Risk of Retinal Vein Occlusion Following End-Stage Renal Disease

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Abstract: The aim of the study was to investigate the risk of retinal vein occlusion (RVO) following end-stage renal disease (ESRD). The study was designed as a retrospective, nationwide, matched cohort study. The subjects were ESRD patients identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), code 585. The study cohort included 92,774 ESRD patients registered between January 2000 and December 2009 at the Taiwan National Health Insurance Research Database. An age- and sex-matched control group comprised 92,774 patients (case:control = 1:1) selected from the Taiwan Longitudinal Health Insurance Database 2000. Information for each patient was collected from the index date until December 2011. The incidence and risk of RVO were compared between the ESRD and control groups. The adjusted hazard ratio (HR) for RVO after adjustment for potential confounders was obtained by Cox proportional hazard regression analysis. Kaplan–Meier analysis was used to calculate the RVO cumulative incidence rate. The main outcome measure was the incidence of RVO following ESRD.

In total, 904 ESRD patients (0.97%) and 410 controls (0.44%) had RVO ($P < 0.0001$) during the follow-up period, leading to a significantly elevated risk of RVO in the ESRD patients compared with controls (incidence rate ratio = 3.05, 95% confidence interval = 2.72–3.43). After adjustment for potential confounders including diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and coronary artery disease, ESRD patients were 3.05 times more likely to develop RVO in the full cohort (adjusted hazard ratio = 3.05, 95% confidence interval = 2.64–3.51). In addition, hypertension patients showed high incidence rate of RVO in the ESRD group compared with controls (incidence rate ratio = 1.71, 95% confidence interval = 1.44–2.03) and maintained significant risk of RVO after adjustment for other confounders in the cohort (adjusted hazard ratio = 1.39, 95% confidence interval = 1.20–1.60).

ESRD increases the risk of RVO. For ESRD patients, we recommend education regarding RVO in addition to blood pressure control to prevent subsequent RVO.

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Abbreviations: BRVO = branch retinal vein occlusion, CI = confidence interval, CIC = catastrophic illness certificate, CRVO = central retinal vein occlusion, eGFR = estimated glomerular filtration rate, 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 = National Health Insurance Research Database, PY = patient-years, RVO = retinal vein occlusion, SD = standard deviation.

INTRODUCTION

End-stage renal disease (ESRD) is the most severe form and the last stage of chronic kidney disease, requiring dialysis or transplant treatment. ESRD, a leading cause of morbidity and mortality worldwide, is an important public health issue. Recently, there has been a rapid increase in the prevalence and incidence of ESRD not only in Western and Asian populations but also in developing and developed countries worldwide.[1–3] Taiwan has been a country with a particularly high incidence and prevalence of ESRD compared with other countries.[4–6]

Retinal vein occlusion (RVO), classified into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), is a common and sight-threatening retinal vascular disorder.[7] The pathogenesis of RVO is not yet fully understood. A combination of factors contributes to RVO, for example, vein compression over the arteriovenous crossing particular in eyes with increased arterial rigidity and arteriosclerosis, thrombus formation following vessel wall degeneration, and hematological factor dysregulation.[7–10] In addition, increased levels of proinflammatory mediators and reduced levels of anti-inflammatory cytokines have been detected in the vitreous fluid of RVO patients.[11,12] Thus, inflammation within the ocular tissue has been implicated in the pathogenesis and formation of RVO.[11,12]

Of particular note is the fact that defective renal microcirculation leading to microvascular disease is a prominent pathological feature in ESRD.[13–15] These microvascular abnormalities involve focal or generalized arteriolar narrowing, and the latter are more frequent in ESRD.[16,17] In fact, the major causes of RVO are arteriolar narrowing related to arteriosclerosis and arteriovenous nicking associated with arteriovenous compression. ESRD patients are at a higher risk for developing venous thromboembolism,[18–20] which is usually associated

with atherosclerosis;[18,21] and hypercoagulation disorders associated with platelet dysfunction and uremic toxin retention.[18,21,22] ESRD exhibits increased levels of proinflammatory markers; thus, inflammation has been implicated in the development of ESRD.[12,23,24] In addition to the apparently common pathogenic mechanisms, ESRD and RVO share common 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 RVO.

