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Epidemiology and risk factors of coronary artery aneurysm in Taiwan

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Abstract

Objectives: Coronary artery aneurysm (CAA) was a usually asymptomatic and rare diseases. There is limited epidemiological data of CAA in Asian or world.

Design: A retrospective case-cohort study

Setting: A population-based database study from the Taiwan's National Health Insurance Research Database, included participants between 2005 and 2013.

Participants: CAA patients by using diagnostic code (ICD: 414.11) with CAA examinations.

Outcome measures: The incidence and mortality of CAA were calculated. Furthermore, we also conducted matching non-CAA patients according to age, gender, index year at a 1:10 ratio to explore risk factors for CAA by logistic regression.

Result: A total of 1397 CAA patients were identified during 2005 to 2011. The average annual incidence and mortality of CAA in Taiwan were 0.87 and 0.05 per 100,000 population. Otherwise, the adjusted odds ratios (aOR) for coronary atherosclerosis, hypertension, dyslipidemia and diabetes were 7.97, 2.09, 2.48 and 1.51, respectively. Of note, aortic dissection (aOR: 6.76), aortic aneurysm (aOR: 5.82) and systemic lupus erythematosus (aOR: 4.09) were found significantly associated with CAA.

Conclusion: Epidemiology of CAA in Taiwan was low. Aside from cardiovascular risk factors, aortic diseases and systemic lupus erythematosus need to be further investigated in CAA patients.

Strengths and limitations of this study

1. In this nationwide epidemiology study involving retrospective analysis of a claims database, we evaluated the epidemiology and risk factors for CAA in Asian country.
2. The major limitation of the study was no laboratory data on coronary angiography data and lifestyle habits of the patients.
3. As a retrospective observational analysis, this study only provides associative information from case-control study.

Introduction

Coronary artery aneurysm (CAA) is a rare finding in patients referred for coronary angiography. It is characterized by abnormal dilatation of the vessel lumen defined as a lumen with diameter that exceeds more than 1.5-fold the diameter of the normal vessel lumens adjacent to it or as the largest coronary vessel lumen.[1] Previous case series on angiography have reported a wide range of prevalence from 0.2% to 6.0.[1-4] Two other case series in Taiwan indicated that 0.25%–2.6% of patients had CAA.[5, 6] Although CAA commonly coexists with atherosclerosis,[1, 7] various potential causes such as congenital, inflammatory and connective tissue disorders, and other factors have been noted in the literature.[8, 9] Among these risk factors, Kawasaki disease is well recognized as the main cause in children; it occurs predominantly in Asian countries.[10, 11] The pathogenesis of CAA is postulated to be the degradation of the extracellular matrix of the media by matrix metalloproteinases and is considered to be similar to that of other aneurysms in larger vessels.[12, 13] Instead of presenting as a benign entity, CAA shows the clinical manifestations of coronary artery diseases such as angina and acute coronary syndrome.[14-16] At present, information regarding CAA and its related risk factors is lacking in Asian countries. Accordingly, our aim was to investigate the epidemiology and risk factors for CAA in a Taiwanese population.

Methods

Data sources

We obtained specific dataset of all CAA patients in Taiwan from the NHIRD. All medical records comprising outpatient care, inpatient care, emergency care, and prescriptions from 2004 to 2012 were used for analysis in the epidemiologic study.

For the case-control study, we selected controls from the Longitudinal Health Insurance Database (LHID2005), which contained one million samples that were randomly selected from the NHIRD and were representative of 23 million people in Taiwan. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20130199). Current NHIRD and hospital regulations and guidelines did not mandate informed consent in this retrospective case-control study. All procedures performed were in accordance with the ethical standards of the institutional research committee and the directives of the Declaration of Helsinki.

Study population

To identify patients diagnosed with CAA, we used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 414.11. Patients who had two outpatient diagnoses or one inpatient diagnosis of CAA between January 1, 2005 and December 31, 2011were identified. The index date was defined as the date of first diagnosis of

CAA. Patients who were diagnosed with CAA based on imaging studies, including coronary angiography, echocardiography, computed tomography, magnetic resonance imaging, and cardiac catheterization, within 90 days (3 months) before or after the index date were enrolled.

In the case-control study, cases included adult subjects who were hospitalized with a diagnosis of CAA between January 1, 2005 and December 31, 2011. Patients younger than 20 years and those who were diagnosed with CAA in the outpatient clinic were excluded. In the case group, the first hospitalization date for CAA was assigned as the index date. For the control selection, 10 patients were randomly selected for each case by matching age, sex, and index year of case diagnosis. The first admission date within the same year of CAA diagnosis was assigned as the index date for the control group.

Survival status

According to the validation by Cheng et al. of in-hospital mortality in the NHIRD,[17] we defined death as "4" or "A" status record upon discharge and "disenrollment" insurance status in the Registry for Beneficiaries. On the other hand, patients admitted because of an emergent reason, but without follow-up data were considered as death, which was also confirmed by checking the insurance status.

Covariates

In the epidemiologic study, we analyzed the age and sex, characteristics of subjects with

respect to geographical region, urbanization, and monthly insurance premiums in New Taiwan Dollars. In the case–control study, covariates for analysis included demographics and related risk factors.[8, 18-23] A period of one year before the index date was reserved for covariate evaluation in both groups.

Statistical analysis

Incidence, which was presented as number per 100,000, was defined as the number of patients with a newly-diagnosed CAA divided by the total Taiwanese population in each year. Mortality, which was presented as number per 100,000, was defined as the number of patients who died divided by the total Taiwanese population in each year. For trend analysis, the Cochran–Armitage test was used to detect any significant change in incidence or mortality during the study period. The demographic data of total population in Taiwan were obtained from the Statistics, Department of Household Registration, Ministry of the Interior[24].For descriptive statistics, continuous variables were presented as mean ± SD; categorical variables were presented as number and proportion (%).

The odds ratio and 95% confidence interval (95% CI) for the CAA were estimated by conditional logistic regression analysis for matched pairs data and were adjusted for the study covariates. The results were expressed as three models adjusted for different variables: Model 1, demographics and traditional cardiovascular diseases, except diabetes; Model 2,

demographics, diabetes and other risk factors; and Model 3, all variables mentioned above. Spearman's correlation coefficient was used to detect collinearity among variables. Data processing and statistical analysis were performed with SAS version 9.4 (SAS Inc., Cary, NC).

