Risk of Retinal Vein Occlusion in Patients With End-Stage Renal Disease: A 12-Year, Retrospective, Nationwide Cohort Study in South Korea

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PURPOSE. The present study aimed to evaluate the risk of retinal vein occlusion (RVO) in Korean patients with end-stage renal disease (ESRD).

METHODS. In this retrospective, nationwide, propensity score–matched cohort study, subjects were randomly enrolled from the 12-year longitudinal Korean National Health Insurance Service–National Sample Cohort 2002–2013 database comprising 1 million subjects. The ESRD group comprised 988 patients newly diagnosed with ESRD from 2003 onward by washing out data from 2002. The comparison group comprised 4940 (5 for each patient with ESRD) randomly selected propensity score–matched individuals not diagnosed with ESRD. Each sampled patient was tracked until 2013 for RVO development. Multiple conditional Cox regression analysis was performed to compare the risk of RVO between the two groups.

RESULTS. The mean follow-up period was 7.37 years. The incidence of RVO was 3.95% in the ESRD group and 2.17% in the comparison group (P = 0.001). ESRD was associated with greater risk of RVO development after adjustment for possible confounders (adjusted hazard ratio [HR], 2.122; 95% confidence interval [CI], 1.396–3.226; P = 0.0004). The 50- to 60-year (adjusted HR, 2.635; 95% CI, 1.100–6.313; P = 0.0297) and 60- to 70-year (adjusted HR, 2.544; 95% CI, 1.059–6.110; P = 0.0368) age groups exhibited higher risk of RVO compared with the <40-year age group. Hyperlipidemia (adjusted HR, 1.670; 95% CI, 1.176–2.371; P = 0.0042) and hypertension (adjusted HR, 1.896; 95% CI, 1.165–3.086; P = 0.01) were also associated with RVO.

CONCLUSIONS. An association between ESRD and subsequent RVO development was found after adjustment for possible confounding factors.

Keywords: retinal vein occlusion, end-stage renal disease, association

Retinal vein occlusion (RVO) is classified into central RVO and branch RVO, according to the site of occlusion, and is the second most common cause of retinal vascular disease causing visual loss worldwide after diabetic retinopathy.1–3 Although the definite pathogenesis is not yet fully understood, some combined factors are believed to contribute to RVO, including vein compression over the arteriovenous crossing, particularly in eyes with increased arterial rigidity and arteriosclerosis; thrombus formation following vessel wall degeneration; and dysregulation of hematologic factors.4–6 In addition, increased levels of proinflammatory mediators and decreased levels of anti-inflammatory cytokines have been detected in the vitreous fluid of RVO patients.7,8 Risk factors for RVO include hypertension, hypercholesterolemia, myocardial infarction, diabetes mellitus (DM), and cerebral vascular accidents.9–14 Patients with end-stage renal disease (ESRD), which is the final stage of chronic kidney disease, are dependent on hemodialysis or peritoneal dialysis because of insufficient kidney function and exhibit a very high risk for cardiovascular death and morbidity.15 The retinal and renal circulations share homologous anatomic, physiologic, and pathologic characteristics.16,17 Therefore, ESRD also can be considered a risk factor for RVO; however, few studies have evaluated the association between ESRD and RVO development on the basis of extensive data.18,19 The aim of the present study was to evaluate the risk of RVO in Korean patients with ESRD.

METHODS This study was based on a retrospective cohort analysis of data from the Korean National Health Insurance Service (KNHIS)–National Sample Cohort (KNHIS-NSC) 2002–2013 database. This study protocol was approved by the institutional review board (IRB) of Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. IRB/ethics committee approval was obtained and informed consent was waived.

DATABASE In South Korea, a universal-coverage health insurance system for all citizens was initiated in 1968, and universal health care coverage was achieved in 1989. All individuals born in South

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Korea are given a unique resident registration number and are also registered in the KNHIS system. Furthermore, a large database including socioeconomic variables (residence, year and month of death, cause of death, income level), details of medical treatment, and health examination has been formed using the participants’ medical bill expenses claimed by medical service providers. For the present study, we used the KNHIS-NSC 2002–2013 database for a population-based cohort that was provided by KNHIS in 2015 for research purposes. This database includes 1,025,340 randomly selected patients extracted by sampling in 2002; these account for 2.2% of the total Korean population of 46 million.

In Korea, disabled patients receive a disability certificate, and are enrolled in the Ministry of Health and Welfare after undergoing medical examinations and receiving a diagnosis of disability from a medical institute; the disability review board rates the degree of disability. All disability data are entered in the National Disability Registry and are linked with the KNHIS-NSC database. Specifically, patients with second-degree renal disability are defined as those with chronic renal failure receiving continuous hemodialysis or peritoneal dialysis for >5 months.