A few previous studies have discussed the association between ESRD and RVO, but the results of published studies were limited by the small number of patients or the absence of comparative control data.[25–28] Using a nationwide population-based dataset, we designed a cohort study to investigate the risk of RVO following ESRD in Taiwan.

METHODS

Database

After 1 March, 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 (>98%) of the total Taiwanese population of 22.96 million were enrolled in this program. The data of our cohort study were obtained from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD 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. A public database was used for analysis; therefore, ethical approval and informed consent were waived off 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.

Study Design

This retrospective, nationwide, matched cohort study involved 2 groups of participants: a newly onset ESRD group and a matched non-ESRD (control) group.

Study Participants

Patients and controls were recruited in the period of 2000 to 2009. We included 92,774 ESRD patients who had started their first dialysis treatment after 31 December, 2000 and who had received a catastrophic illness certificate (CIC) with the code number 585 between 1 January, 2000 and 31 December, 2009. Patients with unknown gender or missing data were excluded. Patients diagnosed as having RVO (ICD-9-CM codes 362.35 [CRVO] and 362.36 [BRVO]) before ESRD were also excluded.

For each ESRD case, 1 control without ESRD was randomly selected from the longitudinal Health Insurance Database 2000 (LHID2000), a data subset of the National Health Insurance Research database (NHIRD) that contained entire claim data for 1 million beneficiaries (4.34% of the total population) systemic randomly selected in 2000. There was no significant difference in age, gender, and health care costs between the sample group and all national health insurance enrollees. The 92,774 controls were matched by gender, age,

and index date. The index date for the ESRD patients was the date of their first dialysis, and the index date for the controls was created by matching the date with the ESRD subject's index date. Moreover, the controls diagnosed with RVO before the index date were also excluded. Each patient was followed up to determine the incidence of RVO until the end of 2011 or censored because of death.

To distinguish all patients who had developed RVO, we tracked every patient from his or her index outpatient visit or hospitalization through December 2011. Demographic data (e.g., age and sex) were recorded. Furthermore, we collected 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 factors that increase the risk of RVO. In this study, the inclusion criterion for diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, or coronary was documentation of the condition at least once in the inpatient setting or ≥ 3 times in the ambulatory setting within 1 year before the initial ESRD on dialysis medical service date.

Statistical Analysis

SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC) was used in this study. The demographic characteristics and comorbid disorders between the ESRD and control groups were compared by Pearson chi-square test. The incidence rate was calculated as the number of RVO cases identified during follow-up divided by the total person-years (PY) for each group by age, sex, and select comorbidities. The Poisson regression analysis was performed to calculate the incidence rate ratio (IRR), which demonstrated the comparison in the risk of developing RVO between the ESRD and control groups. The adjusted hazard ratio (HR) for developing RVO was calculated using Cox proportional hazard regression analysis. Cumulative incidence rates for RVO of ESRD were evaluated by Kaplan–Meier analysis, and differences in cumulative-incidence rate curves were analyzed using the log-rank test. In addition, we subdivided the patients into 3 age subgroups for further analysis: <50 years, 50–64 years, and ≥ 65 years. Data are presented as mean $\pm$ standard deviation (SD), and 95% confidence intervals (CIs) are provided when applicable. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographic Data

Between 2000 and 2009, 92,774 ESRD patients and 92,774 controls were recruited after excluding ineligible subjects. Table 1 provides the demographic characteristics and comorbid disorders of ESRD patients and age- and sex-matched controls. The mean age of all participants was 62.21 ± 14.65 years. ESRD patients exhibited a significantly higher prevalence of previously reported comorbidities, such as diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and coronary artery disease, than did the controls. The mean follow-up periods for the ESRD and control patients were 4.69 (SD, 3.26) and 6.49 (SD, 2.95) years, respectively.