Results

Epidemiologic study population

From 2005 to 2011, there were 1493 patients who had at least two CAA diagnoses at an outpatient setting or one CAA diagnosis at an inpatient setting. After excluding 96 subjects who did not have any record of related examinations, a total of 1397 patients with CAA diagnosis were enrolled in our study (**Figure 1**). Among the 1397 patients, mean age was 37.76 ± 31.45years. There were 586 pediatric patients (age <20 years), 430 adults (age≥20 to<65 years), and 381 elderly patients (age ≥65 years), accounting for 41.9%, 30.8%, and 27.3% of the CAA population, respectively (**Table 1**). **Figure 2** shows the detailed age distribution, where in majority of pediatric patients were<5 years of age; in particular, patients who were ≤1 year old comprised 229 patients (23.2%). Furthermore, a male predilection (68.5%) was found, with a male to female ratio of 2.18. Most of the patients with CAA lived in northern Taiwan (39.1%), followed by central (37.1%), southern (22.0%), and

Table 1. Baseline characteristics of CAA population

Variable (N=1397)	Number (%)
Age, year (mean ± SD)	37.76 ± 31.45
Age group (year)	
< 20	586 (41.9)
20-64	430 (30.8)
≥ 65	381 (27.3)
Gender	
Male	957 (68.5)
Female	440 (31.5)
Area	
North	546 (39.1)
Central	518 (37.1)
South	307 (22.0)
East	26 (1.9)
Urbanization	
Urbanized	1019 (72.9)
Rural	378 (27.1)
Monthly Insurance Premiums (NTD)	
<20000	1030 (73.7)
20000-39999	273 (19.5)
≥40000	94 (6.7)

NTD, New Taiwan Dollars.

eastern (1.9%) areas; as high as 72.9% of the patients resided in urban areas. A majority (73.7%) of the patients had a monthly insurance premium of less than 20,000 NTD, which could be attributed to the predominance of young patients in this population.

Incidence and mortality

The average annual incidence of CAA from 2005 to 2011 in Taiwan was 0.87 per 100,000 population. About 200 patients were diagnosed with CAA every year. As shown in **Figure 3**, there was no significant difference in incidence from 2005 to 2011 in the trend test (p=0.2653).

The mortality of the CAA population was low at an average of 0.05 per 100,000 population every year; however, it increased slightly from 0.03 per 100,000 population in 2005 to 0.07 per 100,000 population in 2011 (p=0.0018; **Figure 3**). A total of 80 cases (17 adults and 63 elderly) died during the study period. No case in the pediatric group died; therefore, it may have attenuated the overall mortality. Specifically, the mortality rate in adults was 9.9% at a mean follow-up period of 43.3 ± 25.8 months.

Case-control study population

The selection process of subjects between case and control groups has been shown in **Figure 1**. Of 1397 patients identified in the previous epidemiologic study, we finally enrolled 719 adult patients with a hospitalized diagnosis of CAA as case groups. After matching by age,

sex, and index year, there were7190 subjects in the control group, yielding an overall population of 7909 subjects in the case-control study.

Overall, the age and sex distributions were well matched in the case and control groups (**Table 2**). The mean age of the case group was 62.57 ± 13.91 years and 67.9% were male, which was similar to the control group. There was no significant difference in the urbanization level and monthly insurance premiums. Most of the patients lived in an urban area and had a low monthly insurance premium of less than 40,000 New Taiwan Dollars.

Risk factors associated with CAA

In the logistic regression analysis, the association between traditional cardiovascular risk factors and the presence of CAA was higher than with the general population(**Table 2**). The adjusted odds ratio (aOR) for coronary atherosclerosis (aOR: 7.97; 95% CI: 6.46–9.84), hypertension (aOR: 2.09; 95% CI: 1.73–2.53) and dyslipidemia (aOR: 2.48; 95% CI: 2.06–2.99) were greater than two-fold in Model 1. By multivariate analysis in Model 2, we found that diabetes mellitus (aOR: 1.51; 95% CI: 1.26–1.81), aortic dissection (aOR: 6.76; 95% CI: 1.89–24.14), aortic aneurysm (aOR: 5.82; 95% CI: 2.02–16.83)and systemic lupus erythematosus (aOR: 4.09; 95% CI: 1.32–12.62)were significantly associated with the presence of CAA. After adjusting all variables in Model 3, a reverse association between

Table 2. Odds ratio for risk factors associated with coronary artery aneurysm

Variables	CAA (n=719)	Control (n=7190)	Crude OR	Model 1 [a] Adjusted OR	Model 2 [b] Adjusted OR	Model 3 [c] Adjusted OR
Demographics[#]						
Age	62.57 (13.91)	62.57 (13.92)	-	-	-	-
Male sex	488 (67.9)	4880 (67.9)	-	-	-	-
Urbanization (urbanized vs. rural)	635 (88.3)	6441 (89.6)	1.04 (0.87-1.24)	0.95 (0.79-1.15)	1.02 (0.85-1.22)	0.95 (0.78-1.15)
Insurance premiums (high vs. low)	84 (11.7)	749 (10.4)	1.15 (0.90-1.47)	0.93 (0.70-1.23)	1.14 (0.89-1.46)	0.92 (0.69-1.21)
Risk factors						
Coronary atherosclerosis	244 (33.9)	354 (4.9)	10.82 (8.85-13.24)*	7.97 (6.46-9.84)*		8.00 (6.47-9.90)*
Hypertension	459 (63.8)	2836 (39.4)	3.19 (2.68-3.80)*	2.09 (1.73-2.53)*		2.12 (1.75-2.58)*
Dyslipidemia	289 (40.2)	1126 (15.7)	3.77 (3.19-4.45)*	2.48 (2.06-2.99)*		2.60 (2.15-3.14)*
Diabetes mellitus	188 (26.1)	1457 (20.3)	1.51 (1.26-1.80)*		1.51 (1.26-1.81)*	0.82 (0.67-1.00)
Cerebrovascular disease	74 (10.3)	710 (9.9)	1.05 (0.81-1.36)		1.02 (0.78-1.32)	0.90 (0.68-1.20)
Peripheral vascular disease	4 (0.6)	59 (0.8)	0.68 (0.25-1.87)		0.66 (0.24-1.82)	0.47 (0.15-1.44)
Varicose vein	2 (0.3)	47 (0.7)	0.43 (0.10-1.75)		0.46 (0.11-1.91)	0.41 (0.09-1.90)
Aortic dissection	4 (0.6)	6 (0.1)	6.67 (1.88-23.62)*		6.76 (1.89-24.14)*	3.78 (0.77-18.49)
Aortic aneurysm	6 (0.8)	9 (0.1)	6.67 (2.37-18.73)*		5.82 (2.02-16.83)*	3.96 (1.19-13.20)*
Systemic lupus erythematosus	5 (0.7)	10 (0.1)	5.00 (1.71-14.63)*		4.09 (1.32-12.62)*	3.26 (0.94-11.28)
Rheumatoid arthritis	9 (1.3)	48 (0.7)	1.89 (0.92-3.86)		1.80 (0.87-3.73)	1.40 (0.60-3.25)
Inflammatory bowel disease	1 (0.1)	31 (0.4)	0.32 (0.04-2.36)		0.35 (0.05-2.54)	0.49 (0.07-3.67)

* $P < 0.05$; [#] Age and gender for matching were not analyzed in models. OR, odds ratio; Different covariates were analyzed in three models: [a] demographics plus traditional cardiovascular diseases except diabetes; [b] demographics plus diabetes and other risk factors; [c] all covariates mentioned above.

diabetes mellitus and CAA was found. For the discrepancy, we found a moderate collinearity between diabetes mellitus and cardiovascular risk factors (Supplementary **eTable 1** online); therefore, the results in Model 2 may be more reasonable to interpret and explain.

