


Chronic kidney disease as a potential risk factor for retinal vascular disease

A 13-year nationwide population-based cohort study in Taiwan

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Abstract

We investigate whether patients with chronic kidney disease (CKD) are at increased risk of retinal vascular disease (RVD). Data was collected from the Taiwan National Health Insurance system and included patients newly diagnosed with CKD between 2000 and 2012. The endpoint of interest was a diagnosis of RVD. Follow-up data of 85,596 patients with CKD and 85,596 matched comparisons (non-CKD) from 2000 to 2012 were analyzed. Patients with CKD were found to have a significantly higher cumulative incidence of RVD (Kaplan–Meier analysis, log-rank test $P < .0001$). Through multivariate Cox regression analysis, the CKD group was found to have higher risk of developing RVD (adjusted hazard ratio (HR) [95% confidence interval (CI)]: 2.30 [2.16–2.44]) when compared to the control cohort. When comparison of CKD group and non-CKD group was stratified by gender, age and comorbidities (hypertension, diabetes, and hyperlipidemia), the higher risk of RVD in patients with CKD remained significant in all subgroups. Patients with CKD were found to have higher risk of developing RVD in this cohort study. In addition, CKD imposed the same risk for RVD development in all age groups and in patients with or without hypertension or diabetes. Thus, patients with CKD should be vigilant for symptoms of RVD. Understanding the link between CKD and RVD could lead to the development of new treatment and screening strategies for both diseases.

Abbreviations: CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, OPD = outpatient department, RVD = retinal vascular disease, RVO = retinal vein occlusion, SD = standard deviation.

Keywords: age, chronic kidney disease, diabetes, gender, hypertension, hyperlipidemia, retinal vascular disease

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C-JL and C-HC contributed equally to this work.

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Chronic kidney disease may increase the risk of subsequent retinal vascular disease. Although hypertension and diabetes are possible risk factors associated with retinal vascular disease, chronic kidney disease plays a pivotal role in retinal vascular disease development.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Chronic kidney disease (CKD) is defined by indicators of renal damage, including functional imaging of the kidney or proteinuria (albumin to creatinine ratio), and decreased renal function (below thresholds of estimated glomerular filtration rate).^[1] CKD is increasingly recognized as a global public health problem. During 2015-2016, the prevalence of CKD in the U.S. was 14.2%.^[2] The estimated global CKD prevalence is between 11% and 13%.^[3] In Taiwan, the estimated prevalence is 15.46%.^[4] CKD is not only associated with possible progression to advanced renal failure which is renal replacement therapy-dependent, but also increased risks of cardiovascular complications, premature mortality, and/or decreased quality of life.^[4]

The eye has similar vascular structures as the kidney. Moreover, the inner retina and glomerular filtration barrier share similar developmental pathways.^[5,6] Richard Bright first reported the association between renal disease and blindness in 1836.^[7] Several studies have also found associations of CKD with retinal vein occlusion and diabetic retinopathy.^[8,9] In addition, retinal microvascular parameters have been shown to be predictive of CKD.^[10] CKD shares common vascular risk factors with retinal vascular diseases (RVD), such as diabetes, hypertension, smoking, and obesity.^[5,11] The pathophysiology between the 2 entities includes inflammation, oxidative stress, endothelial dysfunction, and microvascular dysfunction.^[12]

RVD refers to a range of ocular diseases that affect the retina blood vessels, the most common of which include hypertensive retinopathy, retinal vein occlusion (RVO), retinal artery occlusion, and diabetic retinopathy. Although RVD usually affects both eyes, it is often undetected in the early stages. Frequently, by the time it is diagnosed, RVD has already progressed to an advanced stage and caused irreversible damage.^[13,14]

Previous studies have found evidence for relationships between RVO and end-stage renal disease or early stage CKD.^[15-17] However, few studies have examined the association between RVD and CKD through large-scale longitudinal study design. Therefore, we conducted a 13-year nationwide cohort study by analyzing claims data from the Taiwan National Health Insurance (NHI) Research Database (NHIRD) with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to investigate the risk of RVD in patients with CKD and to evaluate the impact of comorbidities including hypertension, diabetes, and hyperlipidemia in the Taiwanese population.

