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End Stage Renal Disease as a Potential Risk Factor for Retinal Vein Occlusion

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Abstract: End stage renal disease (ESRD) has been reported to be an important risk factor for systemic vascular disease. Retinal vein occlusion (RVO) is closely related with cardiovascular diseases; however, its association with ESRD had not been reported. The aim of the study was to investigate whether ESRD is a risk factor for RVO, including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). This population-based study is based on the longitudinal data from Taiwan National Health Insurance Research Database. The study cohort comprised 5344 patients with diagnosis of ESRD on hemodialysis or peritoneal dialysis during the period from January 1996 to December 2011. For each ESRD patient, we selected 20 non-ESRD patients matched on age and sex. Each ESRD patient and his/her controls were followed from the initiation of renal dialysis until either the diagnosis of RVO or censorship. Kaplan–Meier method was used to compare the hazard of RVO between cohorts. Stratified Cox proportional hazard models were applied to estimate the hazard ratio (HR) adjusted by the comorbidities of RVO including diabetes mellitus (DM), hypertension, hypercholesterolemia, and hypertriglyceridemia. After stratifying by DM status, the statistics were applied again to examine the associations among the DM cohort and non-DM cohort.

The 16-year RVO cumulative incidence for ESRD cohort was 2-fold to the non-ESRD (1.01% vs 0.46%). After matching with age, sex, hypertension, and hypercholesterolemia, the adjusted HR was 1.46 (95% confidence interval = 1.07–2.01, P value = 0.018). By further excluding patients with DM, the adjusted HR escalated to 2.43 (95% confidence interval = 1.54–3.83, $P < 0.001$). In contrast, there was no significant risk of ESRD on RVO in the DM patients (HR = 1.03). We conclude that among the non-DM patients, ESRD cases had significantly higher RVO rate than the non-ESRD, which indicates that ESRD maybe a potential risk factor for the development of RVO in nondiabetic patients.

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Abbreviations: BRVO = branch retinal vein occlusion, CI = Confidence Interval, CRVO = central retinal vein occlusion, DM = diabetes mellitus, ESRD = end stage renal disease, HR = hazard ratio, RVO = retinal vein occlusion, TNHI = Taiwan National Health Insurance.

INTRODUCTION

Retinal vein occlusion (RVO) is a major cause of visual loss, most in middle and elderly age groups.¹ Clinical manifestations of RVO include visual deterioration, congested veins, retinal hemorrhage, retinal ischemia, extravasations of lipid, macular edema, and optic disc edema; neovascular glaucoma might develop in cases with wide nonperfused retina, which, if without treatment would lead to a painful, blind eye.^{2–5} Treatment of RVO included laser photocoagulation,^{6,7} administration of thrombolytic agents,⁸ and surgical interventions.^{9–11} Intravitreal injections of steroid or anti-VEGF agents were widely used in recent years,^{12–14} which are effective in reducing macular edema and improving visual acuity in most cases; however, most patients still suffer from repeated intravitreal injections.¹⁵ Risk factors for RVO include hypertension, hypercholesterolemia, myocardial infarction, diabetes mellitus (DM), and cerebral vascular accident.^{16–21} End stage renal disease (ESRD) has been reported to be an important risk factor for systemic vascular disease, such as cerebral vascular disease, coronary heart disease, carotid artery atherosclerosis.^{22,23} RVO closely related with cardiovascular diseases; however, its association with ESRD had not been reported. In this population based study, we aimed to investigate the relationship between ESRD and RVO to see whether ESRD with renal dialysis is an independent risk factor for RVO disease, including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

MATERIALS AND METHODS

This study was conducted using a retrospective cohort analysis based on the Taiwan National Health Insurance (TNHI) Research Database. The TNHI program was initiated in 1995 and includes the medical records of >95% of Taiwan's hospitals contracted with TNHI. The coverage rate of the program increased from 92.4% in 1995 to over 96% in 2000, and exceeded over 98% of the Taiwanese population after the inclusion of the military forces in 2001. For research purposes, 1 million residents of Taiwan who were enrolled in the TNHI in 2005 were randomly selected by the National Health Research Institute to constitute the TNHI Research Database, which represents almost 4% of Taiwan's population and was re-sampled by the National Health Research Institute to be consistent with the structure of the general population with respect to sex and age, which make this longitudinal database quite representative of Taiwan's population.