Study Design

This was a retrospective, nationwide, propensity score-matched cohort study.

Participants

We used the International Classification of Diseases, 10th Revision (ICD-10) to extract the ESRD and comparison groups from the KNHIS-NSC database. Patients who had received a certificate for second-degree renal disability with the chronic kidney disease diagnosis code (ICD-10, N18) between January 2003 and December 2011 were included in the ESRD group. We washed out data from 2002 to ensure that only newly diagnosed patients were included in the ESRD group. Patients who received a certificate for second-degree renal disability before the start date of the study and those diagnosed with RVO before ESRD were excluded. The comparison group comprised randomly selected propensity score-matched patients without ESRD from the remaining cohort registered in the database (five for each patient with ESRD). These patients were matched to the ESRD patients for sociodemographic factors (age, sex, and household income) and the year of enrollment (ESRD diagnosis). Eventually, 988 and 4940 patients were enrolled in the ESRD and comparison groups, respectively. All patients were monitored for RVO development until December 2013.

Statistical Analysis

The characteristics of the study population were analyzed using descriptive statistics. We matched the ESRD and comparison groups using propensity score matching. The propensity scores were estimated by logistic regression analysis for the prediction of ESRD occurrence after controlling for age, sex, household income, and year of enrollment. Matching was performed using the greedy macro with the estimated propensity score. An 8-to-1 digit greedy matching algorithm was then used to identify a unique matched control for each ESRD patient according to the propensity score. If a match could not be found, the algorithm sequentially proceeded to the next highest digit match in the propensity score to create “next-best” matches in a hierarchical sequence, until no more matches could be made. Once a match was made, it was not considered again. We identified the association between ESRD and the subsequent incidence of RVO using univariable and multiple conditional Cox proportional hazards regression analyses with hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable model was adjusted for hyperlipidemia, heart failure, hypertension, DM, age, sex, and household income. The cumulative incidence rates for RVO were evaluated by Kaplan-Meier analysis for each year during the 11-year follow-up period (2003–2013; mean, 7.37 years). If a patient died during the study period, did not develop RVO until the end of the study, or did not return to the hospital until the end of the study, the patient was regarded as censored. The follow-up period started from the first date of ESRD diagnosis in the ESRD group and from randomly selected visit dates during years matched with those for the ESRD group in the comparison group. The follow-up ended at the first date of RVO diagnosis or the last follow-up date until 2013. A significance level of 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) for Windows (Microsoft Corporation, Redmond, WA, USA).

Results

Table 1 summarizes the baseline characteristics of the study population based on the time the patients were enrolled. During the 11-year follow-up (mean, 7.37 years), 39 of the 988 ESRD patients and 107 of the 4940 comparison patients developed RVO. Overall, the association with RVO was higher in the ESRD group than in the comparison group (3.95% vs.
The patients in the ESRD group were significantly more likely to exhibit hyperlipidemia, heart failure, hypertension, and DM compared with those in the comparison group (\(P < 0.0001\)). There were no significant differences in sex distribution, age, and household income between the two groups, as these variables were used for matching.

Table 2 displays the HRs for RVO development according to the univariable and multiple conditional Cox regression models. After adjusting for sociodemographic factors, household income, and comorbidities, including hyperlipidemia, heart failure, hypertension, and DM, multiple conditional Cox regression analysis revealed that patients with ESRD were more likely to develop RVO (adjusted HR, 2.122; 95% CI, 1.396–3.226; \(P = 0.0004\)). When the patients were divided into age groups, we found that the association with RVO was higher in the 50- to 60-year (adjusted HR, 2.635; 95% CI, 1.100–6.313; \(P = 0.0297\)) and 60- to 70-year (adjusted HR, 2.544; 95% CI, 1.059–6.110; \(P = 0.0368\)) groups than in the \(<40\)-year group. Other factors showing a significant association with RVO included hyperlipidemia (adjusted HR, 1.670; 95% CI, 1.176–2.371; \(P = 0.0042\)) and hypertension (adjusted HR, 1.896; 95% CI, 1.165–3.086; \(P = 0.0100\)). Differences in sex distribution, household income, and DM did not show a significant association with RVO.

Kaplan-Meier survival analysis revealed higher RVO cumulative incidence rates for the ESRD group than for the comparison group over the 11-year study period, with a significant difference according to the log-rank test (\(P < 0.0001\); Fig.). The mean time until development of RVO was 64.13 \(\pm\) 44.27 months for total groups; 76.14 \(\pm\) 43.65 and 31.17 \(\pm\) 25.36 months for comparison and ESRD groups, respectively.