Incidence Rates of RVO

During the follow-up period, 1314 (1314/185548 [0.71%]) patients developed RVO. A significantly higher proportion of

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

	ESRD (N = 92774) n (%)	Control (N = 92774) n (%)	*P*
Age at index date, y (mean ± SD)	62.21 ± 14.65	62.21 ± 14.65	1.0000
Age at index date, y			
<50	18,030 (19.43)	18,030 (19.43)	1.0000
50–64	29,659 (31.97)	29,659 (31.97)	
≥65	45,085 (48.60)	45,085 (48.60)	
Gender			
Male	46,050 (49.64)	46,050 (49.64)	1.0000
Female	46,724 (50.36)	46,724 (50.36)	
Baseline comorbidity			
DM	48,892 (52.70)	10,185 (10.98)	<0.0001
HTN	76,212 (82.15)	23,203 (25.01)	<0.0001
HPL	18,374 (19.81)	7095 (7.65)	<0.0001
CHF	21,602 (23.28)	1541 (1.66)	<0.0001
CAD	23,628 (25.47)	7136 (7.69)	<0.0001
Follow-up, y (mean ± SD)	4.69 ± 3.26	6.49 ± 2.95	<0.0001

Note: Comparisons were made by Pearson chi-square test.

CAD = coronary artery disease, CHF = congestive heart failure, DM = diabetes mellitus, ESRD = end-stage renal disease, HPL = hyperlipidemia, HTN = hypertension, SD = standard deviation.

ESRD patients (904/92774 [0.97%]) than control patients (410/92774 [0.44%]) developed RVO (Table 2). In addition, there was a significant difference in the RVO incidence between the groups (ESRD patients = 20.79/10000 PY; control = 6.81/10000 PY), and the IRR between the ESRD group and the control group was statistically significant (3.05, 95% CI = 2.72–3.43, *P* < 0.0001; Table 2).

Furthermore, we classified RVO into CRVO and BRVO. The majority of RVO cases in both groups were BRVO: 568/904 (62.83%) in the ESRD group and 280/410 (68.30%) in the control group. There was a significant difference in the incidence of BRVO between the 2 groups (ESRD patients = 13.06/10000 PY; control = 4.65/10000 PY) (IRR = 2.81, 95% CI = 2.44–3.24, *P* < .0001; Table 2). There was also a significant difference in the incidence of CRVO between the 2 groups (ESRD patients = 7.73/10000 PY; control = 2.16/10000 PY) (IRR = 3.58, 95% CI = 2.92–4.38, *P* < 0.0001; Table 2).

After the 2 groups were divided by age, we found that ESRD patients <50 years old had the highest incidence rate (25.41/10000 PY), followed by patients aged 50 to 64 years, and patients ≥65 years old. We found significant higher IRRs for all ESRD age groups compared with their age-matched controls (Table 2). Particularly, the incidence in ESRD patients aged <50 years was 12.71 times higher than that in controls within the same age range (IRR = 12.71, 95% CI = 8.51–18.99, *P* < .0001).

Male ESRD patients had an RVO incidence of 21.46/10000 PY, whereas male control patients had an RVO incidence of only 6.20/10000 PY, leading to a significant IRR between male ESRD patients and their controls (IRR = 3.46, 95% CI = 2.91–4.11, *P* < 0.0001). Regarding female patients, a significant difference was also noted between female ESRD patients and their controls (IRR = 2.73, 95% CI = 2.33–3.20, *P* < 0.0001; Table 2).

In the ESRD group, the incidence rates of RVO, from the highest to the lowest, were in the order of patients with hypertension (20.08/10000 PY), hyperlipidemia (18.16/10000 PY), coronary artery disease (15.54/10000 PY), diabetes mellitus (14.52/10000 PY), and congestive heart failure (13.48/10000 PY). The IRR for RVO associated with comorbid hypertension, hyperlipidemia, and coronary artery disease indicated significantly greater risks in ESRD patients with the condition compared with their controls: 1.71 (95% CI = 1.44–2.03) for hypertension, 1.69 (95% CI = 1.20–2.37) for hyperlipidemia, and 1.62 (95% CI = 1.14–2.28) for coronary artery disease (Table 2); however, this was not observed for the presence of diabetes mellitus or congestive heart failure.

Table 3 provides the crude and adjusted HRs for RVO, by cohort, during the follow-up period. After adjusting for age, sex, and select comorbid conditions, ESRD remained an independent risk factor for RVO (adjusted HR = 3.05, 95% CI = 2.64–3.51). Significant risk factors for RVO in both groups included age 50 to 64 years old (adjusted HR = 1.27, 95% CI = 1.10–1.46, *P* < 0.05) and hypertension (adjusted HR = 1.39, 95% CI = 1.20–1.60, *P* < 0.05), whereas gender, diabetes mellitus, hyperlipidemia, congestive heart failure, or coronary artery disease were not independent risk factors for RVO.

