Relationship between heart failure and central serous chorioretinopathy: A cohort study in Taiwan

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Abstract

Background: Both central serous chorioretinopathy (CSCR) and heart failure (HF) are disorders with a complex pathogenesis, whereas the two diseases might share similar pathogenesis. This study aimed to evaluate whether patients with HF are exposed to potential risk of CSCR by using the National Health Insurance Research Database (NHIRD).

Methods: Data were collected from the NHIRD over a 14-year period. Variables were analyzed with the Pearson chi-square test and Fisher's exact test. The risk factors for disease development were examined by adjusted hazard ratio (aHR). Kaplan–Meier analysis was performed to compare the cumulative incidence of CSCR.

Results: A total of 24 426 patients with HF were enrolled in the study cohort, and there were 24 426 patients without HF in the control cohort. The incidence rate of CSCR was higher in the study cohort than in the control cohort (aHR = 4.572, $p < 0.001$). CSCR occurred more commonly in males than in females. The overall incidence of CSCR was 30.07 per 100 000 person-years in the study cohort and 23.06 per 100 000 person-years in the control cohort. Besides, subgroup analysis revealed that no matter in gender or age group, HF patients were in an increased risk of CSCR diagnosis (male/female, aHR = 3.268/7.701; 20-59 years/≥60 years, aHR = 3.405/5.501, $p < 0.001$).

Conclusion: HF is a significant indicator for CSCR. Patients with HF should stay alert for potential disorder of visual impairment. Further prospective studies to investigate the relationship between HF and CSCR could provide more information.

Keywords: Central serous chorioretinopathy; Cohort study; Epidemiology; Heart failure

1. INTRODUCTION

Central serous chorioretinopathy (CSCR) is a disorder with a complex pathogenesis. CSCR is characterized by leakage of fluid from the choroid through a focal disrupted retinal pigment epithelium (RPE) barrier into the subretinal space, causing serous retinal detachment and/or RPE detachment. The mean annual incidence rate in a Caucasian population was reported to be 0.0058%,[1] and that reported in the Taiwan population was 0.021%.[2] Although the pathogenesis of CSCR is multifactorial, exposure to endogenous or exogenous corticosteroids has been identified as a risk factor for CSCR in several studies.[3–5]

Heart failure (HF) is a complex and life-threatening disease during which the heart pumps insufficient blood into the systemic circulation to meet the body's needs. In HF patients, impaired ventricular function reduces blood flow and activates the renin–angiotensin–aldosterone system. Aldosterone is a major endogenous mineralocorticoid that induces dysfunction of coronary vessel endothelial cells. Increased vessel permeability via activation of mineralocorticoid receptor (MR) causes fluid accumulation, leading to tissue remodeling and organ congestion that worsen HF.[6–8] Besides, MR is also found in the neuroretina and choroid, and the associated fluid accumulation makes it crucial in the pathogenesis of CSCR.[9–11]

The aim of this study was to investigate the association between HF and CSCR via data collection from the National Health Insurance Research Database (NHIRD) of Taiwan.

2. METHODS

2.1. Research database

Beginning in 1995, the National Health Insurance (NHI) program was launched in Taiwan. The NHI covers nearly the total population in Taiwan and currently covers approximately 23

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million people. The NHIRD contains all claims data from the NHI program. Data related to basic parameters, such as gender, age, diagnosis, insurance premium, season, location, urbanization level, and level of care, can be obtained in the NHIRD. In addition, these data are available in electronic format for clinicians to conduct statistical studies. Therefore, we analyzed this nationwide population database to explore the relationship between HF and CSCR.

2.2. Study participants

This is a retrospective cohort study. As shown in Fig. 1, we used the NHIRD to identify patients with clinical diagnoses of HF and CSCR according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code (ICD-9-CM code for central serous retinopathy: 362.41; HF: 428). We also used ICD-9-CM codes to identify, differentiate, and analyze comorbidities in CSCR patients. We replaced the Charlson comorbidity index (CCI) with the (CCI_R) (CCI excluding diabetes mellitus [DM], hypertension [HTN], renal disease, pneumonia, liver disease, and coronary artery disease [CAD]) because the removed diseases were also variables in this study. From 2000 to 2013, this study identified 28 441 individuals who met the inclusion criteria, and 4015 patients were excluded according to the exclusion criteria. Ultimately, the study cohort was 24 426 individuals. The control cohort was assembled with the same criteria as the study cohort using onefold propensity score matching by gender, age, and index year; namely, the comparison cohort also included 24 426 individuals. Over the 14-year follow-up, 162 patients were diagnosed with CSCR including 90 individuals in the study cohort and 72 individuals in the control cohort (Fig. 1). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.3. Ethical considerations

The NHIRD encodes personal patient information to maintain privacy. Patient consent is not required to access NHIRD data. The Institutional Review Board of the Tri-Service General Hospital approved this study and waived the consent requirement (TSGHIRB No. 2-105-05-082).