We additionally performed a sensitivity analysis by subgroup analysis to confirm whether ESRD still raises the risk for RVO development.
Risk of RVO in Patients With ESRD

### DISCUSSION

In the present study, we examined 5928 sociodemographically matched subjects extracted from a nationwide database of 1,025,340 randomly selected individuals to determine the relationship between ESRD and RVO. The results revealed a temporal relationship between newly developed ESRD and subsequent RVO development during the 11-year follow-up period after adjustment for sociodemographic factors, household income, and comorbidities, including hyperlipidemia, heart failure, hypertension, and DM. To the best of our knowledge, only in Taiwan were there longitudinal epidemiologic studies with extensive data evaluating the association between ESRD and RVO.\(^{18,19}\) As an epidemiologic study, confirming reproducibility is a crucial aspect. In addition, South Korea and Taiwan are the only countries in East Asia in which a nationwide cohort database is established for the entire nation. However, Taiwan and South Korea differ in terms for which a nationwide cohort database is established for the entire nation. However, Taiwan and South Korea differ in terms

### TABLE 3. The Risk for RVO According to the Presence of ESRD by Subgroup Analyses in Subjects With and Without Comorbidities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR for RVO</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>No</td>
<td>2.39</td>
<td>1.190–4.797</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.957</td>
<td>1.156–3.314</td>
</tr>
<tr>
<td>Heart failure</td>
<td>No</td>
<td>2.548</td>
<td>1.622–4.003</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.025</td>
<td>0.374–2.808</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>1.957</td>
<td>1.156–3.314</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.985</td>
<td>1.279–2.999</td>
</tr>
<tr>
<td>DM</td>
<td>No</td>
<td>3.049</td>
<td>1.351–6.883</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.889</td>
<td>1.161–3.074</td>
</tr>
</tbody>
</table>

The HRs for RVO between the ESRD and comparison groups were calculated from multiple conditional Cox regression adjusted for sociodemographic factors and comorbidities. Reference for HRs is the comparison group.

according to the presence or absence of each comorbidity (Table 3). For subgroup analyses, the groups were stratified into patients with hypertension, hyperlipidemia, DM, and heart failure and those without these comorbidities. The risk of RVO according to the presence of ESRD was examined in the subgroups using multiple conditional Cox regression analysis after being adjusted for sociodemographic factors and comorbidities. ESRD increased the risk of RVO compared with that in the comparison group among subjects with hypertension (HR 1.958) or hyperlipidemia (HR 1.957) or DM (HR 1.889), and those without hyperlipidemia (HR 2.390) or DM (HR 3.049) or heart failure (HR 2.548), whereas ESRD was not significantly associated with an increased risk of RVO among subjects with heart failure. A subgroup without hypertension was difficult to analyze because of an insufficient number of patients to form a subgroup (\(n = 16\)).

Several factors can explain the association between ESRD and RVO. Of these, one of the major pathogenic mechanisms is arteriosclerosis, which is a predominant arterial pathology and is frequently observed in patients with ESRD.\(^{15}\) Factors implicated for arteriosclerosis in these patients include activation of the renin-angiotensin-aldosterone system, advanced glycation end-products, increasing circulating asymmetrical dimethylarginine, inflammation, endothelial dysfunction, and factors promoting vascular calcification, including hyperphosphatemia, hyperparathyroidism, and decreased synthesis of 1,25-dihydroxyvitamin D.\(^{15,20}\) The retinal vein is compressed at the arteriovenous crossing in RVO. This thin-walled vein lies between the more rigid thick-walled artery and retina.\(^{21,22}\) In this setting, sclerosis of the retinal artery in ESRD patients may promote further compression of the vein to result in turbulent blood flow that induces endothelial damage and thrombosis, ultimately contributing to downstream venous occlusion.\(^{13}\)

Considering the association between renal dysfunction and retinopathy lesions,\(^{35–26}\) arteriosclerosis, which is common in ESRD patients, may increase the risk of RVO.

The second factor is hypercoagulability, which is widely observed in patients with chronic kidney disease. Thrombosis-favoring hematoologic alterations in patients with renal insufficiency have been revealed in numerous studies.\(^{25–37}\) Increased levels of procoagulant factors, such as factor V Leiden, factor VIIIc, thrombin-antithrombin complex, von Willebrand factor, and D-dimers, are observed in these patients.\(^{28,32,33}\) Downregulation of anticoagulant function and impaired fibrinolysis also play important roles in the hypercoagulable status in patients with chronic kidney disease.\(^{28}\) A high prevalence of inherited or acquired thrombophilic disorder, such as activated protein C resistance, which reflects factor V Leiden or protein S or C deficiency, and antithrombin III deficiency is observed in patients with ESRD.\(^{30,31}\) Moreover, dialysis, which is routinely performed for ESRD patients, itself can further aggravate hypercoagulability.\(^{32}\)