The study cohort were patients newly diagnosed with ESRD on hemodialysis or peritoneal dialysis during the study period from January 1996 to December 2011. Each patient was

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ascertained by the criterion of receiving dialysis treatment for >2 times and treatment period of >3 months. Note that patients diagnosed with ESRD before the study start date, and diagnosed with RVO before ESRD (traced back to 1996 when the NHI database became operational) were excluded in advance to limit the study to newly diagnosed cases. After these exclusions, a total of 5344 patients with ESRD were included in the study cohort. For each patient on dialysis, roughly 20 patients who matched the age and sex were randomly selected from the patients out of the rest of the 1 million sample who had never been diagnosed with ESRD during the studied period. As a result, a total of 99,440 patients were assigned to a comparison cohort (some older ESRD cases might have had fewer controls to be matched with). In each matched stratum, an ESRD patient and his/her matched non-ESRD controls were followed up from the first day of receiving dialysis for the ESRD case until either the diagnosis of RVO or censorship (ie, termination of insurance or study period). In such way, the starting follow-up time for an ascertained ESRD and his/her non-ESRD controls is aligned. All cases in the database were counted only once. Before analysis, temporal consistency among the dates of birth, diagnosis, and clinical visits of each patient was checked to ensure accuracy. The matching and subsampling were conducted by using SAS 9.3 (SAS Institute Inc., NC).

We took into account the effects of the comorbidities of RVO, which includes DM, hypertension, hypercholesterolemia, and hypertriglyceridemia. DM and hypertension were ascertained by >3 clinical diagnoses or at least 1 hospitalization. Hypercholesterolemia and hypertriglyceridemia were ascertained by >2 clinical diagnoses or at least 1 hospitalization. A patient

is then considered having a comorbidity if the first diagnosed date of that comorbidity is before the follow-up (ie, first ESRD diagnosis.) The International Classification of Diseases code version 9 (ICD-9) codes for the diseases are listed in the Appendix, <http://links.lww.com/MD/A517>.

Due to the dependence between the case and his/her matched controls within each stratum, the Mantel–Haenszel odds ratio (OR_{MH}) instead of regular odds ratio was used to separately measure the univariate association between ESRD and RVO, as well as ESRD and CRVO and BRVO. Kaplan–Meier plots and log-rank tests were used to test the differences in the time of developing RVO between the ESRD and non-ESRD cohorts. For the multivariate analysis, stratified Cox proportional hazard models were applied to examine the association among ESRD on dialysis and RVO, adjusting for potential confounding factors that include DM, hypertension, hypercholesterolemia, and hypertriglyceridemia. If a comorbidity was found to have versatile effects on RVOs, we further repeated the above analysis stratified by the status of that comorbidity, to explore its interaction effect with ESRD. The inclusion/exclusion of patients was shown in supplementary Figure, <http://links.lww.com/MD/A517>.

The study used only the encrypted chart records, and had been approved by the National Changhua University institution review board with IRB no. 102001 for not using informed consent.

RESULTS

Table 1 shows that among the 5344 ESRD patients, 54 had developed RVO, including 23 CRVO and 34 BRVO (with 3