The Kaplan–Meier survival analyses revealed higher RVO cumulative incidence rates in the ESRD patients than in the control patients, and the log-rank test was also significant (*P* < 0.001; Figure 1).

DISCUSSION

To the best of our knowledge, our study is the largest-scale population-based study that has been conducted to explore the relationship between ESRD and subsequent RVO. We analyzed 92,774 ESRD patients and 92,774 control subjects. We found that the incidence rate of RVO in ESRD patients was 3.05 times higher than that of controls, and that the relative risk of RVO for patients with ESRD was increased 3.05 times in the full cohort after adjusting for age, sex, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure, and coronary artery disease.

The association between renal dysfunction and RVO has been explored previously in only 4 population-based cohort

TABLE 2. Risk of RVO for ESRD and Control Groups

Characteristics	ESRD				Controls				IRR (95% CI)	P
	N	RVO	PY	Rate*	N	RVO	PY	Rate*		
All	92,774	904	434,755.07	20.79	92,774	410	602,266.75	6.81	3.05 (2.72–3.43)	<0.0001
CRVO		336 (37.17)		7.73		130 (31.70)		2.16	3.58 (2.92–4.38)	<0.0001
BRVO		568 (62.83)		13.06		280 (68.30)		4.65	2.81 (2.44–3.24)	<0.0001
Age, y										
<50	18,030	286	112,538.00	25.41	18,030	26	130,063.42	2.00	12.71 (8.51–18.99)	<0.0001
50–64	29,659	376	148,115.93	25.39	29,659	132	197,120.51	6.70	3.79 (3.11–4.62)	<0.0001
≥65	45,085	242	174,101.13	13.90	45,085	252	275,082.81	9.16	1.52 (1.27–1.81)	<0.0001
Gender										
Male	46,050	450	209,721.54	21.46	46,050	182	293,354.54	6.20	3.46 (2.91–4.11)	<0.0001
Female	46,724	454	225,033.52	20.17	46,724	228	308,912.21	7.38	2.73 (2.33–3.20)	<0.0001
Comorbidity										
DM	48,892	291	200,372.88	14.52	10,185	73	57,576.31	12.68	1.15 (0.89–1.48)	0.2996
HTN	76,212	691	344,182.69	20.08	23,203	161	137,154.25	11.74	1.71 (1.44–2.03)	<0.0001
HPL	18,374	144	79,308.75	18.16	7095	43	39,953.66	10.76	1.69 (1.20–2.37)	0.0026
CHF	21,602	113	83,805.01	13.48	1541	6	7973.73	7.52	1.79 (0.79–4.07)	0.1638
CAD	23,628	148	95,254.45	15.54	7136	41	42,633.01	9.62	1.62 (1.14–2.28)	0.0066

Note: Poisson regression analysis was performed to calculate the incidence rate ratio.

BRVO = branch retinal vein occlusion, CAD = coronary artery disease, CHF = congestive heart failure, CRVO = central retinal vein occlusion, DM = diabetes mellitus, ESRD = end-stage renal disease, HPL = hyperlipidemia, HTN = hypertension, IRR = incidence rate ratio, PY = person-years.

*Rate: per 10000 person-years.

studies.[25–28] Our report was consistent with the Beaver Dam Eye Study, which reported that higher serum creatinine levels (>1.4 mg/dL) were associated with the development of RVO in a 15-year follow-up period.[26] In addition, the Hisayama study disclosed that chronic kidney disease, defined as the presence of proteinuria with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, increased the risk of RVO development.[25] Recently, Chen et al[28] also suggested that ESRD was a potential risk factor for RVO in a population-based cohort study. In a comparison of the 2 reports, we have attempted to prove the strength of our study by clarifying the statistical validity of our findings. The 92,774 ESRD cohort in our study was obtained from the NHIRD, which comprises 22.60 million individuals (>98%) of the total Taiwanese population, in contrast to the 5344 ESRD patients in Chen's study that were obtained from the LHID2000, a data subset of the NHIRD that contained entire claim data for 1 million beneficiaries (4.34% of the total population) systemic-randomly selected in 2000. Our study is based on a true nationwide and population-based dataset including a large sample of ESRD patients (92,774 ESRD cohort), which further increases the precision of risk appraisal and elevates the power of statistics in comparison with Chen's study. However, our results were inconsistent with those of the Blue Mountains Eye Study, which demonstrated that serum creatinine level did not constitute a significant risk factor for RVO over 10 years of follow-up.[27] This disagreement may be explained by differences in ethnicity, study populations, or study methods. For instance, in our study, we identified ESRD based on a CIC with the code number 585 instead of the creatinine level or eGFR value, which may reduce the selection bias.