2. Patients and methods

2.1. Data source

Taiwan's National Health Insurance Administration (NHIA) set up the NHIRD based on the single-payer NHI program. This program was inaugurated on March 1, 1995 and provides coverage to over 99% of all residents in Taiwan. We accessed the Longitudinal Health Insurance Database (LHID), a component of the NHIRD, which includes 1,000,000 insureds randomly selected from the 2000 Registry for Beneficiaries. All medical claims included both inpatient and outpatient visits and medical treatment for each insured from the start of 1996 to the end of 2012. To comply with the Personal Information Protection Act, the identification of each insured in the LHID was re-coded. The study protocol was conducted according to the principles described in the Declaration of Helsinki and institutional review

board/ethics committee approval was obtained by the Institutional Review Board of China Medical University Hospital, Taiwan.

2.2. Study subjects

We collected patients newly diagnosed with CKD (ICD-9-CM 580-589, 403 m 753, 250.4, 274.1, 440.1, 442.1, 447.3, 572.4, 642.1, and 646.2) between 2000 and 2012. Patients with at least 3 medical visits for CKD were defined as new cases and the first visit date for CKD was defined as the index date. Those with a diagnosis of CKD prior to 2000 were excluded. The endpoint was a new diagnosis of RVD (ICD-9-CM 362.01-362.07, 362.10-362.17, and 362.30-362.37). The end date of follow-up was December 31, 2013. Those with a history of RVD (ICD-9-CM 362.01-362.07, 362.10-362.17, 362.29, and 362.30-362.37) were excluded. Subjects without medical visits for eye diseases were also excluded.

The comorbidities assessed included hypertension (ICD-9-CM code 401-405, A26), diabetes (ICD-9-CM code 250 and A181), and hyperlipidemia (ICD-9-CM code 272). Controls were randomly selected from populations without histories of CKD. They were frequency-matched by age group (<20, 20-39, 40-64, and 65+ years old), gender, ophthalmologic outpatient department (OPD) before the index date, and index-year at a ratio 1:1. We included only patients with at least one medical visit for ophthalmology before enrolling into the study. After this restriction, we matched the ophthalmologic OPD visits between both groups.

2.3. Study endpoint

The clinical endpoint was a diagnosis of RVD. Patients with at least 2 medical visits for RVD, separated for at least 7 days, were defined as the endpoint to ensure the validity of the diagnosis. All study subjects were followed from the index date until the endpoint. Those without endpoint development were followed until the date of withdrawal from the program or the end of 2012, whichever occurred first. In this study, the demographic characteristics included age group (<20, 20-39, 40-64, and 65+ years old), gender, comorbidities, and ophthalmologic OPD before the index date.

2.4. Statistical analyses

A Chi-Squared test was used to assess the difference of demographic characteristics between the CKD cohort and comparison cohort from 2000 to 2012. A *t*-test was employed to assess the difference of the mean OPD visit for ophthalmology between 2 cohorts. Continuous variables, such as age and follow-up time, were shown as mean and standard deviation (SD) and analyzed using the Wilcoxon rank sum test. We estimated the cumulative incidences of RVD for both the CKD and comparison cohorts using the Kaplan-Meier method, and examined the difference between the 2 curves using the log-rank test. A multivariable Cox model was adjusted for continuous age, gender, comorbidities, and OPD visits for ophthalmology before the index date. Univariate and multivariable Cox proportional regression analysis measuring hazard ratio (HR) and 95% confidence interval (CI) were used to assess the association between CKD and the risk of developing RVD. The incidence density rate of RVD (per-1000years) was calculated for CKD

Table 1
Baseline characteristics of patients.

	Chronic kidney disease (n = 85,596)		Nonchronic kidney disease (n = 85,596)		P value*
	n	%	N	%	
Gender					>.99
Male	38355	44.8	38355	44.8	
Female	47241	55.2	47241	55.2	
Age, yr					>.99
20–39	11310	13.2	11310	13.2	
40–64	38772	45.3	38772	45.3	
65–100	35514	41.5	35514	41.5	
Mean (SD) [†]	59.7 (16.3)	59.6 (16.3)	0.008		
Comorbidity					
Hypertension	53479	62.5	30896	36.1	<.0001
Diabetes	38169	44.6	15533	18.1	<.0001
Hyperlipidemia	31022	36.2	14147	16.5	<.0001
Follow-up time, yr [†]	6.45 (4.83)		7.55 (4.71)		<.0001

* P value using Chi-Squared for the comparisons between with and without chronic kidney disease.

[†] Average age and follow-up time using Wilcoxon rank-sum test for verification.

