRD patients and controls (IRR, 4.69; 95% CI, 3.24–6.80; $P < 0.0001$; Table 2).

The incidence rates for RAO among patients with diabetes mellitus (6.10/10,000 PY), hypertension (6.06/10,000 PY), hyperlipidemia (6.95/10,000 PY), and congestive heart failure (6.14/10,000 PY) were similar and higher than that among patients with coronary artery disease (4.86/10,000 PY) in the ESRD group. The IRR for RAO among patients with diabetes mellitus, hypertension, and hyperlipidemia revealed a significantly higher risk in ESRD patients than in controls: 3.60 (95% CI, 1.89–6.85) for diabetes mellitus, 3.04 (95% CI, 2.05–4.50) for hypertension, and 2.79 (95% CI, 1.42–5.47) for hyperlipidemia (Table 2). However, this was not observed for patients with coronary artery disease or congestive heart failure.

Table 3 provides the crude and adjusted HRs for RAO during the follow-up period. After adjusting for age, sex, and the selected comorbidities, ESRD remained an independent risk factor for RAO (adjusted HR, 2.78; 95% CI, 2.02–3.84). Both HD and PD were independent risk factors for the development of RAO after adjusting for other confounding factors in the total cohort (adjusted HR [95% CI], 3.66 [2.34–5.73] for PD and 2.67 [1.92–3.70] for HD). The risk of RAO was not significantly different between patients who underwent PD or HD. Significant risk factors for RAO in both groups included an age of 50 to 64 years (adjusted HR, 1.40; 95% CI, 1.03–1.91; $P < 0.05$) and hypertension (adjusted HR, 2.07; 95% CI, 1.50–

TABLE 2. Risk of RAO in the ESRD and Control Groups*

		ESRD			Controls					
Characteristics	N	RAO	PY	Rate†	N	RAO	PY	Rate†	IRR (95% CI)	*P*
All	93,766	237	441,609	5.37	93,766	73	610164.2	1.20	4.49 (3.45–5.83)	<0.0001
CRAO		136 (57.38%)		3.08		46 (63.01%)		0.75	4.09 (2.92–5.71)	<0.0001
BRAO		101 (42.62%)		2.29		27 (36.99%)		0.44	5.17 (3.38–7.90)	<0.0001
Age (y)										
<50	18,214	57	114541.74	4.98	18,214	5	131442.57	0.38	13.08 (5.24–32.64)	<0.0001
50–64	29,971	107	150657.08	7.10	29,971	25	200388.79	1.25	5.69 (3.68–8.80)	<0.0001
≥65	45,581	73	176410.14	4.14	45,581	43	278332.79	1.54	2.68 (1.84–3.90)	<0.0001
Gender										
Male	46,552	114	213086.03	5.35	46,552	37	296412.64	1.25	4.29 (2.96–6.21)	<0.0001
Female	47,214	123	228522.93	5.38	47,214	36	313751.50	1.15	4.69 (3.24–6.80)	<0.0001
Comorbidities										
DM	49,442	124	203131.92	6.10	10,244	10	58894.05	1.70	3.60 (1.89–6.85)	<0.0001
HTN	77,124	212	349840.06	6.06	23,590	28	140304.73	2.00	3.04 (2.05–4.50)	<0.0001
HPL	18,602	56	80564.33	6.95	7099	10	40173.65	2.49	2.79 (1.42–5.47)	0.0028
CHF	21,818	52	84756.53	6.14	1688	4	8777.22	4.56	1.35 (0.49–3.72)	0.5666
CAD	23,892	47	96640.40	4.86	7297	12	43905.69	2.73	1.78 (0.94–3.35)	0.0748

BRAO = branch RAO; CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, CRAO = central RAO; DM = diabetes mellitus, ESRD = end-stage renal disease, HPL = hyperlipidemia, HTN = hypertension, IRR = incidence rate ratio, PY = person-years, RAO = retinal artery occlusion.

*Poisson regression analysis was performed to calculate the incidence rate.

†Rate: per 10,000 PY.

2.86; $P < 0.05$). Gender, diabetes mellitus, hyperlipidemia, congestive heart failure, and coronary artery disease were not independent risk factors for RAO. Kaplan–Meier analyses revealed higher RAO cumulative incidence rates in the ESRD group than in the control group; the findings of log-rank tests were also significant ($P < 0.0001$; Figure 1).