Our findings demonstrated an association between RVO and ESRD. A pathogenic mechanism common to both conditions is the involvement of microvascular retinopathy. Retinal microvascular signs, such as focal or generalized retinal arteriolar narrowing and arteriovenous nicking, are more frequent in patients with ESRD.[13,16,17] In fact, the retinal microvascular signs are considered characteristic of ESRD and an indicator of impaired renal function. Many studies, such as the Atherosclerosis Risk in Communities and the Multi-Ethnic Study of Atherosclerosis studies, reported an association between arteriolar narrowing or arteriovenous nicking and markers of renal dysfunction or renal damage.[13,14,17] It is true that retinal and renal circulation have similar anatomy and pathophysiology[17,29] owing to homologous developmental pathways and similar structural features of the inner retina and glomerular filtration barrier.[16,30,31] Interestingly, retinal microvascular signs are also common in patients with RVO.[25–27] The population-based Blue Mountains Eye Study and Beaver Dam Eye Study showed that arteriolar narrowing or arteriovenous nicking are significant predictors of RVO development.[26,27] Retinal microvascular signs may be markers of generalized microvascular disease from vascular endothelial dysfunction[32] in the retina and the glomeruli, making vessels more vulnerable to occlusion, and ultimately leading to RVO formation. Furthermore, ESRD is a strong predictor of systemic arteriosclerosis, including retinal arteriosclerosis contributing to retinal arteriolar narrowing and arteriovenous nicking. The retinal sclerotic arteriolar walls may compress the underlying veins at arteriovenous crossings. Subsequently, the compression may lead to reduced blood flow, facilitating thrombus formation, downstream venous occlusion, and RVO.[25]

The risk of hypercoagulation disorders is increased in ESRD patients,[18–20] possibly due to a dysregulation of the coagulation cascade, the platelets, and the vessel wall.[18,21,22] The interaction between these different components is changed by uremic toxins and metabolic compounds accumulating during renal insufficiency.[22] In addition, many acquired and

TABLE 3. Crude and Adjusted Hazard Ratios for RVO During Follow-Up

Cohort	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
ESRD		
Yes	2.98[*] (2.65–3.35)	3.05[*] (2.64–3.51)
No	1.00	1.00
Age, y		
<50	1.00	1.00
50–64	1.12 (0.97–1.29)	1.27[*] (1.10–1.46)
≥65	0.82[*] (0.71–0.95)	0.97 (0.84–1.13)
Gender		
Female	1.00	1.00
Male	0.98 (0.88–1.09)	0.98 (0.88–1.09)
Comorbidity		
DM		
Yes	1.11 (0.98–1.25)	0.65[*] (0.57–0.75)
No	1.00	1.00
HTN		
Yes	2.07[*] (1.85–2.32)	1.39[*] (1.20–1.60)
No	1.00	1.00
HPL		
Yes	1.24[*] (1.06–1.44)	1.03 (0.87–1.21)
No	1.00	1.00
CHF		
Yes	0.98 (0.81–1.18)	0.67[*] (0.55–0.82)
No	1.00	1.00
CAD		
Yes	1.06 (0.91–1.24)	0.90 (0.76–1.06)
No	1.00	1.00

Note: The adjusted hazard ratio for developing RVO was calculated using Cox proportional hazard regression analysis.

CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, DM = diabetes mellitus, ESRD = end-stage renal disease, HPL = hyperlipidemia, HTN = hypertension.