Other vascular diseases, such as cerebrovascular disease, peripheral vascular disease and varicosities, were not statistically significant risk factors for CAA. Similarly, rheumatoid arthritis and inflammatory bowel disease failed to show significant differences between the two groups.

Discussion

The average annual incidence of CAA from 2005 to 2011 in Taiwan was 0.87 per 100,000 population, with around 200 new cases every year. There was no increasing trend in the incidence of CAA during this period.

Based on case series on angiography, the incidence of CAA ranged from 0.2%to 6.0%,[2, 4] and was higher at 3.0% to 9.4%[25, 26] when diagnosed by computed tomography coronary angiography. Two reported case series in Taiwan on 10120 and 924 patients[5, 6] accounted for a prevalence of 0.2% and 2.6%, respectively. Despite the low incidence of CAA in our study, it may be incomparable with that of previous reports owing to different sources of the sample population; we retrieved the CAA population from the NHIRD, whereas other studies derived their data from angiography case series.

It is believed that CAA to be detected more frequently with the advent of advanced

imaging studies and as interventional management of coronary artery disease become more common.[27] Nonetheless, a series in northern Greece[3] showed that the prevalence of coronary artery ectasia remained unchanged during the study period from 1995 to 2003, which was in consistent with our results. A possible explanation for the low incidence of CAA in our study and other literature may be the fact that CAA is usually asymptomatic until the size becomes large enough to induce complications; only patients with ischemic symptoms and admitted for further examinations will be diagnosed.

The average annual mortality rate of patients with CAA in our study was 0.05 per 100,000 population. Based on our results, all cases of death occurred in patients >20 years; therefore, mortality may have been attenuated by the pediatric population. However, if we focused on the adult population, an overall mortality rate of 9.9% at a mean follow-up of 43.3 ± 25.8 months was noted.

The mortality of patients with CAA varies widely among different studies. The 5-year mortality reached as high as 29% in the United States, based on a case series by Baman et al.[20] Similarly, the Coronary Artery Surgery Study[1] found that patients with CAA as well as a coexistent coronary stenosis had a 26% mortality at five years. In contrast, other countries have a lower mortality rate ranging from1.4% to 10.7%.[6, 28-33] This discrepancy may be owing to a more severe obstructive coronary artery disease and longer follow-up time in the two studies. On the other hand, a small case series comprising 24 patients with CAA in

Taiwan[6] reported a mortality rate of 9.1%, which was similar to the results of our study despite a younger population and shorter follow-up time.

In contrast to previous angiography case series in adults, the present study had access to information on both pediatric and adult patients with CAA. The mean age of the pediatric population was 3.16 ± 3.66 years. Up to 95.7% of children were diagnosed with Kawasaki disease. Similar to other epidemiologic reports in Taiwan,[11, 34, 35] our results showed that most patients with Kawasaki disease were under 5 years of age; infants ≤1 year of age comprised the majority of this population. Kawasaki disease is a systemic vasculitis that commonly involves the coronary arteries and is considered the main cause of nonatherosclerotic coronary artery aneurysm in young children.[23, 36] From our results, the disease burden of Kawasaki disease in Taiwan and its risk for developing CAA cannot be overlooked. For young patients who present with an ischemic heart syndrome, such as angina and myocardial infarction, CAA should be considered and treatment should be started as soon as possible.

In the multivariate analysis, traditional cardiovascular risk factors, including coronary atherosclerosis, hypertension, dyslipidemia and diabetes, were independently associated with CAA.

Coronary atherosclerosis is a well-established risk factor for CAA in literature.[1, 8, 20, 36, 37] For Asian countries, a small series containing 24 CAA patients in Taiwan reported over 60% patients had multivessel disease.[6] In China, another two series showed a even higher proportion

of coronary artery disease in patients with CAA.[26, 38] There are various etiologies of CAA being extensively discussed, among which atherosclerosis remains the most common factor and accounts for over 50% of acquired CAA in adults.[1, 8, 23, 36] It has been hypothesized that atherosclerosis is linked to aneurysm formation through a process of inflammation extending into the tunica media from the tunica intima, which eventually causes degeneration of the cystic medial.[23, 39] For mechanic factors, the blood flow through the stenotic area in atherosclerotic vessels may cause turbulent and reversed flow, which can induce endothelial damage and increase wall stress and subsequently result in post-stenotic dilatation.[9, 40]

Some studies have reported that hypertension was more common in patients with CAA,[21, 26, 41, 42] whereas no significant difference was found in other series.[20, 22, 28, 37, 41, 43] Only one study showed a lower frequency of hypertension in patients with CAA.[6] Nichols et al[23] indicated that hypertension was related to aortic and cerebral artery aneurysms; therefore an association between hypertension and CAA may be expected. However, they drew a conclusion that there was no significant association between hypertension and CAA after reviewing the literature. On the other hand, Markis et al[44] suggested that hypertension may play a role in the development of CAA, perhaps through accelerating the process of media destruction. Another viewpoint from Yip et al,[6] they proposed that the formation of CAA may be explained by the law of LaPlace, in which the wall stress is in direct proportion to intramural pressure. In the hypertensive state, intramural pressure against the vessel wall leads

to dilatation of the coronary arteries.

Similarly, there were some studies showing that dyslipidemia was more prevalent in patients with CAA,[6, 20, 26, 41] in contrast to other reports.[18, 22, 28, 37, 43, 45, 46] Evidence indicates dyslipidemia is a major contributor to atherosclerosis, which is characterized by the deposition of lipids and fibrous elements in the arteries and further formation of the atheroma.[39] In view of atherosclerosis, it may be reasonable that our study showed a positive association between dyslipidemia and the presence of CAA.

It is noteworthy that an inverse association between diabetes and the presence of CAA had been reported in several studies,[18, 20, 21, 28, 46] but not in others.[31, 33, 40, 47, 48] A previous meta-analysis[49] indicated diabetes as a protective factor for the occurrence of CAA, with a pooled OR of 0.65 (95% CI, 0.54–0.77). For positive association, it was reported that hyperglycemia can trigger arterial inflammation and increase the risk of atherosclerosis,[39] which is a risk factor for CAA. Nonetheless, debate on whether CAA is a variant of atherosclerosis still exists.[50] Conversely, some authors proposed that the protective effect of diabetes may be from negative arterial remodeling[46] and increased matrix volume[49] of the coronary arteries.

