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MAJOR ARTICLE

Association Between Coronary Artery Disease and Herpes Zoster: A Cohort Study in Taiwan

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Background. Coronary artery disease (CAD) and herpes zoster represent significant health burdens, and their potential interrelationships remain understudied. This cohort study aimed to address the existing knowledge gap by systematically exploring whether people with CAD are at increased risk for developing herpes zoster.

Methods. Using the 2006–2015 claims data of the National Health Insurance Program in Taiwan, we identified participants aged ≥20 years with a new diagnosis of CAD as the CAD group. We selected sex- and age-matched participants without CAD as the non-CAD group. The incidence rate of herpes zoster at the end of follow-up was calculated. A multivariable Cox proportional hazards regression model was used to measure the hazard ratio and 95% CI for herpes zoster associated with covariables.

Results. The overall incidence rate of herpes zoster was 1.14-fold greater in the CAD group as compared with the non-CAD group (6.52 vs 5.74 per 1000 person-years; 95% CI, 1.08–1.20). After controlling for covariables, the adjusted hazard ratio of herpes zoster was 1.21 (95% CI, 1.14–1.27) for the CAD group as compared with the non-CAD group.

Conclusions. This cohort study provides valuable insights into the potential association between CAD and the risk of developing herpes zoster. The findings may have implications for preventive strategies of herpes zoster in people with CAD. Further research and collaboration with diverse groups will be critical to validate and extend our findings.

Keywords. cohort study; coronary artery disease; herpes zoster; preventive strategies.

Coronary artery disease (CAD) is a leading cause of death in developed and developing countries, and global data reveal that the prevalence of CAD is about 5% to 8% [1, 2]. Although the clinical manifestations and consequences of CAD have been extensively studied, few studies have investigated the potential interrelationships between CAD and the risk of developing herpes zoster. CAD is characterized by conditions such as advanced age, chronic inflammation, immune dysfunction, endothelial dysfunction, and psychosocial stress, as well as comorbid conditions such as diabetes mellitus and hypertension [3–8]. We make a rational hypothesis that all of the aforementioned conditions might lead to an increased susceptibility to the reactivation of latent infections, including the varicella-zoster virus, which is responsible for herpes zoster.

Herpes zoster, commonly known as shingles, manifests as a painful rash and is associated with considerable morbidities, particularly in vulnerable populations [9–11]. To date, some chronic disorders are associated with an increased likelihood of developing herpes zoster [12–14], but there is a paucity of research investigating the potential link between CAD and the probability of developing herpes zoster. The complex interplay between CAD and the probability of developing herpes zoster remains an evolving area of research. Understanding the potential relationships between these diseases could have profound implications for clinical practice and public health strategies. Therefore, we carried out a cohort study to evaluate whether there is an association between CAD and the probability of developing herpes zoster in the research population.

METHODS

Data Source

The National Health Insurance Program in Taiwan was established by the government in 1995. It operates as a nationwide single-payer health insurance system designed to provide comprehensive medical coverage to all citizens. By the end of 2022, the National Health Insurance Program in Taiwan had enrolled approximately 99.9% of the country's population, which amounts to about 23.78 million citizens [15]. We utilized the

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2006–2015 claims data of the National Health Insurance Program in Taiwan as the data source. These data contain the medical information of 2 million beneficiaries, including all records on outpatient, inpatient, emergency, and medication use.

Study Design and Participants

The null hypothesis is that there is no significant association between CAD and the probability of developing herpes zoster. The alternative hypothesis is that there is a significant positive association between CAD and the probability of developing herpes zoster. We carried out a population-based retrospective cohort study to statistically evaluate whether the observed data support the null hypothesis of no association or the alternative hypothesis of a positive association in the study population. The CAD group comprised adults aged ≥20 years with a new diagnosis of CAD (based on *ICD-9* codes 410–414; *International Classification of Diseases, Ninth Revision*). The index date for the CAD group was defined as the date on which the patient was diagnosed with CAD. For each adult with CAD, 1 adult without a diagnosis of CAD was randomly selected for the non-CAD group. The CAD and non-CAD groups were meticulously matched for sex, age, and comorbidities through 1:1 propensity score matching with the nearest-neighbor matching method (Figure 1). The index date for the non-CAD group was set on January 1, 2006. Participants who had a prior diagnosis of herpes zoster were excluded from the study. In addition, those with a follow-up period <1 month were excluded from the study.