[*]$P < 0.05$.
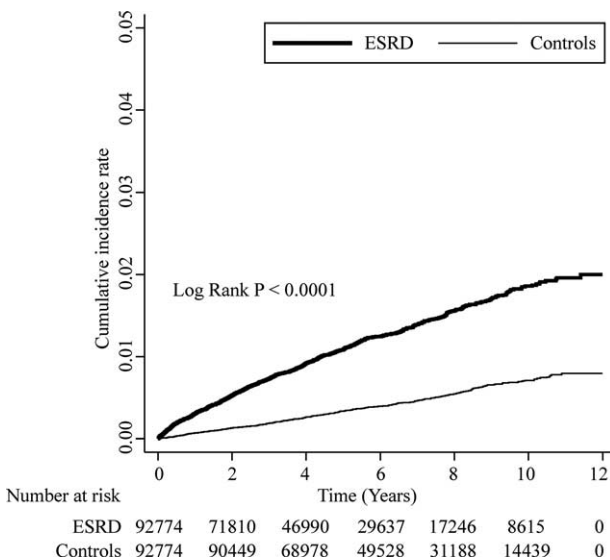
FIGURE 1. Kaplan–Meier curve of cumulative incidence of RVO in patients with ESRD and controls during the follow-up period. ESRD = end-stage renal disease, RVO = retinal vein occlusion.

inherited factors also play an important role in hypercoagulation of ESRD such as protein C or S deficiency, and hyperhomocysteinemia.[33,34] It is worthy to note that thrombophilia is a well-known risk factor of RVO, and that Virchow triad (hemodynamic changes [venous stasis], degenerative changes of the vessel wall, and blood hypercoagulability) is an important pathogenesis factor for RVO.[35] Risk factors that predispose to coagulation abnormalities and thrombophilic abnormalities in RVO patients have been studied recently.[36,37] Many studies have shown that increased blood viscosity, protein C or S deficiency, hyperhomocysteinemia, and factor V Leiden mutation may participate in the RVO formation.[10,37,38] Therefore, thrombophilia or hypercoagulation common in ESRD may contribute to the development of RVO.

Of particular note is the fact that there is increased inflammation in ESRD. Patients with ESRD have increased levels of proinflammatory markers involving C-reactive protein, tumor necrotic factor-α, and interleukin-6.[12,23,24] In addition, increased levels of fibrinogen and plasma tissue factor have been observed in ESRD patients, which contribute to not only coagulation but also to inflammation.[24,39,40] The fact that hypercytokinemia is a typical feature of ESRD may be because of the accumulation of proinflammatory cytokines due to decreased renal elimination or increased generation as a consequence of induction by uremic toxin, volume overload, or

oxidative stress.[41,42] Furthermore, the inflammations have been implicated in the pathogenesis and clinical consequences of retinal vein occlusion. Many recent laboratory and clinical studies have shown that proinflammatory factors such as inter-leukin-6, interleukin-8, monocyte chemoattractant protein-1, and vascular endothelial growth factor are significantly elevated in patients with CRVO.[11,12] These studies demonstrated that the inflammation may play a role of in the molecular pathways contributing to the vision-impairing results of RVO.[11,12] Inflammation may be the link between ESRD and subsequent RVO formation.

RVO is a common and vision-threatening retinal vascular disorder. Many comorbidities have been associated with RVO, including hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, and coronary artery disease.[7,10,43] In this study, we found that hypertension was a significant risk factor for RVO in ESRD patients with the condition, compared with their controls. In addition, hypertension was the only significant risk factor for RVO in full cohort. This finding is in agreement with several previous reports that demonstrate hypertension is a major risk factor for RVO.[7,30,31] Hypertension is well known to lead to atherosclerosis, retinal microvascular wall damage, and thromboembolism formation, ultimately contributing to the development of RVO.[44,45] Retinal microvascular signs such as focal or generalized retinal arteriolar narrowing and arteriovenous nicking are common manifestations in RVO patients. These signs are also common in ESRD patients, suggesting that retinal arteriolar narrowing is associated with hypertension-associated ESRD.[13,14,16,17,44] ESRD patients with hypertension should be advised to control their blood pressure because of significant association with subsequent RVO.