As a whole, the association between diabetes and CAA is currently not well-defined. We deduce that the conflicting results may have arisen from the different selection criteria for the control group and the small sample size in some series. Most of the studies selected controls

from a cohort undergoing coronary angiography, whereas ours derived their subjects from the general population. The burden of cardiovascular disease on the controls may be more severe in the other series than in ours.

In the current study, we also found a significantly positive association between aortic dissection, aortic aneurysm, and systemic lupus erythematosus and the presence of CAA.

Aortic aneurysms have been reported to be prevalent in patients with CAA,[26, 42, 51] and patients with aortic aneurysms also had a higher frequency of CAA.[52-54] It had been speculated that CAA and aortic aneurysms share a similar histology and pathogenic process, which is generalized impairment of the wall of the entire arterial system.[51, 55] The matrix metalloproteinases, a group of enzymes with the capacity to degrade various components of the extracellular matrix in the arterial wall, have been found with elevated levels both in patients with CAA[56] and patients with aortic aneurysms.[57] This finding implicated that aortic and coronary aneurysms may develop through the similar process of increased destruction of extracellular matrix.

With respect to systemic lupus erythematosus, an increasing number of case reports have indicated its relationship with CAA in recent years.[58-63] In addition, systemic lupus erythematosus was found to be associated with aortic aneurysms.[64, 65] Systemic lupus erythematosus is a chronic inflammatory disease and associated with cardiac manifestations, such as pericarditis, myocarditis, valvular disease and coronary artery disease.[66] It was

suggested that CAA resulted from severe coronary inflammation through the deposition of immune globulin and complement.[67] At other aspects, systemic lupus erythematosus was thought to induce accelerated atherosclerosis, which was a risk factor for aneurysms.[68] Although there were reports suggesting the relationship between systemic lupus erythematosus and development of CAA, the exact pathogenesis remains poorly understood.

To the best of our knowledge, this was the first population-based study investigating the epidemiology and risk factors for CAA in Taiwan. Using a specific NHIRD dataset on all patients with CAA, we were able to provide an explicit age distribution, including both pediatric and adult populations. This was unavailable in angiographic series enrolling mainly adult subjects. Furthermore, we analyzed potential risk factors for CAA by performing a case–control study through multivariate analysis, which may disclose certain rare risk factors associated with CAA.

However, there were some limitations in the current study. First, we were unable to estimate the prevalence because not all patients in the epidemiologic study were available for follow-up. Second, our data were obtained from a claim-based database, which did not include information on aneurysm features, such as size, shape, location, number of aneurysms, and degree of stenosis. In addition, we could not differentiate between aneurysm and ectasia in this study. Third, the control group selected from the general population may have had less opportunity to undergo examinations to detect atherosclerosis and aortic aneurysm. For this

reason, the control group may have had fewer related events than the case group. Finally, cardiovascular risk factors of smoking and obesity were unavailable from our database.

In conclusion, the incidence of CAA in Taiwan was low and did not increase from 2005 to 2011. Kawasaki disease was predominant in children with CAA. Aside from the cardiovascular diseases, factors such as aortic disease and systemic lupus erythematosus, may predispose adults to develop CAA.

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Author contributions

Chein-Tang Fang, Yaw-Bin Huang, and Chung-Yu Chen designed the data collection instruments, conceptualized and designed the study, drafted the initial manuscript and approved the final manuscript as submitted. Chein-Tang Fang, Yi-Ping Fang and Chung-Yu Chen carried out the initial analyses, critically reviewed the manuscript, and all authors approved the final manuscript as submitted.

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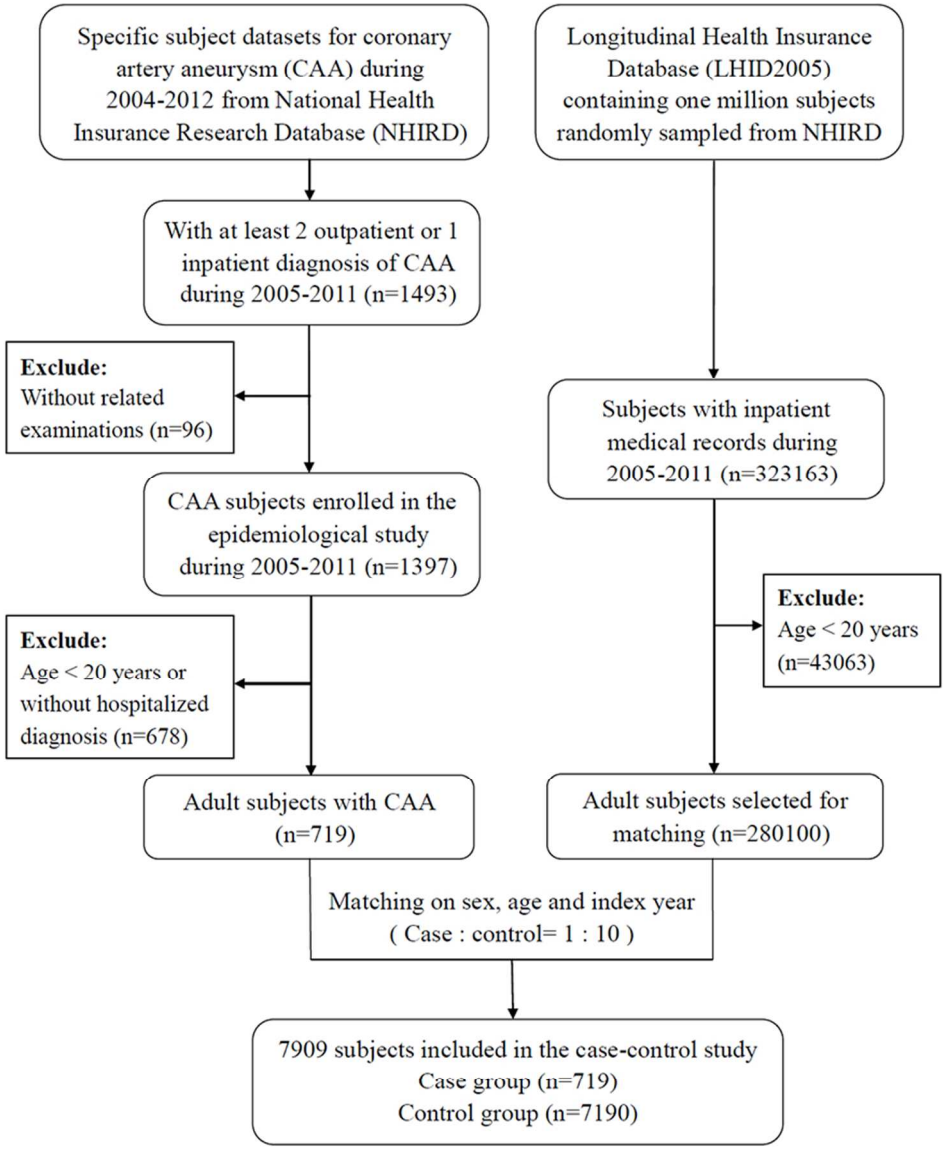
Figure Legends

Figure 1.Flow chart of the study population.