TABLE 1. Distribution of RVOs and Comorbidities Between ESRD and Non-ESRD

		ESRD (N = 5344) Count (%)	Non-ESRD (N = 99,040) Count (%)	OR _{MH} [*]	P Value
Age at diagnosis (mean ± SD)		61.04 ± 15.88	60.47 ± 15.39	1	Matched
Sex	Male	2676 (50.07%)	49,378 (49.66%)	1	Matched
	Female	2668 (49.93%)	50,062 (50.34%)		
Follow-up years (mean ± SD)		7.34 ± 4.53	7.08 ± 4.55		
RVO	Yes	54 (1.01%)	455 (0.46%)	2.27	<0.0001
	No	5290 (98.99%)	98,585 (99.54%)		
Incidence (per 10,000 person-year)		13.77 (10.10,17.45) [†]	6.47 (5.87,7.06)		
CRVO	Yes	23 (0.43)	153 (0.15)	2.83	<0.0001
	No	5321 (99.57)	98,887 (99.85)		
Incidence (per10000 person year)		5.87 (3.47,8.26)	2.17 (1.83–2.52)		
BRVO	Yes	34 (0.64%)	346 (0.35%)	1.89	0.0003
	No	5310 (99.36%)	98,694 (99.65%)		
Incidence (per 10,000 person-year)		8.67 (5.76,11.59)	4.92 (4.40,5.43)		
Hypertension [‡]	Yes	4916 (91.99%)	58,120 (58.45%)	9.91	<0.0001
	No	428 (8.01%)	41,320 (41.55%)		
Hypercholesterolemia	Yes	807 (15.10%)	11,333 (11.40%)	1.39	<0.0001
	No	4537 (84.90%)	88,107 (88.60%)		
Hypertriglyceridemia	Yes	315 (5.89%)	3595 (3.62%)	1.68	<0.0001
	No	5029 (94.11%)	95,845 (96.38%)		
DM	Yes	3038 (56.85%)	28,347 (28.51)	3.51	<0.0001
	No	2306 (43.15%)	71,093 (71.49)		

BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, DM = diabetes mellitus, ESRD = end stage renal disease, OR_{MH} = Mantel–Haenszel odds ratio, RVO = retinal vein occlusion.

^{*}OR_{MH} summarizes the odds ratios across matched strata, to cope with the dependency within stratum.

[†]95% confidence interval of incidence rate.

[‡]A patient is considered having a comorbidity (hypertension ~ diabetes) if the first diagnosed date of that comorbidity is before the follow-up (the beginning of ESRD).

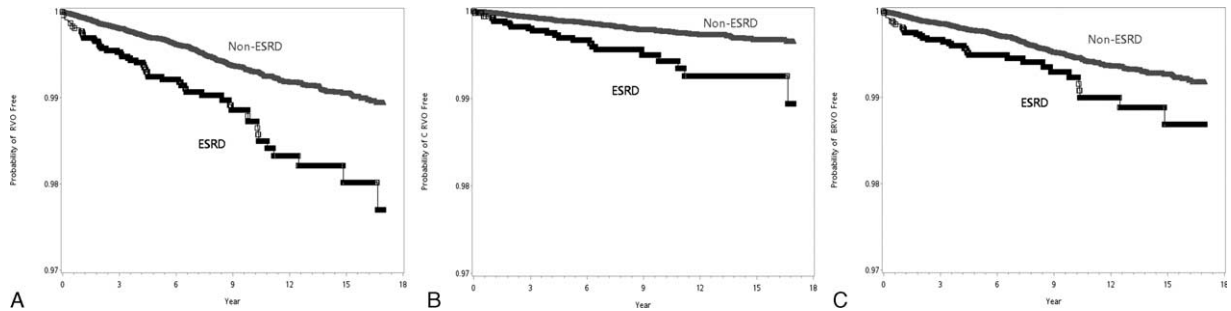


FIGURE 1. Kaplan–Meier plots. Time to the disease events in ESRD groups and non-ESRD group. A, RVO-event (either CRVO or BRVO); B, CRVO-event; C, BRVO-event. BRVO=branch retinal vein occlusion, CRVO=central retinal vein occlusion, ESRD=end stage renal disease, RVO=retinal vein occlusion.

patients who had both). Among the 99,440 matched control patients, 455 had developed RVO (153 CRVOs and 346 BRVOs).