SD = standard deviation.

cohort and comparison cohort. The risk of RVD in the CKD and comparison cohorts was stratified by age group, gender, and comorbidities, using Cox proportional hazard regression. All analyses were performed using SAS statistical software, version 9.4 for Windows (SAS Institute, Cary, NC). The level of significance was set at $P < .05$ at two-tailed test. The Wilcoxon rank-sum test was used for verification of average age and follow-up time.

3. Results

3.1. Baseline data

Follow-up data of 85,596 patients with CKD and 85,596 matched comparisons (non-CKD) from 2000 to 2012 were analyzed. The gender and age distributions were comparable in both groups according to initial grouping design (Table 1). The follow-up time (year) was 6.45 ± 4.83 (mean \pm SD) in CKD group

and 7.55 ± 4.71 in non-CKD group ($P < .0001$) (Table 1). As for comorbidities, the proportion of patients with hypertension, diabetes, and hyperlipidemia were higher in the CKD group than in the non-CKD group (CKD vs non-CKD: 62.5% vs 36.1%, $P < .0001$ for hypertension, 44.6% vs 18.1% for diabetes, $P < .0001$, and 36.2% vs 16.5% for hyperlipidemia, Table 1).

3.2. Time-to-event analysis

Using Kaplan–Meier survival statistics, crude overall survival curves showed that cumulative incidence of RVD was significantly higher in the CKD group (log-rank test $P < .001$, Fig. 1). After adjusting for confounding factors, patients with CKD were still found to have significantly a higher cumulative incidence of RVD (Kaplan–Meier analysis, log-rank test $P < .001$, Fig. 2). With Cox regression analysis, the CKD group was found to have higher risk of developing RVD (adjusted hazard ratio (HR) [95%

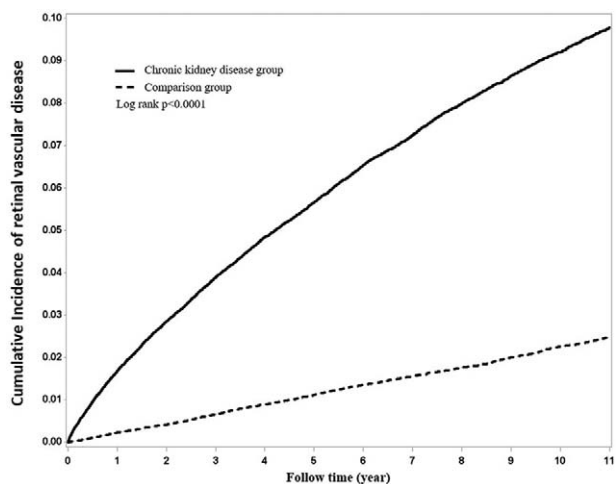


Figure 1. Using Kaplan–Meier survival statistics, it showed crude overall survival curves by with and without chronic kidney disease. (Log-rank $P < .0001$).

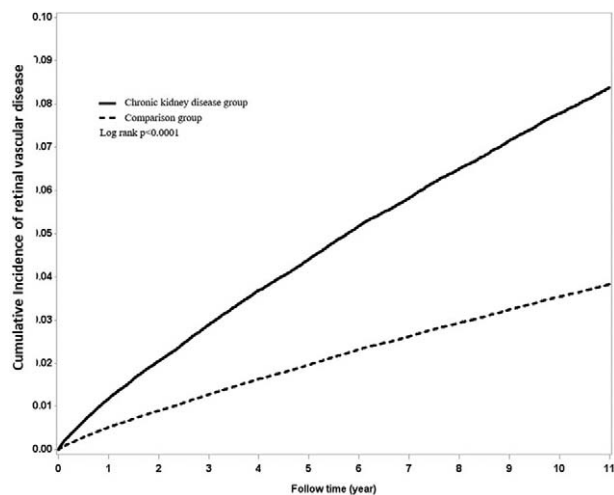


Figure 2. Using Kaplan–Meier survival statistics, it showed adjusted confounding factors survival curves by with and without chronic kidney disease. (Log-rank $P < .001$).

Table 2
Cox model measured hazard ratios and 95% confidence interval of retinal vascular disease associated with gender, age, and comorbidities.