Figure 2.Age distribution of the CAA population

Figure 3. (a) Incidence of CAA population during 2005-2011.(b) Mortality of CAA population during 2005-2011



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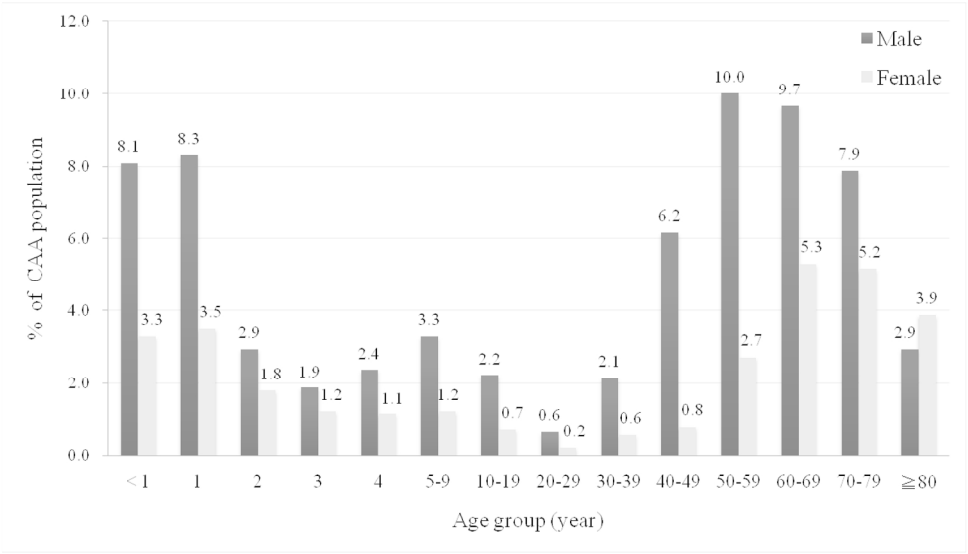

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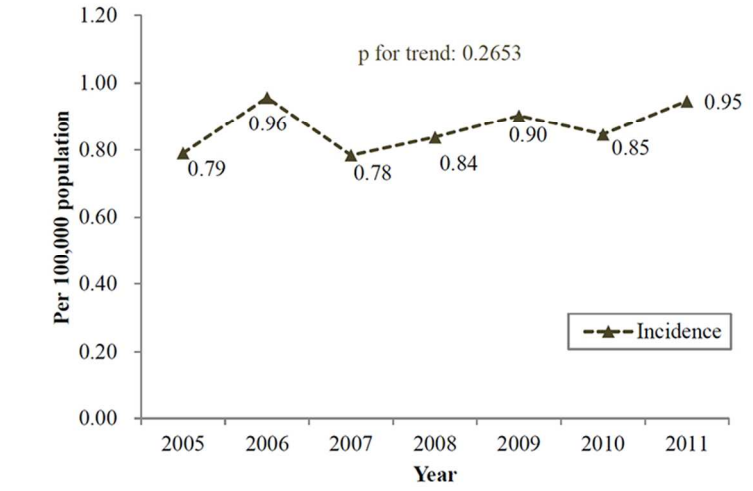
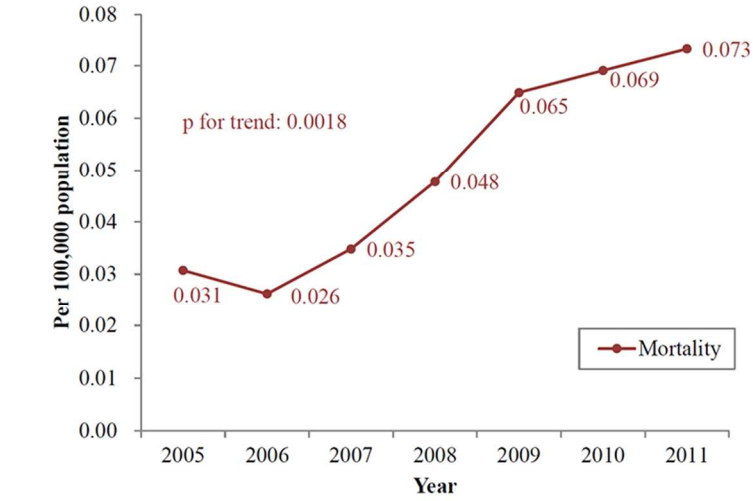


(a)



(b)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	10-13
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	110
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Epidemiology and risk factors of coronary artery aneurysm in Taiwan: A population-based case-control study

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Abstract

Objectives: Coronary artery aneurysm (CAA) was a usually asymptomatic and rare disease. There is limited epidemiological data of CAA in Asian or world.

Design: A retrospective case-control study.

Setting: A population-based database study from the Taiwan's National Health Insurance Research Database, included participants between 2005 and 2011.

Participants: CAA patients by using ICD-9-CM code: 414.11 with CAA examinations.

Outcome measures: The incidence rate and mortality rate of CAA were calculated. Furthermore, we also conducted matching non-CAA patients according to age, gender, index year at a 1:10 ratio to explore risk factors for CAA by conditional logistic regression.

Result: A total of 1397 CAA patients were identified during 2005 to 2011, including 41.9 % pediatrics and 58.1% adults. The incidence rate and mortality rate of CAA in Taiwan were 0.87 and 0.05 per 10^5 person-years. The adjusted odds ratios (aOR) for coronary atherosclerosis, hypertension, dyslipidemia and diabetes were 7.97, 2.09, 2.48 and 1.51, respectively. Of note, aortic dissection (aOR: 6.76), aortic aneurysm (aOR: 5.82) and systemic lupus erythematosus (aOR: 4.09) were found significantly associated with CAA.

Conclusion: In Taiwan, CAA patients were distributed both in pediatric and adult population. Aside from cardiovascular risk factors, aortic diseases and systemic lupus erythematosus need to be further investigated in CAA patients.

Strengths and limitations of this study

1. In this nationwide epidemiology study involving retrospective analysis of a claims database, we evaluated the epidemiology and risk factors for CAA in Asian country.
2. The major limitation of the study was no laboratory data on coronary angiography data and lifestyle habits of the patients.
3. As a retrospective observational analysis, this study only provides associative information from case-control study.