2.4. Statistical analysis

The Pearson chi-square test and Fisher's exact test were used to evaluate differences in categorical variables, such as gender, age group, and insurance premium, and statistical significance was defined as $p < 0.05$. After adjustment of the variables, univariate and multivariate Cox regression analyses were employed to evaluate the adjusted hazard ratio (aHR) for the influence of HF on developing CSCR. Kaplan–Meier analysis was performed to estimate the cumulative incidence of CSCR in these two cohorts. All statistical analyses were performed using SPSS software (Version 22.0; SPSS Inc., Chicago, IL, USA).

3. RESULTS

Table 1 shows the demographic characteristics of both cohorts. The mean age was 59.66 ± 14.60 years in the study cohort and 59.47 ± 12.58 years in the control cohort. The difference was not significant ($p = 0.123$). In addition, there was no significant difference in gender or age group in both groups. Regarding insurance premiums New Taiwan dollar (NT$) in both cohorts, approximately half of the enrolled patients were in the <18 000 group (55.57%), followed by the 18 000 to 34 999 group (37.30%) and the >35 000 group (7.14%). The insurance premium (NT$) in the study cohort was lower than that in the control cohort ($p < 0.001$). In the comorbidity comparison, patients with HF had higher rates of DM, hyperlipidemia, HTN, chronic kidney

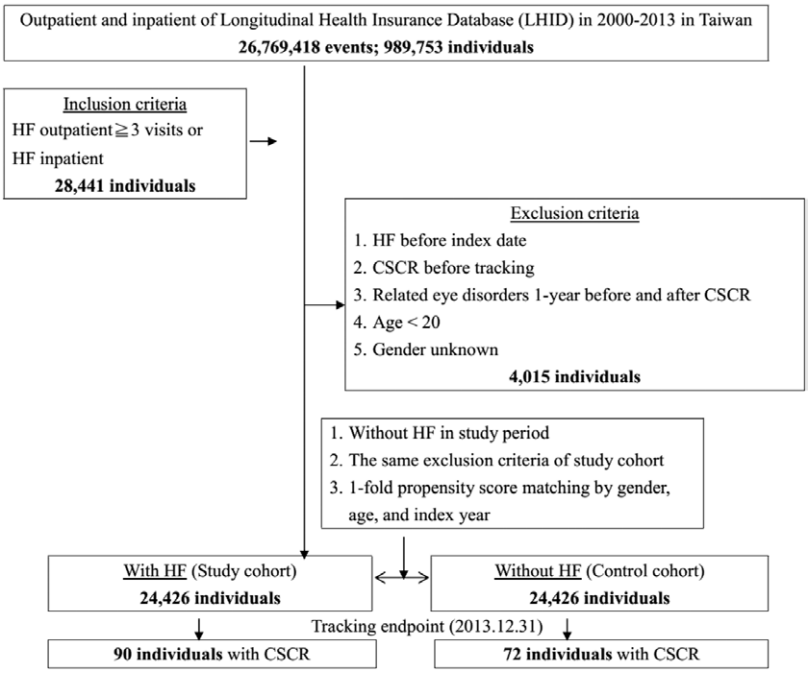


Fig. 1 Flowchart of the study sample selection from the NHIRD in Taiwan. Related eye disorders were as follows: degenerative myopia (ICD-9-CM 360.21), hemorrhagic RPE detachment (ICD-9-CM 362.43), exudative AMD (ICD-9-CM 362.52), macular hole (ICD-9-CM 362.54), hereditary retinal dystrophies (ICD-9-CM 362.7), focal chorioretinitis (ICD-9-CM 363.0), disseminated chorioretinitis (ICD-9-CM 363.1), Harada's disease (ICD-9-CM 363.22), angioid streak (ICD-9-CM 363.43), or malignant neoplasm of the choroid (ICD-9-CM 190.6). AMD, Age-related macular disease; CSCR, central serous chorioretinopathy (ICD-9-CM 362.41); HF, heart failure (ICD-9-CM 428); ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NHIRD, National Health Insurance Research Database; RPE, retinal pigment epithelium.