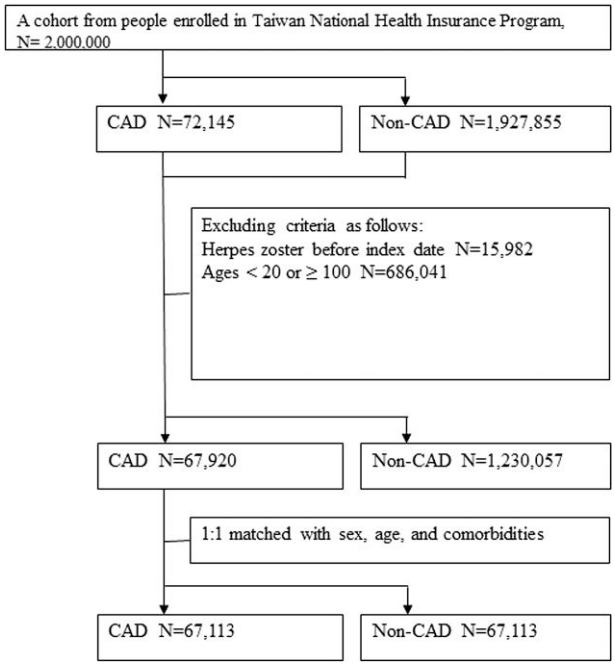

Figure 1. Flowchart for selection of study participants. CAD, coronary artery disease.

Comorbidities

Comorbidities in the study included alcohol-related disease, autoimmune disease, cancer, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension. All comorbidities were diagnosed by *ICD-9* codes. Information regarding prior vaccination for herpes zoster was not included as a variable.

Major Outcome

The major outcome of the cohort study was a new diagnosis of herpes zoster during the follow-up period (based on *ICD-9* code 053). All study participants were followed until they were newly diagnosed with herpes zoster or to the end of 2015.

Statistical Analysis

The chi-square test and *t* test were used to compare differences in covariables between the CAD and non-CAD groups. A Kaplan-Meier curve was applied to present the cumulative incidence of herpes zoster for the CAD group and the non-CAD group during the cohort period. The log-rank test was applied to provide an overall comparison of the Kaplan-Meier curve. The incidence rate of herpes zoster was calculated as the event number of herpes zoster identified during the follow-up period, divided by the total follow-up person-years for each group. The assumption of proportional hazards was examined with a test of scaled Schoenfeld residuals. It was not violated. After controlling for covariant factors, a multivariable Cox proportional hazards regression model was conducted to examine the association between CAD and the risk of developing herpes zoster. The hazard ratio (HR) and 95% CI were utilized to estimate the strength of the association. $P < .05$ is considered significant. SAS software was used in all analyses (version 9.4 for Windows; SAS Institute Inc).

RESULTS

Demographic Characteristics

The demographic characteristics of the study population are summarized in Table 1. The cohort study included 67 113 participants in the CAD group, with 56.3% being male. The non-CAD group had an identical number of participants and a similar distribution of males. While the CAD and non-CAD groups were matched for sex, age, and comorbidities through propensity score matching, notable differences in mean age persisted between the groups. Specifically, the CAD group had a mean age of 59.9 years, while the non-CAD group had a mean age of 60.4 years (*t* test, $P < .001$). The proportions of autoimmune disease, cerebrovascular disease, chronic kidney disease, and diabetes mellitus were statistically higher in the CAD group, but the proportions of chronic liver disease

and chronic obstructive pulmonary disease were statistically higher in the non-CAD group (chi-square test, $P < .05$).