ESRD is Associated With Higher Risk of CRVO

Table 1 also lists the univariate odds ratio OR_{MH} of RVO summarized from the 16-year study period. The OR_{MH} of RVO for the ESRD patients on dialysis was 2.27-fold that for the non-ESRD patients, with P value < 0.0001 from the log-rank test. The Kaplan–Meier plot in Figure 1A shows the gap of time to RVO-event between ESRD and non-ESRD. After adjusting for all comorbidities in a stratified Cox regression (Table 2), the hazard ratio (HR) remained significant at 1.50 (95% confidence interval [CI]:1.13–1.99) with a P value = 0.006. As hypertension and hypercholesterolemia are significant, we further randomly took the 1-to-10 subsamples of ESRD and non-ESRD that matched the status of these comorbidities and rerun the stratified Cox regression. The results remain significant, with HR as 1.46 (95% CI:1.07–2.01) with a P value = 0.018, also significant in the model was diabetes.

From separate analysis of CRVO and BRVO, the unadjusted OR_{MH} were 2.81 and 1.83, with P values < 0.0001 and 0.0006, respectively (Table 1 and Figure 1B,C), whereas the adjusted HRs by Cox regression were reduced to 1.87 (CI: 1.20–2.91) and 1.26 (CI: 0.89–1.80), with P values of 0.0006 and 0.2, respectively (Table 2, top). After further matching with

hypertension, and hypercholesterolemia, the adjusted HRs were 1.72 (CI: 1.03–2.86) and 1.29 (CI: 0.87–1.90), with P values 0.037 and 0.2, respectively (Table 2, bottom). The effect of dialysis on BRVO was not as significant as that on CRVO in the multivariate analysis.

To further elaborate the interaction effect between diabetes and dialysis, we conducted a separate analysis for the diabetes group (3038 ESRD cases + matched control), and nondiabetes group (2306 ESRD cases + matched control).

Analysis Stratified by Diabetes

Table 3 shows that after matching with age, sex, hypertension, and hypercholesterolemia, the ESRD patients with diabetes are roughly 2.7 years older than the ESRDs without diabetes. For the diabetes group, the univariate OR_{MH} of RVO for ESRD to non-ESRD, as well as that of CRVO and BRVO were all not significantly different from 1. It is interesting to observe that ESRD group had the lower prevalence of comorbidity than non-ESRD group among diabetic patients, but had higher comorbidity prevalence among nondiabetic patients. DM seems to have some interaction effect with the other 3 comorbidities on ESRD. Therefore in Table 4, we did separate analyses for DM and non-DM with significant comorbidities being matched to eliminate the unbalancing.

The result remained nonsignificant by Cox regression in Table 4, with HRs 0.98, 1.06, and 0.96 for RVO, CRVO, and

TABLE 2. Results of Cox Regression for RVO CRVO and BRVO

(1)	RVO			CRVO			BRVO		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
ESRD	1.50	(1.13,1.99)	0.0056	1.87	(1.20,2.91)	0.0058	1.26	(0.89,1.80)	0.1981
Hypertension	5.00	(3.76,6.65)	<.0001	3.54	(2.26,5.55)	<0.0001	5.27	(3.80,7.30)	<0.0001
Hypercholesterolemia	1.22	(0.98,1.55)	0.0764	0.98	(0.64,1.48)	0.9092	1.32	(1.01,1.72)	0.0396
Hypertriglyceridemia	0.71	(0.47,1.15)	0.1739	0.86	(0.42,1.75)	0.6686	0.70	(0.41,1.20)	0.1898
DM	1.21	(1.01,1.45)	0.0384	1.67	(1.23,2.28)	0.0011	1.03	(0.83,1.27)	0.8137
(2) Match hypertension and hypercholesterolemia									
ESRD	1.46	(1.07,2.01)	0.0182	1.72	(1.03,2.86)	0.0372	1.29	(0.87,1.90)	0.202
Hypertriglyceridemia	0.82	(0.48,1.40)	0.456	0.64	(0.23,1.73)	0.379	0.70	(0.50,1.67)	0.762
Diabetes	1.31	(1.05,1.63)	0.0175	1.99	(1.35,2.92)	0.0005	1.03	(0.81,1.37)	0.680

(1) Age–sex matched, with 5344 ESRD patients and 99,440 non-ESRDs.

(2) Further matched with hypertension and hypercholesterolemia, with 4805 ESRDs and 47,426 non-ESRDs.