Table 1

Baseline characteristics of the study

HF	Total		With		Without		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	***p***
Total	48 852		24 426	50.00	24 426	50.00	
Gender							0.999
Male	25 332	51.85	12 666	51.85	12 666	51.85	
Female	23 520	48.15	11 760	48.15	11 760	48.15	
Age (y)	59.57 ± 13.63		59.66 ± 14.60		59.47 ± 12.58		0.123
Age group (y)							0.999
20-59	19 786	40.50	9893	40.50	9893	40.50	
≧60	29 066	59.50	14 533	59.50	14 533	59.50	
Insurance premium (NT$)							<0.001
<18 000	26 933	55.13	13 573	55.57	13 360	54.70	
18 000-34 999	18 170	37.19	9 110	37.30	9 060	37.09	
≧35 000	3749	7.67	1743	7.14	2006	8.21	
DM							<0.001
Without	45 555	93.25	22 004	90.08	23 551	96.42	
With	3297	6.75	2422	9.92	875	3.58	
Hyperlipidemia							<0.001
Without	47 018	96.25	23 181	94.90	23 837	97.59	
With	1834	3.75	1245	5.10	589	2.41	
HTN							<0.001
Without	42 719	87.45	20 305	83.13	22 414	91.76	
With	6133	12.55	4121	16.87	2012	8.24	
CKD							<0.001
Without	47 220	96.66	22 937	93.90	24 283	99.41	
With	1632	3.34	1489	6.10	143	0.59	
Peptic ulcer							0.003
Without	47 658	97.56	23 777	97.34	23 881	97.77	
With	1194	2.44	649	2.66	545	2.23	
Psychiatric diseases							<0.001
Without	47 114	96.44	23 457	96.03	23 657	96.85	
With	1738	3.56	969	3.97	769	3.15	
Allergic respiratory diseases							<0.001
Without	47 723	97.69	23 777	97.34	23 946	98.03	
With	1129	2.31	649	2.66	480	1.97	
CAD							<0.001
Without	46 532	95.25	22 443	91.88	24 089	98.62	
With	2320	4.75	1983	8.12	337	1.38	
CCI_R	0.29±0.92		0.31±0.89		0.27±0.95		<0.001
Season							<0.001
Spring (March–May)	12 140	24.85	6708	27.46	5432	22.24	
Summer (June–August)	7482	15.32	5597	22.91	1885	7.72	
Autumn (September–November)	6814	13.95	5603	22.94	1211	4.96	
Winter (December–February)	22 416	45.89	6518	26.68	15 898	65.09	
Location							<0.001
Northern Taiwan	20 576	42.12	10 492	42.95	10 084	41.28	
Middle Taiwan	13 566	27.77	6767	27.70	6799	27.84	
Southern Taiwan	11 522	23.59	5236	21.44	6286	25.73	
Eastern Taiwan	2898	5.93	1794	7.34	1104	4.52	
Outlets islands	290	0.59	137	0.56	153	0.63	
Urbanization level							<0.001
1 (the highest)	14 342	29.36	7219	29.55	7123	29.16	
2	17 988	36.82	9739	39.87	8249	33.77	
3	5352	10.96	2087	8.54	3265	13.37	
4 (the lowest)	11 170	22.86	5381	22.03	5789	23.70	
Level of care							<0.001
Hospital center	8348	17.09	5870	24.03	2478	10.14	
Regional hospital	11 374	23.28	8930	36.56	2444	10.01	
Local hospital	29 130	59.63	9626	39.41	19 504	79.85	

p, chi-square/Fisher's exact test on categorical variables and *t* test on continuous variables. CCI_R = Charlson comorbidity index removed HF, DM, HTN, CKD, and CAD.
CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; HTN = hypertension.

disease (CKD), peptic ulcers, psychiatric disease, allergic respiratory diseases, and CAD. The CCI_R value was 0.31 ± 0.89 in the study cohort and 0.27 ± 0.95 in the control cohort (p < 0.001). In addition, more individuals in the study cohort than in the control cohort lived in northern, eastern Taiwan and higher urbanized areas and received therapy in hospital centers and regional hospitals (p < 0.001).