Introduction

Coronary artery aneurysm (CAA) is a rare finding in patients referred for coronary angiography. It is characterized by abnormal dilatation of the vessel lumen defined as a lumen with diameter that exceeds more than 1.5-fold the diameter of the normal vessel lumens adjacent to it or as the largest coronary vessel lumen.[1] Previous case series on angiography have reported a wide range of prevalence from 0.2% to 6.0% in the wrold.[1-4] In Taiwan, Wang et al. reported 25 patients had CAA (0.25%) in 10120 patient cohort. [5] Furthermore, one case series indicated that there were 24 patients (2.6%) had aneurysmal dilatation in 924 AMI patients undergoing PCI from 1993 to 2001.[6]

Although CAA commonly coexists with atherosclerosis,[1, 7] various potential causes such as congenital, inflammatory and connective tissue disorders, and other factors have been noted in the literature.[8, 9] Among these risk factors, Kawasaki disease is well recognized as the main cause in children; it occurs predominantly in Asian countries.[10, 11] The pathogenesis of CAA is postulated to be the degradation of the extracellular matrix of the media by matrix metalloproteinases and is considered to be similar to that of other aneurysms in larger vessels.[12, 13] Instead of presenting as a benign entity, CAA shows the clinical manifestations of coronary artery diseases such as angina and acute coronary syndrome.[14-16]

Despite Kawasaki disease is a significant risk factor for the development of CAA, especially for children, information regarding CAA and its related risk factors in adult population is limited in Asian countries. Accordingly, our aim was to investigate the

epidemiology and risk factors for CAA in a Taiwanese population.

Methods

Data sources

We obtained specific dataset of all CAA patients from Taiwan's National Health Insurance Research Database (NHIRD). All medical records comprising outpatient care, inpatient care, emergency care, and prescriptions from 2005 to 2011 were used for analysis in the epidemiologic study.

For the case-control study, we selected controls from the Longitudinal Health Insurance Database (LHID2005), which contained one million samples that were randomly selected from the NHIRD and were representative of 23 million people in Taiwan. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20130199). NHIRD data were de-identified by scrambling the identification codes of both patients and medical facilities, and released to the public for research purposes. Therefore, current NHIRD and hospital regulations and guidelines did not mandate informed consent in this retrospective case-control study due to we used anonymous nature of the database. All procedures performed were in accordance with the ethical standards of the institutional research committee and the directives of the Declaration of Helsinki.

Study population

To identify patients diagnosed with CAA, we used the International Classification of

Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 414.11. Patients who had two outpatient diagnoses or one inpatient diagnosis of CAA between January 1, 2005 and December 31, 2011 were identified. The index date was defined as the date of first diagnosis of CAA. Patients who were diagnosed with CAA based on imaging studies, including coronary angiography, echocardiography, computed tomography, magnetic resonance imaging and cardiac catheterization, within 90 days (3 months) before or after the index date were enrolled.

In the case-control study, cases included adult subjects who were hospitalized with a diagnosis of CAA between January 1, 2005 and December 31, 2011. Patients younger than 20 years and those who were diagnosed with CAA in the outpatient clinic were excluded. In the case group, the first hospitalization date for CAA was assigned as the index date. For the control selection, 10 patients were randomly selected for each case by matching age, sex, and index year of case diagnosis. The first admission date within the same year of CAA diagnosis was assigned as the index date for the control group.

Survival status

According to the validation by Cheng et al. of in-hospital mortality in the NHIRD,[17] we defined death as "4" or "A" status record upon discharge and "disenrollment" insurance status in the Registry for Beneficiaries. On the other hand, patients admitted because of an emergent reason, but without follow-up data were considered as death, which was also confirmed by checking the insurance status.

Covariates

In the epidemiologic study, we analyzed the age and sex, characteristics of subjects with respect to geographical region, urbanization, and income group at baseline. Income group was defined by the individual average monthly income during a year period before index date and classified as low (< NTD$20,000 or < US$625) and high (≥ NT$20,000 or ≥ US$625). In the case–control study, covariates for analysis included demographics and related risk factors. On the basis of previous evidences, related risk factors included coronary atherosclerosis,[8, 18, 19] hypertension,[18-21] dyslipidemia,[19-21] diabetes mellitus,[19-22] cerebrovascular disease,[8] peripheral vascular disease,[8] varicose vein,[18, 23] aortic dissection,[24] aortic aneurysm (AA),[24, 25] systemic lupus erythematosus (SLE),[8] rheumatoid arthritis,[8] inflammatory bowel disease.[8] Furthermore, we defined atherosclerosis, hypertension, and hyperlipidemia as traditional cardiovascular risk factors.[20, 21] A period of one year before the index date was reserved for covariate evaluation in both groups.

Statistical analysis

Incidence rate, which was presented as number per 10^5 person-years, was defined as the number of patients with a newly-diagnosed CAA divided by the total Taiwanese population in each year. Mortality rate, which was presented as number per 10^5 person-years, was defined as the number of patients who died divided by the total Taiwanese population in each year. For trend analysis, the Cochran–Armitage test was used to detect any significant change in

incidence rate or mortality rate during the study period. The demographic data of total population in Taiwan were obtained from the Statistics, Department of Household Registration, Ministry of the Interior[26]. For descriptive statistics, continuous variables were presented as mean ± SD; categorical variables were presented as frequency and proportion (%).

The odds ratio and 95% confidence interval (95% CI) for the CAA were estimated by conditional logistic regression analysis for matched pair's data and were adjusted for the study covariates. The results were expressed as three models adjusted for different variables: Model 1, demographics and traditional cardiovascular risk factors; Model 2, demographics and related risk factors, excluding traditional cardiovascular risk factors; and Model 3, demographics and related risk factors. Spearman's correlation coefficient was used to detect collinearity among variables. Data processing and statistical analysis were performed with SAS version 9.4 (SAS Inc., Cary, NC).

Results

Epidemiologic study population

From 2005 to 2011, there were 1493 patients who had at least two CAA diagnoses at an outpatient setting or one CAA diagnosis at an inpatient setting. After excluding 96 subjects who did not have any record of related examinations, a total of 1397 patients with CAA diagnosis were enrolled in our study (**Figure 1**). Among the 1397 patients, mean age was 37.76 ± 31.45 years. There were 586 pediatric patients (age <20 years), 430 adults (age≥20 to <65

years), and 381 elderly patients (age ≥65 years), accounting for 41.9%, 30.8%, and 27.3% of the CAA population, respectively (**Table 1**). **Figure 2** shows the detailed age distribution, where in majority of pediatric patients were < 5 years of age; in particular, patients who were ≤ 1 year of age comprised 229 patients (23.2%). Furthermore, a male predilection (68.5%) was found, with a male to female ratio of 2.18. Most of the patients with CAA lived in northern Taiwan (39.1%), followed by central (37.1%), southern (22.0%), and eastern (1.9%) areas; as high as 72.9% of the patients resided in urban areas. A majority (73.7%) of the patients were low income group, which could be attributed to the predominance of young patients in this population.