In addition, there are nontraditional risk factors for thrombosis, such as inflammation and hyperhomocysteinemia. Proinflammatory markers, such as C-reactive protein, IL-6, TNF-α, and fibrinogen, are increased in patients with chronic kidney disease.\(^{33,34}\) Chronic inflammation can induce atherosclerosis and thrombosis, which contributes to increased cardiovascular risk.\(^{33,35}\) In addition, ESRD patients also exhibit an elevated plasma homocysteine level, which is associated with thrombosis and cardiovascular disease.\(^{36–38}\) Dysregulation of coagulation and anticoagulation is reported as a major risk factor for RVO.\(^{12,21,39,40}\) Moreover, acquired or genetic thrombophilia can increase the risk of RVO.\(^{39–40}\) A number of recent studies have also demonstrated that inflammation plays an important role in the onset and progression of RVO.\(^{7,8,41}\) Furthermore, small case-comparison studies and a meta-analysis of these studies reported that hyperhomocysteinemia is associated with RVO.\(^{42–44}\) Because hypercoagulability is a risk factor for RVO, patients with ESRD, who usually exhibit a hypercoagulable state, may be at increased risk for RVO.

In the present study, age, hypertension, and hyperlipidemia also were found to be significantly associated with RVO. In addition, when comorbidities, age, sex, and household income were considered together, age showed the highest adjusted HR for RVO. In particular, the 50- to 60-year and 60- to 70-year groups showed the highest HRs (adjusted HRs, 2.655 and 2.544, respectively). With the exception of ESRD, hypertension and hyperlipidemia showed the highest HRs after age, in the same order. This result is consistent with those of previous studies.\(^{3,45,46}\) The most recognized risk factors for RVO include...
age and systemic vascular disorders. A recent meta-analysis of published studies suggested that 48% of RVO cases can be attributed to hypertension, 20% to hyperlipidemia, and 5% to diabetes. In the present study, DM did not demonstrate a significant association with RVO development, although we expected to find an association between the two. Accordingly, we searched the previous literature for epidemiologic studies and found many reporting the lack of an association between DM and RVO. One study even reported DM to be a protective factor. The association between DM and RVO could be weak, but considering that diabetes is the cause of many cardiovascular diseases, more research is necessary to clarify this. Because of the high level of global medical care, many patients with diabetes have been referred for ophthalmologic screening by the internal medicine department and are undergoing early treatment before the development of a serious retinal vascular abnormality. Because this study was an epidemiologic analysis that depended only on diagnostic code, there may be limitations because of the mixed population of patients without any distinction with regard to the severity of diabetes (e.g., HBA1c). There is a possibility that these factors weakened the association between DM and RVO in epidemiologic studies.

A major limitation of the present study is the potential inaccuracy of the ICD code–dependent diagnoses of RVO and ESRD in combination with the disability certificate provided by the Ministry of Health and Welfare. We performed this double screening process to select a more selective and precise patient population that met the criteria for ESRD. However, studies that rely solely on databases that do not reflect the patient’s actual clinical status still have fundamental limitations. In addition, RVO with nasal occlusion may be less diagnostic because it is less symptomatic and can be missed to diagnose. However, this may not have had a significant impact on the overall statistical results because this condition could occur with similar probability in the ESRD group and the comparison group.

The following additional limitations of this study should be noted: the possible misclassification of diagnoses for RVO, ESRD, and comorbidities; possible underreporting of asymptomatic RVO or ESRD; possibility of a delayed diagnosis of RVO or ESRD due to delayed visits to physicians; higher possibility of bias among comparison patients from medical claim records than among comparison patients from the general population who have not received medical care; and possible limitations in extending the results to whole ethnic groups, considering this study included the South Korean population.

Because ESRD patients have a poor general condition, ophthalmologic problems, which are not life threatening, tend to be neglected. However, recently, treatment for RVO has been developed with remarkable therapeutic effects and simplicity compared with earlier treatment strategies, and there is no burden on the general body condition. Furthermore, as health care resources are being expended, the survival of patients with ESRD has increased. Therefore, for a satisfactory quality of life with good vision during the elongated life span, it is recommended to educate ESRD patients who have visual impairment to actively receive retinal examinations and treatment.

In conclusion, we found an association between ESRD and subsequent RVO development during an 11-year follow-up period after adjustment for possible confounding factors, and the ESRD patients exhibited an approximately 2-fold higher HR relative to the comparison group. Nephrologists can educate ESRD patients about the possibility of RVO, and ophthalmologists should perform more careful fundus examinations when examining ESRD patients.

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