Incidence Density of Herpes Zoster

Table 2 presents the incidence densities of herpes zoster in the CAD and non-CAD groups over the follow-up period. The incidence rate of herpes zoster was 6.52 per 1000 person-years among participants with CAD. In contrast, the incidence rate of herpes zoster was 5.74 per 1000 person-years in the non-CAD group. The CAD group had a higher incidence rate of herpes zoster than the non-CAD group (incidence rate ratio, 1.14; 95% CI, 1.08–1.20). As stratified by sex and age, the incidence rates of herpes zoster were all higher in the CAD group than in the non-CAD group. Participants in the CAD group aged 65 to 84 years had the highest incidence rate of herpes zoster (8.85 per 1000 person-years).

In Figure 2, the Kaplan-Meier curve illustrates that the cumulative incidence of herpes zoster was higher for the CAD group than the non-CAD group during the study period ($P < .001$). In addition, the average follow-up duration was 5.29 years in the CAD group and 9.74 years in the non-CAD group. The difference in average follow-up suggests that the non-CAD group was observed for a longer period vs the CAD group.

Table 1. Baseline Information Between the CAD and Non-CAD Groups

	CAD (n = 67 113)		Non-CAD (n = 67 113)		
Variable	No.	%	No.	%	*P* Value[a]
Sex					>.999
Male	37 759	56.3	37 759	56.3	
Female	29 354	43.7	29 354	43.7	
Age, y					<.001
20–39	4309	6.4	4185	6.2	
40–64	38 320	57.1	36 768	54.8	
65–84	22 520	33.6	24 128	36.0	
≥85	1964	2.9	2032	3.0	
Mean ± SD	59.9 ± 13.5		60.4 ± 13.6		<.001[b]
Baseline comorbidities					
Alcohol-related disease	260	0.4	245	0.4	.504
Autoimmune disease	1306	2.0	1196	1.8	.026
Cancer	2581	3.9	2562	3.8	.787
Cerebrovascular disease	6232	9.3	5486	8.2	<.001
Chronic kidney disease	3969	5.9	3403	5.1	<.001
Chronic liver disease	6513	9.7	7249	10.8	<.001
Chronic obstructive pulmonary disease	6618	9.9	6965	10.4	.002
Diabetes mellitus	14 929	22.2	14 587	21.7	.024
Hyperlipidemia	18 288	27.3	18 051	26.9	.145
Hypertension	32 842	48.9	32 987	49.2	.428

Abbreviation: CAD, coronary artery disease.

[a]Chi-square test unless indicated otherwise.

[b]*t* test.

Herpes Zoster Associated With Covariables

Variables significant in the univariable model were included in the multivariable model (Table 3). After adjustment for sex, age, alcohol-related disease, autoimmune disease, cancer, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension, the multivariable Cox proportional hazards regression model revealed that the HR for the development of herpes zoster in participants with CAD was calculated as 1.21 when compared with those without CAD (95% CI, 1.14–1.27). The results indicate a statistically significant association between CAD and an increased risk of herpes zoster.

DISCUSSION

In this present work, we found that the overall incidence rate of herpes zoster was 1.14-fold higher in the CAD group as compared with the non-CAD group. The association is expected to persist after adjusting for relevant confounding factors (HR, 1.21). To date, many studies have shown that herpes zoster infection would correlate with a greater risk of cardiovascular events [16–18]. One meta-analysis showed that herpes

Table 2. Incidence Density of Herpes Zoster Stratified by Sex and Age

	CAD				Non-CAD					
Variable	No.	Events	Person- Years	Incidence[a]	No.	Event	Person- Years	Incidence[a]	IRR[b]	95% CI
All	67 113	2315	354 797	6.52	67 113	3748	653 428	5.74	1.14	1.08–1.20
Sex										
Male	37 759	1160	195 177	5.94	37 759	1940	368 184	5.27	1.13	1.05–1.21
Female	29 354	1155	159 620	7.24	29 354	1808	285 244	6.34	1.14	1.06–1.23
Age, y										
20–39	4309	37	22 380	1.65	4185	53	41 600	1.27	1.30	.85–1.97
40–64	38 320	1148	201 664	5.69	36 768	1879	359 547	5.23	1.09	1.01–1.17
65–84	22 520	1076	121 604	8.85	24 128	1712	232 585	7.36	1.20	1.11–1.30
≥85	1964	54	9150	5.90	2032	104	19 696	5.28	1.12	.80–1.55

Abbreviations: CAD, coronary artery disease; IRR, incidence rate ratio.