BRVO=branch retinal vein occlusion, CI=confidence interval, CRVO=central retinal vein occlusion, DM=diabetes mellitus, ESRD=end stage renal disease, HR=hazard ratio, RVO=retinal vein occlusion.

TABLE 3. Distribution of RVOs and Comorbidities Between ESRD and non-ESRD Stratified by Diabetes and Nondiabetes

	Diabetes				Nondiabetes			
	ESRD (N = 2743) Count (%)	Non-ESRD (n = 11,212) Count (%)	OR _{MH} *	P Value	ESRD (n = 1983) Count (%)	Non-ESRD (n = 12,930) Count (%)	OR _{MH} *	P Value
Age at diagnosis (mean ± SD)	64.75 ± 10.87	65.63 ± 10.09	1	Matched	62.09 ± 15.10	61.02 ± 15.71	1	Matched
Sex								
Male	1345 (49.03)	5172 (46.13)	1	Matched	1001 (50.48)	6695 (51.78)	1	Matched
Female	1398 (50.97)	6040 (53.87)	0.88	0.650	982 (49.52)	6235 (48.22)	2.67	<0.0001
RVO	18 (0.66)	79 (0.70)	0.98	0.971	27 (1.36)	60 (0.46)	3.03	0.0026
CRVO	2725 (99.34)	11,133 (99.30)	0.87	0.680	1956 (98.64)	12,870 (99.54)	2.12	0.0048
BRVO	8 (0.29)	33 (0.29)	1	Matched	10(0.50)	20 (0.15)	1	Matched
Hypertension†	2735 (99.71)	11,179 (99.71)	0.98	0.804	1973 (99.50)	12,910 (99.85)	1.15	0.320
Hypercholesterolemia	11 (0.40)	49 (0.44)	0.87	0.804	18 (0.91)	50 (0.39)	1.15	0.320
Hypertriglyceridemia	2732 (99.60)	11,163 (99.56)	1	Matched	1965 (99.09)	12,880 (99.61)	1	Matched
	2659 (96.94)	11,060 (98.64)	1	Matched	1679 (84.67)	10,202 (78.90)	1	Matched
	84 (3.06)	152 (1.36)	1	Matched	304 (15.33)	2728 (21.10)	1	Matched
	509 (18.56)	2659 (23.72)	0.98	0.804	179 (9.03)	834 (6.45)	1.15	0.320
	2234 (81.44)	8553 (76.28)	0.98	0.804	1804 (90.97)	12,096 (93.55)	1.15	0.320
	213 (7.77)	944 (8.42)	0.98	0.804	62 (3.13)	328 (2.54)	1.15	0.320
	2530 (92.23)	10,268 (91.58)	0.98	0.804	1921 (96.87)	12,602 (97.46)	1.15	0.320

BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, ESRD = end stage renal disease, OR_{MH} = Mantel-Haenszel odds ratio, RVO = retinal vein occlusion.

* OR_{MH} summarizes the odds ratios across matched strata, to cope with the dependency within stratum.

† A patient is considered having a comorbidity (hypertension ~ diabetes) if the first diagnosed date of that comorbidity is before the follow-up (the beginning of ESRD).

TABLE 4. Results of Cox Regression for RVO, CRVO, and BRVO Stratified by Diabetes Status

		Diabetes (n = 13955)			Nondiabetes (n = 14913)		
		HR	95% CI	P Value	HR	95% CI	P Value
RVO	ESRD	0.98	(0.58, 1.64)	0.950	2.43	(1.54, 3.83)	<0.0001
	Hypertriglyceridemia	0.62	(0.25, 1.51)	0.289	2.10	(0.85, 5.71)	0.108
CRVO	ESRD	1.06	(0.49, 2.29)	0.888	2.77	(1.29, 5.93)	0.0088
	Hypertriglyceridemia	0.58	(0.14, 2.42)	0.458	1.19	(0.16, 8.71)	0.867
BRVO	ESRD	0.96	(0.50, 1.85)	0.907	1.93	(1.12, 3.31)	0.0172
	Hypertriglyceridemia	0.59	(0.19, 1.90)	0.378	2.16	(0.79, 5.94)	0.135

Each ESRD and non-ESRD pair was matched with age, sex, hypertension, and hypercholesteremia. Effect of ESRD is significant in nondiabetes group only.

