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Association between retinal vein occlusion and risk of heart failure: A 12-year nationwide cohort study

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ABSTRACT

Backgrounds: Retinal vein occlusion (RVO) is one of the major causes of visual impairment in elderly people. Risk factors for RVO are also common risk factors for cardiovascular disease, including heart failure (HF). However, the association between RVO and HF has not been evaluated.
Methods and results: A retrospective propensity-score matched cohort study was conducted using national representative 1 million samples from the Korea National Health Insurance Service. The RVO group included patients with a first diagnosis of either central or branch RVO (n = 1754) and the comparison group included randomly selected patients (n = 8749) who were matched to sociodemographic factors and the year of RVO diagnosis. In the longitudinal cohort, HF developed in 11.6% and 8.0% of patients in the RVO and comparison groups, respectively, ($p < 0.001$) during the 11-year follow-up period (median, 7.6 years). RVO was significantly associated with an increased risk of HF after multivariable adjustment (HR = 1.36; 95% CI, 1.16–1.60). In terms of HF subtypes, RVO was associated with the risk of ischemic HF but not with the risk of non-ischemic HF. The effect size (~HR) for HF by RVO was larger in patients without each comorbidity than in patients with each comorbidity.
Conclusions: Our observational study on nationwide data suggests that RVO is associated with an increased risk of the incidence of HF, especially ischemic HF. An optimal surveillance strategy and referring from ophthalmologists to cardiologists should be considered in the presence of one or more additional HF risk factors in patients with RVO.

1. Introduction

The blood system in the retina includes the central retinal artery and central retinal vein, and each artery and vein has four main branches. Retinal vein occlusion (RVO), which is classified as central RVO (CRVO) and branch RVO (BRVO), is one of the major causes of visual impairment in middle-aged and elderly people [1,2]. Thrombosis; compression of the vein by an adjacent atherosclerotic artery; and hematologic alterations, including decreased blood flow and increased blood viscosity or plasma homocysteine level have been associated with RVO [3–6]. Older age and traditional cardiovascular risk factors such as hypertension, diabetes mellitus (DM), and dyslipidemia are identified risk factors for RVO [7–10]. These risk factors for RVO are also common risk factors for systemic vascular diseases such as cardiovascular or cerebrovascular disease [11,12]. Recently, in a well-designed study using Danish national registries, BRVO was associated with an increased risk of cardiovascular and cerebrovascular disease [13]. However, the relationship between RVO and heart failure (HF) has not been evaluated until now. In the present study, we examined whether the incidence of HF was increased among patients who had been diagnosed with RVO using a nationwide representative sample of 1,025,340 adults from the National Health Insurance Service National Sample Cohort 2002–2013 (NHIS-NSC 2002–2013) in South Korea.

2. Methods

2.1. Statement of ethics

This study adhered to the tenets of the Declaration of Helsinki, and the NHIS-NSC 2002–2013 project was approved by the Institutional Review Board of the Korean National Health Insurance Service (KNHIS). The need for written informed consent was waived. The design of this

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study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea (4-2015-0186).

2.2. KNHIS and database

The national health insurance started to cover the entire population of South Korean from 1989. Therefore, every South Korean is enrolled in the KNHIS. The KNHIS control all medical costs among beneficiaries, medical providers, and the government. Almost all the medical data, including diagnostic codes, drugs, and personal information, therefore are centralized in large databases. Each South Korean resident was assigned a unique identification number at birth, and this number was used by the KNHIS to identify each individual. Thus, the health care claim data are not omitted or duplicated. Moreover, the Korean Classification of Diseases (KCD), which is a similar system to the International Classification of Diseases (ICD), was used by the KNHIS. The current study used the NHIS-NSC 2002–2013 database, which was released by the KNHIS in 2015 for research purposes. The data comprised 1,025,340 nationally representative random subjects in 2002; stratified random sampling was performed using 1476 strata by age (18 groups), sex (two groups), and income level (41 groups: 40 health insurance beneficiaries and one medical aid) among a Korean population of 46 million in 2002.