It is worth noticing that diabetes mellitus patients with ESRD did not exhibit a significantly higher IRR of RVO than diabetes mellitus patients without ESRD. Several studies have shown that RVO is accelerated by diabetes mellitus.[7,46] Prolonged hyperglycemia can contribute to atherosclerosis and subsequent microvascular damage such as retinal arteriolar narrowing, thromboembolism, and inflammation, ultimately contributing to the development of RVO.[46] Diabetes mellitus itself is a risk factor of RVO, regardless of ESRD. Therefore, it was actually surprising that diabetes mellitus appeared as a protective factor instead of a significant risk factor for RVO in the full cohort (adjusted HR: 0.65, 95% CI = 0.57–0.75; Table 3), particularly in the ESRD groups (incidence rate of RVO: all ESRD patients = 20.79/10000 PY; ESRD patients with diabetes mellitus = 14.52/10000 PY; Table 2). A possible explanation as to why diabetes mellitus acted as a protective factor for RVO in the ESRD group is that diabetes mellitus patients probably visit the ophthalmologist more often, and have a higher incidence rate of diabetic retinopathy than patients without diabetes mellitus. Once diabetic retinopathy is diagnosed, diabetes mellitus patients undergo several rounds of treatment including panretinal photocoagulation and pharmacological therapy with circulation-improving drugs or an intravitreous antivascular endothelial growth factor agent. These treatments may inhibit the development of RVO due to destroyed arteriosclerotic vessels, reduced thromboembolism, or reduced inflammation. However, the exact reason needs to be clarified in future investigations.

Of particular note is the fact that the incidence rate of RVO in congestive heart failure patients with ESRD was not higher than that in controls. Moreover, congestive heart failure was not a significant risk factor for RVO in the full cohort. Poppas et al[47] showed that congestive heart failure resulting from systolic dysfunction causes low forward flow and decreased cardiac output leading to hypotension. Several studies demonstrated that congestive heart failure is common among ESRD patients, and that subsequent anemia is associated with worsening of cardiac and renal status.[48–50] Horwich et al[49] suggested that anemia is also related to an impaired hemodynamic profile, including low blood pressure. A possible explanation for the protective role of congestive heart failure against the development of RVO may be the hypotension or anemia resulting from congestive heart failure.

There are several strengths in our study. The study is based on a nationwide and population-based dataset including a large sample of ESRD patients, which increases the precision of risk appraisal and elevates the power of statistics. In addition, the selection bias in referral centers and chances of misdiagnosis are reduced because visual disturbance patients visit an ophthalmologist rather than a general practitioner. Furthermore, the study is a cohort study monitoring the RVO incidence in ESRD and comparison cohorts with maximum longitudinal data of 10 years. Finally, because hypertension, diabetes mellitus, hyperlipidemia, congested heart failure, and coronary artery disease were taken into account as confounding factors to adjust the hazard ratio of RVO in ESRD patients, our results are reliable.

There are some limitations in our study. We cannot confirm that the controls had no ESRD history before January 1996, because the sampled patients' medical history can only be traced back to the year 1996; therefore, our findings could be compromised. In addition, several important confounding factors including body mass index, smoking history, and alcohol consumption could not be accessed. Furthermore, some bias may have introduced because the insurance claims data did not include information on the laboratory data of blood sugar and serum cholesterol levels and current blood pressure. We have considered hypertension, diabetes mellitus, and hyperlipidemia as confounding factors to reduce this problem. Finally, the diagnosis of the ESRD, RVO, and other comorbidity disorders relied on ICD-9-codes, which may lead to disease misclassification.

In summary, our study showed that after adjusting for diabetes mellitus, hypertension, hyperlipidemia, congestion heart failure, and coronary artery disease, ESRD patients showed a significantly higher risk of developing RVO during the follow-up period. The association between ESRD and RVO is possible based on the common manifestation of microvascular retinopathy, which makes retina vessels vulnerable to occlusion, hypercoagulation abnormalities contributing to thromboembolism, and inflammation underlying the molecular pathways of RVO. In addition, hypertension in the ESRD patients showed higher incidence rate of RVO and maintained significant risk of RVO after adjusting for other confounders in the cohort. For patients with ESRD, we recommend education regarding RVO in addition to the adequate control of cardiovascular factors.

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