BRVO = branch retinal vein occlusion, CI = confidence interval, CRVO = central retinal vein occlusion, ESRD = end stage renal disease, HR = hazard ratio, RVO = retinal vein occlusion.

BRVO, respectively. In contrast, for the nondiabetes group, the univariate OR_{MH} of RVO was 2.67 for ESRD to non-ESRD, and that of CRVO and BRVO were 3.03 and 2.12, wherein all were significant with *P* values < 0.0001, 0.0026, and 0.0048, respectively (Table 3, right).

The Kaplan–Meier plots in Figure 2A–C show the difference of time to RVO-, CRVO-, and BRVO-event between ESRD and non-ESRD patients without diabetes. The results did not change even after adjusting for the comorbidity effects of hypertriglyceridemia using a Cox regression. The adjusted HR of RVO as a whole was 2.43 (CI: 1.54, 3.83), with a *P* value < 0.0001, wherein the HR from the stratified analysis was 2.77 (CI: 1.29, 5.93) for CRVO and 1.93 (CI: 1.12, 3.31) for BRVO, with *P* values 0.0088 and 0.017, respectively (Table 4).

Assessment and Bias-Correction for Rare Event

We had repeated the random sampling process while matching the age, sex, hypertension, and hypercholesteremia between ESRD and non-ESRD, and the results came out very similar. There is a potential bias in a maximal likelihood estimate when it is applied to data of small sample sizes and with rare events. In our analysis, the Cox model used the so-called partial-likelihood. Although our sample size was large, the event (RVO) was relatively rare. For this reason, we compared our results from the Cox regression using default settings with that from Cox regression using exact estimation and Cox regression using Firth penalized maximal likelihood,

which are known for their capacity to correct the bias.²⁴ We found that the estimated HRs from these computational extensive methods were almost the same as the those from the stratified Cox regression in Table 2. We were then convinced that the bias due to the rareness of the RVO was negligible in this study.

DISCUSSION

The correlation between retinal venous occlusive disease and some systemic disease has been well established^{16–21}; however, the relationship between ESRD and RVO has only been reported in a few sporadic studies. In 1 study from Japan,⁵ chronic kidney disease was found to be an independent risk factor for RVO, after matching and adjusting for other confounding factors including DM, blood pressure, serum cholesterol, etc. In the report of the Beaver Dam Eye Study,²¹ a 60% higher risk of RVO was observed in persons with elevated serum creatinine levels (1.4 mg/dL); however, in those studies, BRVO and CRVO were taken together as a single-disease group. In our population-based study, ESRD was noted as a potential risk factor for RVO, for both CRVO and BRVO (Table 1); however, after adjusting for other comorbidities, a significant difference was only noted in CRVO, but not BRVO in the Cox-regression model (Table 2). After stratifying DM status, the analysis showed a further increased significance of ESRD as a risk factor in RVO, CRVO, and BRVO in the ESRD cohort, and in the Cox regression model, the statistics became

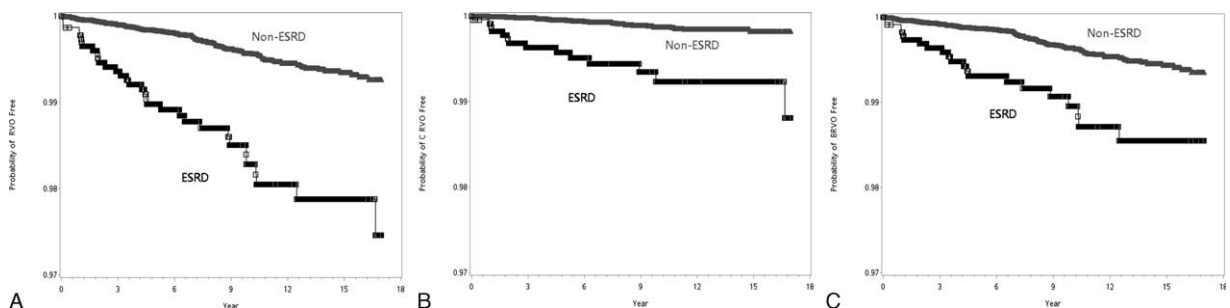


FIGURE 2. Separate analysis for nondiabetes patients. Kaplan–Meier plots for time to the disease events in ESRD groups and in non-ESRD group. A, RVO-event (either CRVO or BRVO); B, CRVO-event; C, BRVO-event BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, ESRD = end stage renal disease, RVO = retinal vein occlusion.