DISCUSSION

According to a thorough review of relevant research, no large-scale population-based study has been conducted to explore the relationship between ESRD and subsequent RAO. We analyzed 93,766 ESRD patients and 93,766 age- and sex-matched control subjects to elucidate this association. The study results indicated a significantly increased risk of RAO in ESRD patients compared with that in controls, and showed that ESRD was still an independent risk factor for RAO in the total sample after taking age, sex, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and coronary artery disease into account.

To our knowledge, no study has demonstrated an association between RAO and ESRD or investigated the pathophysiological association between them. Common pathogenic mechanisms for both conditions include carotid atherosclerosis and plaque formation. Many studies demonstrated that carotid atherosclerosis and plaque formation are common in any stage of chronic renal disease, particularly ESRD being treated conservatively or by dialysis.[22–24] The most important factors for atherosclerosis in patients with ESRD include deranged calcium-phosphate homeostasis and secondary hyperparathyroidism, which are associated with effects on lipoprotein metabolism[25]; hyperuricemia, which is possibly linked to oxidative stress and structural changes of the vessel wall[26,27]; and hyperhomocysteinemia, which can possibly lead to limited bioavailability of nitric oxide, an increase in oxidative stress, stimulation of smooth cell proliferation, and alteration in elastic wall properties.[28] In addition, C-reactive protein, a systemic inflammation marker, and asymmetric dimethylarginine, an endogenous inhibitor of NO synthase, are related to atherosclerosis in the ESRD patients.[29] Once carotid atherosclerosis and plaque develop, emboli may form from the thrombi within the atherosclerosed carotid artery or ulcerated atherosclerotic plaques. The retina is supplied by the central retinal artery, which originates from the ophthalmic artery, the first intracranial branch of the internal carotid artery.[10] Therefore, RAO is a frequently encountered complication of emboli formed from the carotid artery. In fact, Song et al[15] reported that the mean carotid intima-media thickness and total plaque area were significantly higher in patients with RAO than in those without. In addition, carotid atherosclerosis and plaque formation can lead to RAO through serotonin released by platelet aggregation on atherosclerotic plaques in the carotid artery.[11] Serotonin may induce vasospasm of the retinal artery in patients with atherosclerosis and occlude the retinal blood flow, thus participating in the pathophysiology of RAO.[7]

Microvascular retinopathy such as focal or generalized retinal arteriolar narrowing has been reported to be more common in ESRD patients.[16,19,20,30] Microvascular retinopathy is not only a characteristic of ESRD but also an indicator of renal function impairment. Many studies demonstrated associations between a number of retinal vessel characteristics, including arteriolar narrowing, and markers of renal dysfunction and renal damage.[16–18] In fact, the retinal and renal circulations share homologous anatomical and pathophysiological characteristics,[20,31] because the inner retina and glomerular filtration barrier have similar structural features and homologous developmental pathways.[19,32,33] Furthermore, microvascular retinopathy is a common manifestation not only in ESRD patients but also in RAO patients, although microvascular retinopathy is not the major leading cause of RAO. Microvascular retinopathy may be a marker of generalized microvascular disease caused by vascular endothelial dysfunction[34] in the kidneys and retina, increase the susceptibility of the

TABLE 3. Crude and Adjusted Hazard Ratios Obtained Using Cox Proportional Hazards Regression and 95% Confidence Intervals for RAO During the Follow-Up Period for the Study Cohort*

Cohort	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
ESRD (yes vs no)	4.38† (3.37–5.70)	2.78† (2.02–3.84)
No	1.00	1.00
PD	5.56† (3.74–8.33)	3.66†,‡ (2.34–5.73)
HD	4.23† (3.23–5.53)	2.67†,‡ (1.92–3.70)
Age (y)		
<50	1.00	1.00
50–64	1.46† (1.08–1.98)	1.40† (1.03–1.91)
≥65	0.98 (0.72–1.33)	0.97 (0.71–1.34)
Gender		
Female	1.00	1.00
Male	1.00 (0.80–1.25)	1.01 (0.81–1.26)
Comorbidity		
DM		
No	1.00	1.00
Yes	2.22† (1.77–2.78)	1.02 (0.78–1.32)
HTN		
No	1.00	1.00
Yes	3.83† (2.93–5.01)	2.07† (1.50–2.86)
HPL		
No	1.00	1.00
Yes	2.02† (1.54–2.66)	1.27 (0.95–1.69)
CHF		
No	1.00	1.00
Yes	2.17† (1.62–2.90)	1.21 (0.88–1.65)
CAD		
No	1.00	1.00
Yes	1.48† (1.11–1.97)	0.86 (0.63–1.17)

CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, DM = diabetes mellitus, ESRD = end-stage renal disease, HD = hemodialysis, HPL = hyperlipidemia, HTN = hypertension, PD = peritoneal dialysis, RAO = retinal artery occlusion.

*The adjusted hazard ratio for developing RAO was calculated using Cox proportional hazards regression.

†$P < 0.05$.

‡The adjusted hazard ratio of developing RAO was not significantly different between patients who underwent PD or HD.

retinal vessels to occlusion, and participate in RAO development.

We found that ESRD patients aged 50 to 64 years exhibited the highest incidence rate for RAO in the ESRD groups, and this was an independent risk factor after adjusting for other confounding factors in the both groups. It would be logical that the oldest group had the highest incidence rate and the age-dependent incidence rate trend was found in the control group. However, paradoxically, the incidence rate in ESRD patients aged ≥65 years was the lowest. We have attempted to explain the highest incidence rate of RAO in the ESRD patients aged 50 to 64 years and the lowest incidence rate of RAO in the ESRD patients aged ≥65 years by 2 proposed reasons. First, ESRD patients tend to exhibit decreased blood delivery because of intradialytic hypotension. The complication might be more common among elder ESRD populations and may be related to impaired cardiovascular compensation. We proposed that once the blood delivery volume is decreased in elder ESRD populations, embolism formation from the atherosclerotic plaque might be subsequently decreased and the RAO incidence rate might be reduced as a result. Second, we proposed that the death censoring might play a role in explaining the low incidence rate in ESRD patients aged ≥65 years. Among elder ESRD populations, there might be higher proportion of patients who died before RAO development than those in the control group.

RAO, particularly CRAO, is a vision-threatening retinal vascular disease. Some studies have reported several comorbidities associated with RAO, such as hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, and coronary artery disease.[7,35,36] In this cohort study, we evaluated these comorbidities in ESRD patients and controls and found that hypertension was associated with a significantly higher incidence of RAO in the ESRD patients compared with that in the controls, and it was the only significant risk factor for RAO in both groups. This finding is consistent with those in several previous studies demonstrating hypertension to be a major risk factor for RAO.[7] Hypertension is associated with arteriosclerosis, atherosclerosis, retinal vessel wall damage, and thromboembolism, all of which contribute to the development of RAO.[35–37] In addition, several studies disclosed that patients with ESRD and hypertension exhibit accelerated carotid atherosclerosis,[24,38] which is the leading cause of embolism and consequent RAO. Therefore, ESRD patients with hypertension should be advised about blood pressure control. Furthermore, several studies have reported that the incidence of stroke and acute coronary syndrome is significantly high following RAO events.[8,39] This suggests that ESRD patients with hypertension

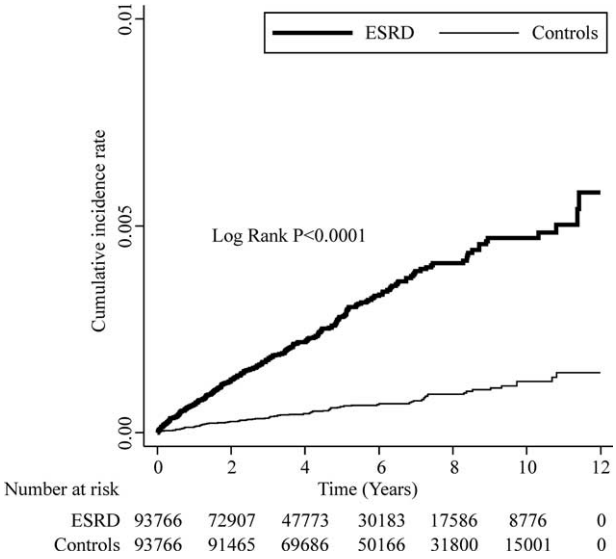

FIGURE 1. Cumulative incidence of retinal artery occlusion (RAO) in patients with end-stage renal disease (ESRD) and controls during the follow-up period.

should be considered for cardiovascular monitoring to ameliorate RAO and prevent stroke.