Variable	Retinal vascular disease			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	PY	IR		
Chronic kidney disease					
No	1463	646846	2.26	1 (reference)	1 (reference)
Yes	5520	552122	9.99	4.35 (4.11–4.61)***	2.30 (2.16–2.44)***
Gender					
Female	3383	566652	5.97	1 (reference)	1 (reference)
Male	3600	632316	5.69	0.93 (0.89–0.98)***	1.03 (0.98–1.08)
Age, yr					
20–39	312	201328	1.54	1 (reference)	1 (reference)
40–64	4095	598115	6.84	4.33 (3.86–4.86)***	2.43 (2.16–2.74)***
65–100	2576	399525	6.44	3.88 (3.45–4.36)***	1.69 (1.49–1.91)***
P for trend				<0.0001	<0.0001
Comorbidity					
Hypertension					
No	2077	697449	2.97	1 (reference)	1 (reference)
Yes	4906	501519	9.78	3.15 (2.99–3.32)***	1.57 (1.48–1.67)***
Diabetes					
No	1702	899928	1.89	1 (reference)	1 (reference)
Yes	5281	299040	17.6	9.03 (8.55–9.54)***	6.37 (6.00–6.77)***
Hyperlipidemia					
No	4091	948579	4.31	1 (reference)	1 (reference)
Yes	2892	250389	11.5	2.54 (2.42–2.67)***	1.00 (0.95–1.05)

* $P < .05$.** $P < .01$.*** $P < .001$.

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 person-years, PY = person-years.
 HR adjusted for gender, age, hypertensive retinopathy, diabetes mellitus, and hyperlipidemia.

CI]: 2.30 [2.16–2.44], $P < .001$) when compared to the control cohort (Table 2).

3.3. The role of CKD after stratification

When comparisons of the CKD and non-CKD groups were stratified by gender and age, higher risks of developing RVD in patients with CKD were found in both genders (adjusted HR: male, 2.35 [2.15–2.56], $P < .001$; female, 2.25 [2.06–2.45], $P < .001$, Table 3) and also in adult patients over 40 years old (adjusted HR: age 20–39, 3.75 [2.55–5.51], $P < .001$; age 40–64, 2.42 [2.22–2.64], $P < .001$; age 65–100, 2.15 [1.96–2.35], $P < .001$, Table 3). The impact of CKD on increasing the risk of RVD occurrence was significant in all age groups over 40 (Fig. 3). When stratified by 3 major comorbidities: hypertension, diabetes, hyperlipidemia, patients with CKD had higher risk of developing RVD compared to matched controls, regardless whether they had either of these comorbidities (Table 3).

3.4. Other possible clinical factors related to RVD

In addition to CKD, we found some clinical factors associated with the occurrence of RVD through the Cox regression analysis (Table 2). For example, subjects over 40 years old were found to have a higher risk of RVD than their younger counterparts (adjusted HR for age 40–64: 2.43 [2.16–2.74], $P < .001$, adjusted HR for age 65–100: 1.69 (1.49–1.91), $P < .001$) (Fig. 3). After adjusting for confounding factors, hypertension and diabetes also contributed additional risk to RVD development (Table 2). Female gender and hyperlipidemia were associated with higher

HR in crude analysis, but the difference became insignificant when the HR was adjusted (Table 2).

4. Discussion

Patients with CKD were found to have higher risk of developing RVD in this cohort study. In addition, CKD imposed the same risk for RVD development in all age groups and in patients with or without hypertension or diabetes. Although old age, hypertension, and diabetes were also high risk factors for RVD development as demonstrated in this study, CKD imposed the same risk for RVD development in all age groups and in patients with or without hypertension or diabetes, as revealed in the results by stratifying patients in different age or comorbidity condition. This implicated the unique role of CKD and possible additional different underlying mechanisms for RVD development when compared to other well-known risk factors.

CKD has been attributed to comorbidities of diabetes,^[9,18] hypertension,^[19–21] and hyperlipidemia.^[22] Patients with CKD were found to have higher risk of developing RVD in this cohort study. In addition to older age, hypertension, and diabetes, the existence of CKD was demonstrated to be an additional crucial factor for RVD development. Moreover, patients with CKD had a higher hazard of RVD compared to non-CKD group after adjusting for gender, age group, and comorbidities of diabetes, hypertension, and hyperlipidemia. CKD is a consequence of microvascular disease.^[23] The correspondence of RVD and CKD might indicate a common pathological change in microvasculature. Mechanisms for these vascular diseases include advanced glycation end product accumulation,^[24] impairment of the nitric

Table 3
Incidence rate and hazard ratio of retinal vascular disease between with and without chronic kidney disease stratified by gender, age, and comorbidities.