2.3. Participants

The RVO group included all patients who received inpatient and outpatient care between January 2003 and December 2007 for the first diagnosis of RVO (KCD code H34.8, which corresponds to the ICD ninth revision, clinical modification [ICD-9-CM] code 362.35, CRVO; or 362.36, venous tributary [branch] occlusion). We excluded subjects who had been treated for RVO in 2002 to eliminate those with chronic conditions and ensure that the RVO group included subjects with only new episodes. A comparison group (five per one RVO patient) matched to the sociodemographic factors (i.e., age, sex, residential area, and household income) and the year of enrollment (RVO diagnosis) was generated. Patients who received inpatient and outpatient care in 2002 for HF (KCD code I50, which corresponds to ICD-9-CM code 428, heart failure) were also considered to have chronic conditions and were excluded. HF was divided into ischemic HF and non-ischemic HF for subgroup analysis. Ischemic HF was defined as ischemic heart disease (KCD code I21-25, which corresponds to the ICD-9-CM code 410-414, ischemic heart disease, except angina pectoris [code 413]) during the entire follow-up period. We included patients who were diagnosed with RVO prior to HF based on their visit date. Finally, 1754 eligible patients with RVO and 8755 patients in the comparison group were identified. Each patient was followed until 2013 to detect HF development.

2.4. Variables

Patients' age (<50; 50–59; 60–69; and ≥70 years), sex, residential area (Seoul, a metropolitan area in Korea; the second area included the largest province, third area included the second largest city, and the second and third largest provinces; and the fourth area included other areas), and household income (≤30%; 30–70%; and ≥70%) were obtained from the database. To evaluate the HF risk by RVO in relatively young adults, the study population was divided into two age groups (<65 years and ≥65 years), and age was adjusted for a 5-year interval in these subgroup analyses. Traditional risk factors, including hypertension, DM, and chronic kidney disease (CKD) [14], were obtained based on the KCD. We defined these comorbidities as any diagnoses between 2003 and 2013 prior to the diagnosis of HF.

2.5. Statistical analysis

Descriptive statistics of the present study were provided. Propensity score matching was performed; we estimated the propensity scores by estimating a logistic regression to predict RVO occurrence using, and so controlled for, the sociodemographic factors including age, sex, residential area, household income, and year of RVO diagnosis. Matching was done 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 RVO patient according to the propensity score. Under this algorithm, if this match could not be found, the algorithm then proceeded sequentially to the next highest digit match on propensity score to make 'next-best' matches, in a hierarchical sequence until no more matches could be made. Once a match is made, the match is not considered again. We identified the association between RVO and the subsequent incidence of HF based on univariable and multivariable Cox proportional hazard regression with hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariable Cox regression was used for the subgroup analysis by age, sex, and subjects with or without each comorbidity. The person-year for each group and incidence rate per 1000 persons-year was calculated. The Kaplan–Meier survival curve for the HF-free survival rate in the RVO and comparison groups was generated for the up to 11-year follow-up period (2003–2013). The follow-up started from the first date of RVO diagnosis in the RVO group, and

Table 1
Characteristics of the study population: comparison (n = 8755) and RVO (n = 1754) group.

Variables	Comparison group (column %)		RVO group (column %)		p value
HF					<0.001
No event	8051	(92.0)	1550	(88.4)	
Event	704	(8.0)	204	(11.6)	
Non-ischemic HF	390	(4.5)	90	(5.1)	0.004
Ischemic HF	314	(3.5)	114	(6.5)	
Hypertension					<0.001
No	3645	(41.6)	387	(22.1)	
Yes	5110	(58.4)	1367	(77.9)	
Diabetes mellitus					<0.001
No	4609	(52.6)	685	(39.1)	
Yes	4146	(47.4)	1069	(61.0)	
Chronic kidney disease					<0.001
No	8559	(97.8)	1663	(94.8)	
Yes	196	(2.2)	91	(5.2)	
Variables for matching					
Year					
2003	1763	(20.1)	353	(20.1)	>0.999
2004	1931	(22.1)	387	(22.1)	
2005	1580	(18.1)	317	(18.1)	
2006	1586	(18.1)	318	(18.1)	
2007	1895	(21.6)	379	(21.6)	
Age group (year)					>0.999
<50	1833	(20.9)	367	(20.9)	
50–59	1992	(22.8)	399	(22.8)	
60–69	2976	(34.0)	597	(34.0)	
≥70	1954	(22.3)	391	(22.3)	
Sex					0.994
Male	4004	(45.7)	802	(45.7)	
Female	4751	(54.3)	952	(54.3)	
Residence					>0.999
Seoul (metropolitan)	1859	(21.2)	373	(21.3)	
Second area	1573	(18.0)	315	(18.0)	
Third area	1921	(21.9)	385	(22.0)	
Fourth area	3402	(38.9)	681	(38.8)	
Household income					0.999
0–30%	1989	(22.7)	398	(22.7)	
30–70%	2966	(33.9)	594	(33.9)	
70–100%	3800	(43.4)	762	(43.4)	

HF = heart failure; RVO = retinal vein occlusion.
Seoul, a metropolitan area in South Korea; the second area included the largest province, the third area included the second largest city, and the second and third largest provinces; and fourth area included other areas.