The diabetes mellitus patients exhibited a significantly higher IRR for RAO in the ESRD group compared with the controls in this study. Many studies have reported that RAO is accelerated by diabetes mellitus.[7,40] Prolonged hyperglycemia can lead to both macrovascular damage such as carotid artery atherosclerosis and microvascular damage such as retinal arteriolar narrowing and contribute to RAO formation.[40] Ishizaka et al also demonstrated that ESRD with hyperglycemia and impaired glucose metabolism increases the risk of and accelerates carotid artery atherosclerosis,[38] indicating an increased risk of RAO in ESRD patients with diabetes mellitus.

With regard to hyperlipidemia, the incidence rate for RAO was significantly higher in the ESRD group than in the controls. Dyslipidemia, particularly elevated low-density lipoprotein (LDL)-C levels, is a well-known classical risk factor for carotid atherosclerosis and also strongly contributes to carotid atherosclerosis progression in ESRD patients.[41–43] The link between hyperlipidemia and RAO can be based on the fact that carotid atherosclerosis is more severe in ESRD patients than in healthy individuals.[44] However, the IRR for RAO was slightly lower for the patients with hyperlipidemia than for those with hyperglycemia and hypertension in the ESRD group. These findings may be explained according to a recent study that reported a decreased carotid atherosclerosis prevalence in ESRD patients over the last decade because of a decrease in LDL-C levels by statin use.[22]

There are several strengths in our study. First, it was a nationwide, population-based study including a large sample of ESRD patients, which increases the precision of risk appraisal and elevates the power of statistics. Second, patients with visual disturbances visit ophthalmologists rather than general practitioners, leading to decreased selection bias in referral centers and chances of misdiagnosis. Third, the study is a cohort study with maximum longitudinal data for 10 years with regard to RAO incidence. Fourth, our results are reliable because hypertension, diabetes mellitus, hyperlipidemia, congested heart failure, and coronary artery disease were considered as confounding factors to adjust the HR for RAO in the ESRD patients.

This study also has some limitations. The sampled patients' medical histories can only be traced back to the year 1996. We cannot confirm if the controls had a history of ESRD before January 1996; therefore, our findings could be compromised. In addition, several important confounding factors, including smoking history, alcohol consumption, and body mass index, could not be assessed. Besides, the insurance claims data did not include information on the current blood pressure and laboratory data for blood sugar and serum cholesterol levels, which may have introduced some bias. To decrease the effects of this problem, we included hypertension, diabetes mellitus, and hyperlipidemia as confounding factors. Additionally, the diagnosis of ESRD, RAO, and other comorbidities relied on ICD-9-codes, which may have led to misclassification. Finally, the incidence rate of RAO in the general population is very low and RAO is a very rare event in ESRD group, which may restrict the application of the study. Although RAO is a very rare event, RAO increases the risk of subsequent stroke and acute coronary syndrome according to previous reports.[8,39] It is very important for clinical practice in the direction that the retinal vessels might be ''mirror'' of the vascular system in general. For the ESRD with subsequent RAO patients, physicians should ideally survey the cardiovascular conditions by approaches such as carotid artery monitoring and cardiac ultrasonography because of the association with RAO and following stroke or acute coronary syndrome.

In summary, our study showed that the risk of RAO was significantly higher in patients with ESRD than in those without, and ESRD remained an independent risk factor after adjusting for diabetes mellitus, hypertension, hyperlipidemia, congestion heart failure, and coronary artery disease in the cohort. The association between ESRD and RAO is based on not only carotid atherosclerosis and plaque formation, which is associated with embolism, and serotonin release but also the common manifestation of microvascular retinopathy, which makes the retinal vessels vulnerable to occlusion. Moreover, hypertension was an independent risk factor for RAO in ESRD patients after adjustment for other confounders in the cohort. These results suggest that clinicians should educate ESRD patients about RAO in addition to ensuring appropriate blood pressure control.

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