Variable	Retinal vascular disease						Crude HR (95% CI)	Adjusted HR (95% CI)
	No			Yes				
	Event	PY	IR	Event	PY	IR		
Gender								
Male	703	304484	2.30	2680	262168	10.2	4.35 (4.01–4.73)***	2.35 (2.15–2.56)***
Female	760	342362	2.21	2840	289954	9.79	4.35 (4.01–4.71)***	2.25 (2.06–2.45)***
Age, yr								
20–39	32	102756	0.31	280	98572	2.84	9.10 (6.31–13.1)***	3.75 (2.55–5.51)***
40–64	720	320104	2.24	3375	278011	12.1	5.31 (4.90–5.76)***	2.42 (2.22–2.64)***
65–100	711	223986	3.17	1865	175539	10.6	3.26 (2.99–3.56)***	2.15 (1.96–2.35)***
Comorbidity								
Hypertension								
No	629	453345	1.38	1448	244104	5.93	4.26 (3.88–4.68)***	2.55 (2.30–2.82)***
Yes	834	193501	4.31	4072	308018	13.2	3.06 (2.84–3.29)***	2.11 (1.95–2.27)***
Diabetes								
No	801	555700	1.44	901	344229	2.61	1.81 (1.65–2.00)***	3.06 (2.82–3.32)***
Yes	662	91146	7.26	4619	207893	22.2	1.61 (1.45–1.78)***	2.81 (2.58–3.05)***
Hyperlipidemia								
No	1090	570258	1.91	3001	378322	7.93	4.12 (3.84–4.41)***	3.02 (2.70–3.36)***
Yes	373	76588	4.87	2519	173800	14.4	2.32 (2.15–2.49)***	2.23 (2.00–2.49)***

* $P < .05$.
 ** $P < .01$.
 *** $P < .001$.

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 person-years, PY = person-years.
 HR adjusted for gender, age, hypertension, diabetes mellitus, and hyperlipidemia.
 Unable to calculate because of there are few or no events in with and without chronic kidney disease cohort.