[a]Incidence: per 1000 person-years.

[b]IRR (95% CI): CAD vs non-CAD.

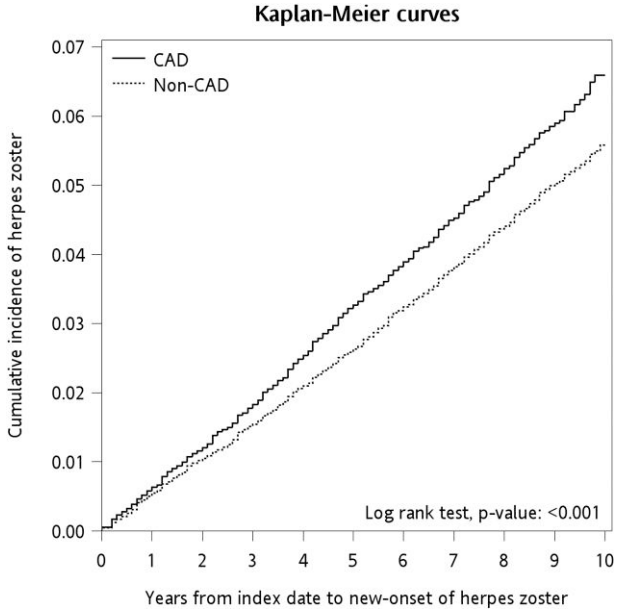

Figure 2. Kaplan-Meier curve shows that the cumulative incidence of herpes zoster was higher for the CAD group than the non-CAD group during the cohort period ($P < .001$). CAD, coronary artery disease.

Table 3. Hazard Ratio and 95% CI of Herpes Zoster Associated With CAD and Covariables

	Crude		Adjusted[a]	
Variable	HR	95% CI	HR	95% CI
Sex: male vs female	.83	.79–.87	.87	.83–.92
Age: every 1 year	1.02	1.02–1.02	1.02	1.02–1.02
Coronary artery disease: yes vs no	1.19	1.13–1.26	1.21	1.14–1.27
Baseline comorbidities: yes vs no				
Alcohol-related disease	.31	.15–.66	.39	.19–.83
Autoimmune disease	1.56	1.34–1.82	1.39	1.19–1.62
Cancer	1.23	1.09–1.39	1.07	.94–1.20
Cerebrovascular disease	1.02	.93–1.12	…	…
Chronic kidney disease	1.11	.99–1.23	…	…
Chronic liver disease	1.05	.97–1.14	…	…
Chronic obstructive pulmonary disease	1.30	1.21–1.40	1.12	1.04–1.21
Diabetes mellitus	1.06	1.00–1.13	.92	.86–.98
Hyperlipidemia	1.16	1.10–1.23	1.17	1.10–1.24
Hypertension	1.20	1.14–1.26	.99	.93–1.04

Abbreviations: CAD, coronary artery disease; HR, hazard ratio.

[a]Adjusted for sex, age, alcohol-related disease, autoimmune disease, cancer, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension.

zoster is significantly associated with a 20% to 30% increase in the odds of cardiovascular events from 3 months to 1 year after onset of herpes zoster [19]. While this meta-analysis highlights the impact of herpes zoster on cardiovascular events, no research has explored whether patients with CAD have a modified risk for developing herpes zoster, which may be explained by the following factors. First, the progression of herpes zoster and CAD involves different timelines. Herpes zoster often presents acutely, and as observed in the meta-analysis, CAD may manifest in the months following the onset of herpes zoster. Yet, the development of CAD is a gradual process that occurs over a long time, and the association between CAD and the occurrence of herpes zoster may have different timelines. This suggests that the impact of CAD on the risk of developing herpes zoster may not be immediate but could manifest over time. Further research should investigate not only whether there is a true association between CAD and herpes zoster but also when such an association becomes apparent. Second, the bidirectional relationship between herpes zoster and cardiovascular disease is a new area of exploration. Due to a lack of prior research investigating the potential link between CAD and the risk of herpes zoster, there is insufficient evidence regarding whether patients with CAD are at increased risk for developing herpes zoster. Therefore, the findings of our cohort study provide valuable insights into this noteworthy association. The intricate interactions between chronic cardiovascular conditions and infectious diseases have been a topic of increasing interest. Our cohort study addresses a notable gap in understanding these potential relationships. It indicates that cardiovascular diseases may influence the susceptibility to certain infectious conditions.