Incidence rate and mortality rate

The incidence rate of CAA from 2005 to 2011 in Taiwan was 0.87 per 10^5 person-years. About 200 patients were diagnosed with CAA every year. As shown in **Figure 3**, there was no significant difference in incidence rate from 2005 to 2011 in the trend test (p=0.2653).

The mortality rate of the CAA population was 0.05 per 10^5 person-years. It increased slightly from 0.03 per 10^5 person-years in 2005 to 0.07 per 10^5 person-years in 2011 (p=0.0018; **Figure 3**). A total of 80 cases (17 adults and 63 elderly) died during the study period. No case in the pediatric group died; therefore, it may have attenuated the overall mortality. Specifically, the mortality in 811 adults were 9.9% (80 cases) at a mean follow-up period of 43.3 ± 25.8 months.

Table 1. Baseline characteristics of CAA population

Variable (N=1397)	Number (%)
Age, year (mean ± SD)	37.76 ± 31.45
Age group (year)	
< 20	586 (41.9)
20-64	430 (30.8)
≥65	381 (27.3)
Gender	
Male	957 (68.5)
Female	440 (31.5)
Area	
North	546 (39.1)
Central	518 (37.1)
South	307 (22.0)
East	26 (1.9)
Urbanization	
Urbanized	1019 (72.9)
Rural	378 (27.1)
Income group*	
Low	1030 (73.7)
High	367 (26.3)

* Income group was defined by the individual average monthly income during a year period before index date and classified as low (< NTD$20,000) and high (≥ NT$20,000).

Case-control study population

The selection process of subjects between case and control groups has been shown in **Figure 1**. Of 1397 patients identified in the previous epidemiologic study, we finally enrolled 719 adult patients with a hospitalized diagnosis of CAA as case groups. After matching by age, sex, and index year, there were 7190 subjects in the control group, yielding an overall population of 7909 subjects in the case-control study.

Overall, the age and sex distributions were well balanced between the case and control groups (**Table 2**). The mean age of the case group was 62.57 ± 13.91 years and 67.9% were male, which was similar to the control group. There was no significant difference in the urbanization level and income group. Most of the patients lived in an urban area and low group.

Risk factors associated with CAA

In conditional logistic regression analysis, association between traditional cardiovascular risk factors and the presence of CAA was higher than with the general population (**Table 2**). The adjusted odds ratio (aOR) for coronary atherosclerosis (aOR: 7.97; 95% CI: 6.46–9.84), hypertension (aOR: 2.09; 95% CI: 1.73–2.53) and dyslipidemia (aOR: 2.48; 95% CI: 2.06–2.99) were greater than two-fold in Model 1. By multivariate analysis in Model 2, we found that diabetes mellitus (aOR: 1.51; 95% CI: 1.26–1.81), aortic dissection (aOR: 6.76; 95% CI: 1.89–24.14), AA (aOR: 5.82; 95% CI: 2.02–16.83) and systemic lupus

Table 2. Odds ratio for risk factors associated with coronary artery aneurysm

Variables	CAA (n=719)	Control (n=7190)	Crude OR	Model 1 [a] Adjusted OR	Model 2 [b] Adjusted OR	Model 3 [c] Adjusted OR
Demographics[#]						
Age	62.57 (13.91)	62.57 (13.92)	-	-	-	-
Male sex	488 (67.9)	4880 (67.9)	-	-	-	-
Urbanization						
rural	191 (26.6)	1964 (27.3)	1	1	1	1
urbanized	528 (73.4)	5226 (72.7)	1.04 (0.87-1.24)	0.95 (0.79-1.15)	1.02 (0.85-1.22)	0.95 (0.78-1.15)
Income group[&]						
low	635 (88.3)	6441 (89.6)	1	1	1	1
high	84 (11.7)	749 (10.4)	1.15 (0.90-1.47)	0.93 (0.70-1.23)	1.14 (0.89-1.46)	0.92 (0.69-1.21)
Risk factors						
Coronary atherosclerosis	244 (33.9)	354 (4.9)	10.82 (8.85-13.24)*	7.97 (6.46-9.84)*		8.00 (6.47-9.90)*
Hypertension	459 (63.8)	2836 (39.4)	3.19 (2.68-3.80)*	2.09 (1.73-2.53)*		2.12 (1.75-2.58)*
Dyslipidemia	289 (40.2)	1126 (15.7)	3.77 (3.19-4.45)*	2.48 (2.06-2.99)*		2.60 (2.15-3.14)*
Diabetes mellitus	188 (26.1)	1457 (20.3)	1.51 (1.26-1.80)*		1.51 (1.26-1.81)*	0.82 (0.67-1.00)
Cerebrovascular disease	74 (10.3)	710 (9.9)	1.05 (0.81-1.36)		1.02 (0.78-1.32)	0.90 (0.68-1.20)
Peripheral vascular disease	4 (0.6)	59 (0.8)	0.68 (0.25-1.87)		0.66 (0.24-1.82)	0.47 (0.15-1.44)
Varicose vein	2 (0.3)	47 (0.7)	0.43 (0.10-1.75)		0.46 (0.11-1.91)	0.41 (0.09-1.90)
Aortic dissection	4 (0.6)	6 (0.1)	6.67 (1.88-23.62)*		6.76 (1.89-24.14)*	3.78 (0.77-18.49)
Aortic aneurysm	6 (0.8)	9 (0.1)	6.67 (2.37-18.73)*		5.82 (2.02-16.83)*	3.96 (1.19-13.20)*
Systemic lupus erythematosus	5 (0.7)	10 (0.1)	5.00 (1.71-14.63)*		4.09 (1.32-12.62)*	3.26 (0.94-11.28)
Rheumatoid arthritis	9 (1.3)	48 (0.7)	1.89 (0.92-3.86)		1.80 (0.87-3.73)	1.40 (0.60-3.25)
Inflammatory bowel disease	1 (0.1)	31 (0.4)	0.32 (0.04-2.36)		0.35 (0.05-2.54)	0.49 (0.07-3.67)

*$P < 0.05$; [#] Age and gender for matching were not analyzed in models. OR, odds ratio; Different covariates were analyzed in three models:
[a] demographics and traditional cardiovascular risk factors; [b] demographics, and related risk factors, excluding traditional cardiovascular risk factors; [c] all covariates;
[&] Income group was defined by the individual average monthly income during a year period before index date and classified as low (< NTD$20,000) and high (≥ NT$20,000).

erythematosus (aOR: 4.09; 95% CI: 1.32–12.62) were significantly associated with the presence of CAA. In Model 3, traditional cardiovascular risk factors and AA were significantly associated with the presence of CAA. For the discrepancy, we found a moderate collinearity between diabetes mellitus and traditional cardiovascular risk factors (Supplementary eTable 1 online).