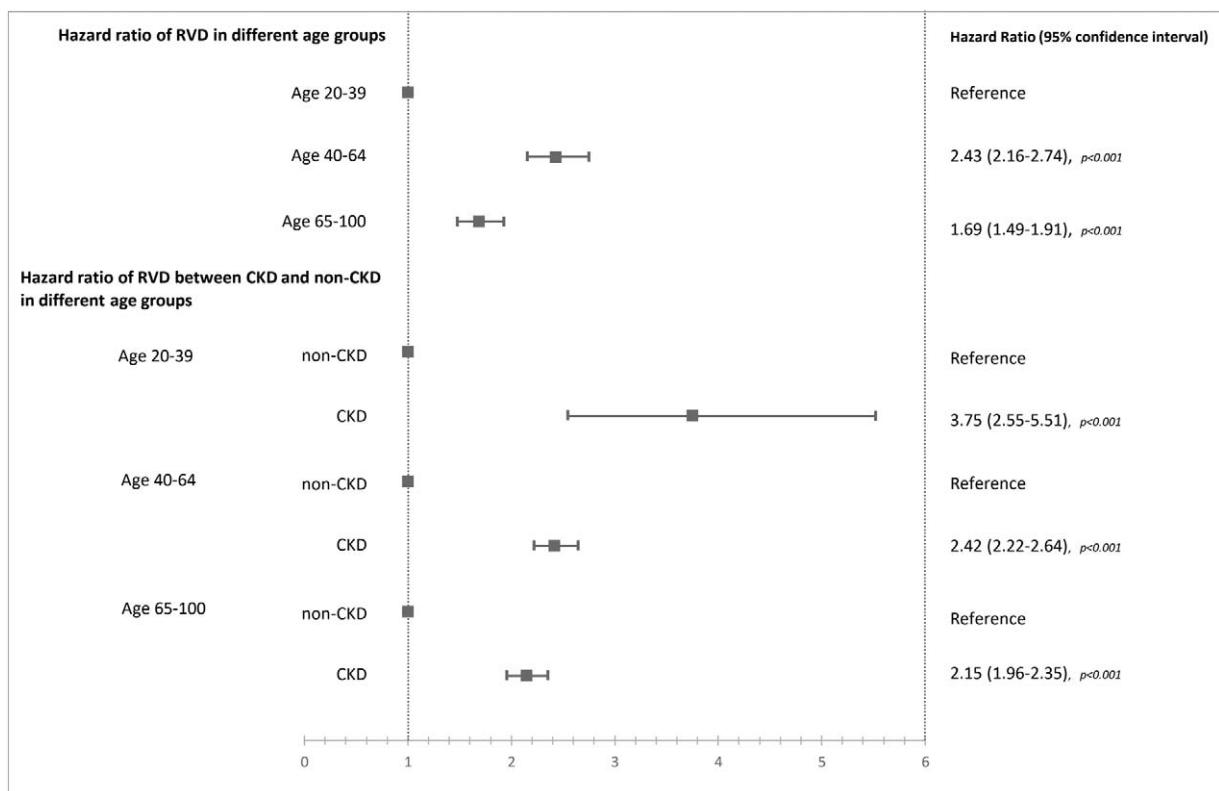


Figure 3. Subjects over 40 years old were found to have higher risk of RVD than their younger counterparts without CKD stratification (adjusted HR for age 40–64: 2.43 [2.16–2.74], $P < .001$, adjusted HR for age 65–100: 1.69 (1.49–1.91), $P < .001$). The influence of CKD on the risk of RVD incidence was all significantly higher in different age groups. (CKD = chronic kidney disease, RVD = retinal vascular disease).

oxide-mediated vasodilator response, over-production of endothelial growth factors, chronic inflammation, hemodynamic dysregulation, impaired fibrinolytic ability, enhanced platelet aggregation, and upregulation of redox-sensitive proinflammatory gene products.^[25]

The microvasculature is narrowed in patients with reduced estimated glomerular filtration rate. The retinal microvasculature can be directly visualized by nonmydriatic retinal fundus photography or optical coherence tomographic angiography.^[26] Focal vascular abnormalities include hard exudates, microaneurysms, hemorrhage, localized vessel narrowing, arteriovenous nicking, and nerve fiber layer infarction.^[27,28] Retinal hemorrhage could be a feature of moderate-severe forms of microvascular retinopathy which would be exaggerated by the bleeding tendency in CKD.^[29]

Diabetes is the primary cause of CKD with multiorgan involvement.^[12,30] Chronic hyperglycemia alters growth factors and cytokines expression in renal glomeruli resulting in an imbalance of the hemodynamics in glomerular cells. Hypertension is a major cause of the decline in glomerular filtration rate in CKD.^[12,31] The mechanisms involving in the progression of renal damage include the systemic BP load, the degree transmitted to the renal microvasculature, and local susceptibility factors to barotrauma.

Age has been found to be a significant risk factor associated with RVO.^[15,32] In addition, when hyperlipidemia, heart failure, hypertension, diabetes, age, sex, and income were considered together, age has showed to be the highest adjusted HR for RVO, especially in subjects over 50.^[15] To the best of our knowledge, few studies on the association between CKD and RVD in different age groups have been published. Therefore, in the present study, we investigated the association between CKD and the risk of RVD in different age groups with or without stratification by CKD. CKD was found to have a significantly higher impact on RVD occurrence in subjects over 40 years old.

Our study has a few limitations. First, diagnoses of CKD and RVD are based solely on ICD codes. However, the Taiwan NHIA has established a mechanism to interview patients and it reviews medical charts to verify diagnosis validity and quality of care. Hospitals receive heavy penalties from the NHIA when discrepancies, overcharging, and malpractice are discovered. Second, as LHIRD claims data are used mainly for administrative billing purposes, it lacks additional clinical information, such as fundus photographic recordings. Studies that rely mainly on database may not comprehensively reflect patients' conditions. Third, these findings may only be related to the Taiwanese population and thus other similar studies should be performed in different countries to see if the association holds. Nevertheless, this also demonstrates the originality of this research. In spite of these limitations, the availability of data on a number of potential risk factors and the large sample size are important strengths of our study that add plausibility to the findings.

In summary, our 13-year cohort study found that patients with CKD have higher risk of developing RVD. For patients with older age, hypertension, and diabetes, the existence of CKD was demonstrated to be an additional crucial factor for RVD development. Retinal vascular changes can be easily visualized by nonmydriatic retinal fundus photography. Traditionally, RVD in CKD patients is found through screening examinations or a visit to an ophthalmologist. RVD diagnosis could therefore be underestimated. Routine examination of retina should be included in the care of CKD patients. Patients with CKD should

be vigilant for symptoms of RVD. Understanding the link between CKD and RVD could lead to the development of new treatment and screening strategies, such as artificial intelligence, for both diseases. (Supplementary material, <http://links.lww.com/MD2/A45>).

Author contributions

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