The cumulative risk of developing CSCR was calculated by the Kaplan–Meier method (Fig. 2). The results showed that the study cohort had a significantly higher rate of developing CSCR than the control cohort (log-rank test p < 0.001). The cumulative risk of CSCR increased steadily annually to 0.37% (90/24 426 individuals) at the endpoint in the study cohort and to 0.29% (72/24 426 individuals) in the control cohort. Furthermore, the difference between both groups was significant during each year of follow-up (p < 0.001 during each year).

Table 2 shows the Cox regression analysis of the risk factors for CSCR. After adjusting for HF, gender, age groups (20-59 years and ≥60 years), insurance premium and preexisting comorbidities including DM, hyperlipidemia, HTN, CKD, peptic ulcer, psychiatric diseases, allergic respiratory diseases, and CAD, only HF (aHR = 4.572, 95% confidence interval [CI] = 3.236-6.461, p < 0.001) and male (aHR = 1.459, p = 0.02) patients have an increased risk of CSCR diagnosis. In addition, patients with HTN had a decreased risk of developing CSCR than those without HTN (aHR = 0.339, p = 0.04). Patients with other comorbidities, such as age groups and insurance premium, and other chronic diseases were not significantly associated with CSCR diagnosis according to hazard ratios (all p > 0.05).

In the subgroup analysis comparing patients with and without HF (Table 3), the overall incidence of CSCR was 30.07 per 100 000 person-years in the study cohort and 23.06 per 100 000 person-years in the control cohort. Both male and female HF patients had an increased risk of developing CSCR (aHR = 3.268 in males and 7.701 in females, p < 0.001). In the age group analysis, HF patients in both age groups were independently associated with an increase risk following CSCR diagnosis than patients without HF (aHR = 3.405 in the age group 20-59 years and 5.051 in the age group of ≥60 years, p < 0.001).

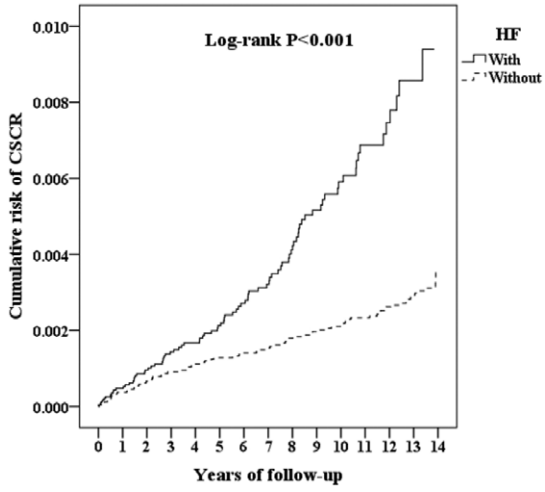
4. DISCUSSION

This population-based study enrolled 24 426 patients in the study cohort and 24 426 patients in the control cohort. We found that the rate of developing CSCR was significantly higher in the study cohort (HF patients) than in the control cohort. Kaplan–Meier analysis also indicated that the cumulative risk of developing CSCR was significantly increased in the study cohort in each year. To our knowledge, no previous study has evaluated the relationship between these two diseases.

Regarding the demographic findings, our study revealed a male predominance (aHR = 1.459, p = 0.02) among CSCR patients, which was similar to previous studies;[1,2,4] In Tittl et al's study,[4] the male–female ratio in the CSCR group and control group was 2.7:1. Tsai et al[2] observed that the mean annual incidence was higher in males than in females and the peak incidence demonstrated a middle age predominance. In Kitzmann et al's study,[1] the incidence was more than five times higher in men than in women, and the incidence rate of CSCR was also higher in middle-aged patients In our study, the age group analysis revealed lower risk of CSCR development in older patients (≧60 years, aHR = 0.812 compared with 20~59 years), but this result was not significant (p = 0.402). Because our study focused on the risk of CSCR development in HF patients, which is different from the abovementioned studies,[1,2,4] the inconsistence could be due to selective bias.

In the present study, patients with HTN were at lower risk of CSCR development (aHR = 0.339, p = 0.04). HTN has been reported to be a risk factor for CSCR in previous studies; however, their findings did not prove causation.[4,5] On the other side, there were also other studies showed opposite results.[1,12] Kitzmann et al[1] conducted a retrospective 4-year population-based study and found that HTN was not a significant risk factor for CSCR. Chen et al[12] also conducted population-based studies and found that the probability of developing HTN in patients with CSCR was not significantly different from that in subjects in the control group. Consistent with the findings of previous studies,[1,12] our study found that HTN was not a risk factor for CSCR development (Table 2). Nevertheless, the relationship between HTN and CSCR is still not well understood and further studies are still needed to explore the mechanism of pathogenesis in CSCR.