The biological plausibility of the relation between CAD and herpes zoster is not the scope of our study. Our review of the literature suggests that several mechanisms could underlie this association. Chronic inflammation, a hallmark of CAD, may compromise immune function, rendering individuals more susceptible to the reactivation of latent infections such as the varicella-zoster virus [20, 21]. Additionally, age-related changes in immune function, endothelial dysfunction, psychosocial stress, and certain comorbidities (eg, diabetes mellitus and hypertension) may contribute to the observed association [3–8].

The strengths of our study include a well-defined cohort design and good methodology, which help to improve the internal validity of the results. However, some limitations should be acknowledged. First, although some confounding variables were included for adjustment, the potential influence of unmeasured variables could not be entirely ruled out. Second, due to the inherent limitations of observational research, our cohort study is unable to definitively prove causation. That is, it is unclear whether CAD leads to herpes zoster or vice versa. Based on the findings reported by our group and others, it is plausible that there could be a bidirectional relationship contributing to both conditions. Third, using *ICD-9* codes has limitations for diagnosing CAD, comorbidities, and herpes zoster, such as potential inaccuracies and the lack of chart review validation. As a result, these codes may sometimes be incorrectly entered or omitted, and the dates recorded for diagnoses may not

accurately reflect the actual timing of when the conditions were identified. Fourth, herpes zoster vaccine is not fully covered by the National Health Insurance Program in Taiwan. If people choose to get herpes zoster vaccine, they pay for the vaccine and any associated administration fees at their own expense. Therefore, vaccinations may not be automatically recorded in systems for insurance claims in Taiwan. The present study did not account for whether people had been vaccinated for herpes zoster as a variable in the analysis. It does likely pose challenges in distinguishing those who have been vaccinated from those who have not. Fifth, the generalizability of our findings to different ethnic groups needs to be considered. Future research should aim to investigate both sides of the association, considering the bidirectional impact of cardiovascular health on herpes zoster and vice versa. Sixth, the non-CAD group was set to start in 2006. If no event occurred, the observation period would be nearly 10 years (until 2015), resulting in a longer follow-up duration of 9.7 years. However, the CAD group was continuously enrolled during the study period (2006–2015), resulting in an average follow-up duration of 5.3 years. For the CAD group, there might be an impact of right censoring due to the shorter follow-up period. This could result in more right-censored data, meaning individuals who did not experience the event before the study ended, as their complete data (up to the point of experiencing the event) are not available within the study period. Right censoring can lead to an underestimation of the true risk of developing herpes zoster because the study does not capture the entire risk period for individuals in the CAD group. Despite this potential underestimation of risk due to right censoring, the study results still showed a higher HR for the CAD group. This finding suggests that there is indeed a significant association between CAD and an increased risk of developing herpes zoster. Seventh, even if patients presented with herpes zoster at another hospital, the diagnosis of herpes zoster was still recorded in the claims data of the National Health Insurance Program in Taiwan. Therefore, the possibility of loss to follow-up due to missed diagnoses can be minimized.

CONCLUSIONS

This cohort study provides compelling evidence that individuals diagnosed with CAD are at an increased risk of developing herpes zoster when compared with those without CAD. Clinicians should be aware of the increased likelihood of herpes zoster and should consider preventive measures such as vaccination in populations with CAD.

Notes

Author contributions. S.-W. L. contributed to the conception of the article, initiated the draft of the article, and approved the final draft. Y.-H. K. and K.-F. L. conducted data analysis.

Patient consent statement. Patient identification numbers had been scrambled to ensure confidentiality. Patient informed consent was not needed. All methods were performed in accordance with relevant guidelines and regulations. Insurance reimbursement claims data used in the study were available for public access. Ethical approval was not needed.

Potential conflicts of interest. All authors: No reported conflicts.

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