significant, for not only CRVO, but also for BRVO (Table 4) after adjusting for other comorbidities.

The association of ESRD and RVO might be multifactorial. Arteriosclerosis is widely present in patients with ESRD.²² The possible mechanisms for arteriosclerosis include chronic inflammation, alteration of extracellular matrix deposition, advanced glycation end products, elevated aldosterone level, and disordered bone marrow mineralization.^{22,23} As stiff arterial wall is one of the major pathogenic factors for both BRVO and CRVO,^{25,26} it is of no surprise that patients with ESRD had an increased risk of RVO. In addition to arteriosclerosis, hypercoagulable status has long been noted in patients with ESRD.^{27,28} The elevated level prothrombin fragment, thrombin-antithrombin complex, and homocysteine in plasma observed in patients with ESRD^{29–33} were also risk factors for RVO.^{25–37} Moreover, dialysis including both hemodialysis or peritoneal dialysis might stimulate the coagulation activity even more,³³ which might further increase the risk of RVO in ESRD patients.

We noted in this study that in ESRD patients, the HR of CRVO is higher than that of BRVO. Although both are venous occlusive diseases, CRVO and BRVO are somewhat different in the pathogenesis. Whereas BRVO mainly happens in patients >40 years of age with stiff arterial wall,^{19,25} CRVO might also happen in young adults, who have not been noted to have arteriosclerosis.²⁶ In addition to the common risk factors including arteriosclerosis, hypertension, hyperlipidemia, and DM for both CRVO and BRVO,^{16–21} other risk factors that might possibly also be correlated with BRVO, such as hypercoagulable status, blood hyperviscosity, and open angle glaucoma, seem to be more associated with CRVO.¹⁹ As elevated intraocular pressure during dialysis might happen in some predisposed patients³⁸ and hypercoagulable blood status is common in ESRD patients, ESRD appears to be more of a risk factor for CRVO than BRVO.

It is interesting to note that the level of significance for developing RVO became more prominent in ESRD patients after excluding DM patients. This might be explained by several reasons. First, DM itself is a risk factor for CRVO and BRVO. It is possible that the damaging effect of DM on vasculature is so predominant that nullifies the additive deleterious effect of ESRD. Second, patients with vascular nephropathy on renal dialysis have been shown to have significantly higher serum concentration of prothrombin fragment as compared with their counterparts with diabetic nephropathy,³³ thus indicating that dialysis might more strongly affect the coagulation profile in the non-DM ESRD patients.

The strength of this study is the large number of ESRD patients as a case cohort, and the long follow-up duration. On the contrary, the limited number of cases developing RVO makes the statistics weaker; further, this analysis was based on insurance claim data without fundus photographic recordings, and for this reason, some patients with asymptomatic BRVO might not have been recorded and the incidence of BRVO might have been underestimated; however, the chance of underestimating the asymptomatic BRVO is likely to be similar in both the case and the control cohort, which might have only minimally affected the final results.

We used both matching and direct adjustment on 4 comorbidities (DM, hypertension, hypercholesterolemia, and hypertriglyceridemia) in addition to age and sex for balancing the health conditions between the ESRD and non-ESRD groups; however, some residual confounding might still exist and potential unmeasured confounders such as atherosclerosis were not

taken into account, which are the nature limitation of this retrospective study.

In conclusion, ESRD is a risk factor for CRVO. After stratifying DM status, it became a risk factor for both CRVO and BRVO; however, for DM patients, ESRD did not have the additive risk of developing RVO, either for CRVO or BRVO.

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