Furthermore, considering HF as a suspected indicator, we conducted a subgroup analysis in this study (Table 3). Patients with HF had a generally increased risk of developing CSCR than the control cohort, regardless of gender or age group analysis, and all groups were statistically significant (p < 0.001). We considered the possible reason is that the study cohort (with HF)



HF	With (N=24,426)	Without (N=24,426)	P
In the tracking of x year(s)	Numbers of CSCR		
1	11	9	<0.001
2	21	16	<0.001
3	30	22	<0.001
4	34	27	<0.001
5	41	31	<0.001
6	49	34	<0.001
7	55	37	<0.001
8	65	43	<0.001
9	73	47	<0.001
10	78	51	<0.001
11	83	55	<0.001
12	85	61	<0.001
13	88	67	<0.001
14	90	72	<0.001

Fig. 2 Kaplan–Meier analysis of the cumulative risk of CSCR among patients aged 20 years and older stratified by HF with the log-rank test. CSCR, central serous chorioretinopathy; HF, heart failure.

Table 2

Factors for CSCR evaluated with Cox regression

Variables	Crude HR	95% CI	95% CI	*p*	Adjusted HR	95% CI	95% CI	*p*
HF								
Without	Reference				Reference			
With	2.773	1.999	3.847	<0.001	4.572	3.236	6.461	<0.001
Gender								
Male	1.474	1.076	2.018	0.016	1.459	1.060	2.006	0.020
Female	Reference				Reference			
Age group (y)								
20-59	Reference				Reference			
≧60	0.796	0.156	1.812	0.345	0.812	0.198	2.102	0.402
Insurance premium (NT$)								
<18 000	Reference				Reference			
18 000-34 999	1.032	0.743	1.434	0.852	1.044	0.741	1.470	0.808
≧35 000	1.271	0.745	2.168	0.380	0.763	0.431	1.350	0.362
DM								
Without	Reference				Reference			
With	0.310	0.099	0.970	0.044	0.448	0.136	1.476	0.186
Hyperlipidemia								
Without	Reference				Reference			
With	0.506	0.162	1.587	0.243	1.040	0.310	3.494	0.949
HTN								
Without	Reference				Reference			
With	0.398	0.147	1.076	0.070	0.339	0.081	0.950	0.040
CKD								
Without	Reference				Reference			
With	0.558	0.138	2.254	0.413	0.331	0.081	1.352	0.123
Peptic ulcer								
Without	Reference				Reference			
With	0.259	0.036	1.850	0.178	0.303	0.042	2.169	0.234
Psychiatric diseases								
Without	Reference				Reference			
With	0.168	0.024	1.201	0.076	0.221	0.031	1.580	0.132
Allergic respiratory diseases								
Without	Reference				Reference			
With	0.542	0.134	2.185	0.389	0.816	0.198	3.357	0.778
CAD								
Without	Reference				Reference			
With	0.702	0.260	1.698	0.485	0.775	0.275	2.188	0.630

Adjusted HR: adjusted variables are listed.

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; CSCR = central serous chorioretinopathy; DM = diabetes mellitus; HF = heart failure; HR = hazard ratio; HTN = hypertension.

was patients who had maladaptive endocrine consequences. Their unstable systemic conditions may have enhanced aldosterone–MR activation and induced multiple organ dysfunction, such as cardiac vasculopathy and CSCR.

Recently, several studies have identified that MRs are found in several tissues/organs, such as the heart, blood vessels, and brain.[6,8,13] Disturbances in the aldosterone–MR system may have pathophysiological consequences in these tissues. In the cardiovascular system, aldosterone–MR activation induces sodium retention, vessel inflammation, fibrosis, remodeling, and endothelial dysfunction, and these effects contribute to cardiovascular dysfunction.[6,14–16] In HF patients, the renin–angiotensin–aldosterone system is persistently activated due to impaired ventricular function-induced inappropriate expansion of the intravascular and extravascular volume, followed by blood stasis, organ congestion, and thrombus formation.[7,17,18] In eyes, MR is also found in the neuroretina and choroid, and the reaction of aldosterone–MR signaling has been studied in vivo.[10,19] Zhao et al identified dilatation and leakage of choroidal vessels and subsequent choroid vasculopathy in an animal model of choroidal thickening, vasodilation, and leakage of the choroidal vessels induced by intravitreal injection of aldosterone.[10] Therefore, aldosterone–MR activation-induced vasculopathy provides an explanation about the relationship between HF and CSCR in our study.

The therapeutic effects of MR antagonists (MRAs) on CSCR have been demonstrated in several studies.[10,20–23] At the choroidal level, Zhao et al[10] noted that aldosterone upregulated the endothelial vasodilatory potassium channel (KCa2.3), and the activation of KCa2.3 induced vasodilation, leakage of the choroidal vessels, and choroidal thickening. In addition, the choroidal thickening can be inhibited by coinjection of MRA. Thus, they treated chronic CSCR patients (over 4 months) with oral MRA (eplerenone), and the therapeutic effect with reduction of subretinal fluid, choroidal thickness, and improved visual acuity was noted. In addition, there are also several studies reported that MRAs are beneficial for treating patients with acute, chronic, recalcitrant, or steroid-induced CSCR.[20–23] In the abovementioned studies, MRA is an alternative therapy for CSCR patients, and the promising results also reveal that CSCR may be associated with MR activation.

Table 3

Factors for CSCR stratified by variables listed in the table evaluated with Cox regression

HF (With vs Without)	With			Without							
Stratified	Event	PYs	Rate (per 10^5 PYs)	Event	PYs	Rate (per 10^5 PYs)	Ratio	Adjusted HR	95% CI	95% CI	*p*
Total	90	299 281.97	30.07	72	312 261.31	23.06	1.304	4.572	3.236	6.461	<0.001
Gender											
Male	48	148 136.40	32.40	49	158 893.22	30.84	1.051	3.268	2.089	5.112	<0.001
Female	42	151 145.57	27.79	23	153 368.09	15.00	1.853	7.701	4.379	13.543	<0.001
Age group (y)											
20-59	38	80 587.26	47.15	31	63 839.18	48.56	0.971	3.405	2.410	4.811	<0.001
≧60	52	218 694.71	23.78	41	248 422.13	16.50	1.441	5.051	3.575	7.138	<0.001

Adjusted HR: adjusted variables are listed in Table 2.

CI = confidence interval; CSCR = central serous chorioretinopathy; HF = heart failure; HR = hazard ratio; PYs = person-years.

Considering MRA as a treatment for CSCR, we also conducted analysis of MRA (spironolactone and eplerenone) treatment and the risk of CSCR in HF cohort. The Kaplan–Meier analysis showed no significant difference in the cumulative risk of CSCR stratified by MRA with log-rank test (Supplementary Figure 2, $p = 0.694$) probably because of the relatively small sample size and event numbers (Supplementary Figure 1). However, HF patients with MRA treatment were at lower risk of CSCR than HF patients without MRA (aHR = 0.697, 95% CI = 0.134-2.805), but the result was also not significant ($p = 0.482$). The possible explanation is that the utilization of MRA in CSCR treatment is not discussed until 2012–2013,[10,20] which is in the late period of our study (2000~2013). Perhaps future study could enroll recent data to make the result more significant.

This study has several limitations. First, this was a retrospective study in nature. Second, database research studies lack imaging examination findings, such as optical coherence tomography and fluorescein angiography findings, to confirm an accurate diagnosis of maculopathy. Third, the main population was Han Chinese in Taiwan, and the study results may not be applicable to another race. Fourth, the cohort enrollment was limited to patients with HF and the control cohort in this study, which could have led to selection bias. However, this study has several strengths. The NHI system was introduced in Taiwan in 1995, so we were able to conduct a longitudinal data analysis over a long-term study period to compare the cumulative incidence of CSCR between the study cohort and control cohort; this study design is more effective than cross-sectional research. Furthermore, it is mandatory for all citizens in Taiwan to enroll in NHI, and the coverage rate is approximately 99%[24]; thus, the data collected in this study were from a nationwide, population-based database that contains medical information of insured people in Taiwan.

In conclusion, the results obtained from the NHIRD provide statistical information regarding HF as an independent indicator for CSCR. Clinicians may consider the diagnosis of CSCR in HF patients with visual impairments and refer these patients early for ophthalmological management. Further prospective studies including clinical diagnosis, serological testing, and angiographic findings would be helpful to elucidate the underlying mechanism between HF and CSCR.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000207.

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