Other vascular diseases, such as cerebrovascular disease, peripheral vascular disease and varicosities, were not statistically significant risk factors for CAA. Similarly, rheumatoid arthritis and inflammatory bowel disease failed to show significant differences between the two groups.

Discussion

The incidence rate of CAA from 2005 to 2011 in Taiwan was 0.87 per 10^5 person-years, with around 200 new cases every year. There was no increasing trend in the incidence rate of CAA during this period. In the United States, there were two studies on angiography reporting CAA prevalence of 0.2% (20/8422) between July 1975 and May 1979, and 4.9% (978/20087) from July 1981 to February 1987.[1-2] A report performed in Greece for coronary angiography showed CAA prevalence of 2.7% (287/10524) from 1995 to 2003.[3] The another case series conducted from 2011 to 2013 in Saudi Arabia found 1115 patients with invasive coronary angiogram had 67 (6%) coronary artery ectasia cases.[4] Furthermore, in China, coronary artery ectasia were identified in 131 of the 1400 older adults (prevalence: 9.4%) when diagnosed by computed tomography coronary angiography.[27] Two case series in Taiwan on 10120 and 924 patients accounted for a prevalence of 0.2% (25 cases) and 2.6% (24 cases), respectively.[5, 6] Comparing with other studies derived data from angiography case series, this study retrieved CAA population from the NHIRD. Therefore, lower incidence rate was found in our study may be the fact that CAA is usually asymptomatic until the size becomes large enough to induce complications; only patients with ischemic symptoms and admitted for further examinations will be diagnosed.

The mortality rate of the CAA population was 0.05 per 10^5 person-years and all cases of death occurred in patients >20 years. For 811 adult population, an overall mortality of 9.9%

(80 cases) was noted in our study. The mortality of patients with CAA varies widely among different studies. The 5-year mortality reached as high as 29% based on a case series in the United States.[19] Similarly, the Coronary Artery Surgery Study[1] found that patients with CAA as well as a coexistent coronary stenosis had a 26% mortality at five years. In contrast, other countries had a lower mortality rate ranging from 1.4% to 10.7%.[28-30] This discrepancy may be owing to a more severe obstructive coronary artery disease and longer follow-up time in the prior two studies. On the other hand, a small case series comprising 24 patients with CAA in Taiwan[6] reported a mortality rate of 9.1%, which was similar to the results of our study despite a younger population and shorter follow-up time.

In contrast to previous angiography case series in adults, the present study had access to information on both pediatric and adult patients with CAA. The mean age of the pediatric population was 3.16 ± 3.66 years. Up to 95.7% of children were diagnosed with Kawasaki disease. Similar to other epidemiologic reports in Taiwan,[11, 31, 32] our results showed that most patients with Kawasaki disease were under 5 years of age; infants ≤1 year of age comprised the majority of this population. Kawasaki disease is a systemic vasculitis that commonly involves the coronary arteries and is considered the main cause of non-atherosclerotic coronary artery aneurysm in young children.[18, 33]

In the present study, traditional cardiovascular risk factors were independently associated with CAA. Coronary atherosclerosis is a well-established risk factor for CAA in

literature.[1, 8, 18] A small series containing 24 CAA patients in Taiwan reported over 60% patients had multi-vessel disease.[6] There are various etiologies of CAA being extensively discussed, among which atherosclerosis remains the most common factor and accounts for 50% of acquired CAA in adults.[18, 33] It has been hypothesized that atherosclerosis is linked to aneurysm formation through a process of inflammation extending into the tunica media, which eventually causes degeneration of the cystic medial.[18]

Some studies have reported that hypertension was more common in patients with CAA,[20, 34] whereas no significant difference was found in other series.[19, 21] Only one study showed a lower frequency of hypertension in patients with CAA.[6] Nichols et al[18] indicated that hypertension was related to aortic and cerebral artery aneurysms; therefore an association between hypertension and CAA might be expected. In addition, Markis et al[35] suggested that hypertension may play a role in the development of CAA, perhaps through accelerating the process of media destruction. Evidence indicates dyslipidemia is a major contributor to atherosclerosis, which is characterized by the deposition of lipids and fibrous elements in the arteries and further formation of the atheroma.[36] In view of atherosclerosis, it may be reasonable that our study showed a positive association between dyslipidemia and the presence of CAA.

It is noteworthy that an inverse association between diabetes and the presence of CAA had been reported in several studies.[19, 20, 22] A previous meta-analysis[37] indicated diabetes as a

protective factor for the occurrence of CAA, with a pooled OR of 0.65 (95% CI, 0.54–0.77). For positive association, it was reported that hyperglycemia can trigger arterial inflammation and increase the risk of atherosclerosis,[36] which is a risk factor for CAA. Nonetheless, debate on whether CAA is a variant of atherosclerosis still exists.[38] Conversely, some authors proposed that the protective effect of diabetes may be from negative arterial remodeling[39] and increased matrix volume[37] of the coronary arteries. As a whole, the association between diabetes and CAA is currently not well-defined.

In our study, the results showed that there were positive association between aortic dissection, AA, and SLE and the presence of CAA. It had been speculated that CAA and AA share a similar histology and pathogenic process, which is generalized impairment of the wall of the entire arterial system.[40] The matrix metalloproteinases, a group of enzymes to degrade various components of the extracellular matrix in the arterial wall, have been found with elevated levels both in patients with CAA and those with AA.[41, 42] With respect to SLE, an increasing number of case reports have indicated its relationship with CAA in recent years.[43-46] In addition, SLE was found to be associated with AA.[47, 48] It was suggested that CAA resulted from severe coronary inflammation through the deposition of immune globulin and complement.[49,50] At other aspects, SLE was thought to induce accelerated atherosclerosis, which was a risk factor for aneurysms.[51] Although there were reports suggesting the relationship between SLE and development of CAA, the exact pathogenesis remains poorly

understood.

To the best of our knowledge, this was the first population-based study investigating the epidemiology and risk factors for CAA in Taiwan. Using a specific NHIRD dataset on all patients with CAA, which were able to provide an explicit age distribution, including both pediatric and adult populations. However, there were some limitations in the current study. First, we were unable to estimate the prevalence because not all patients in the epidemiologic study were available for follow-up. Second, our data were obtained from a claim-based database, which did not include information on aneurysm features, such as size, shape, location, number of aneurysms, degree of stenosis, and life style. In addition, we could not differentiate between aneurysm and ectasia in this study. Third, the control group selected from the general population may have had less opportunity to undergo examinations to detect atherosclerosis and AA. For this reason, the control group may have had fewer related events than the case group.

In conclusion, CAA patients were distributed both in pediatric and adult population in Taiwan. Kawasaki disease was predominant in children with CAA. Aside from the cardiovascular diseases, factors such as aortic disease and SLE, may predispose adults to develop CAA. The results of this study are limited by the lack of available data on process and effectiveness of management and medical therapy of CAA. Future studies are recommended to evaluate pharmacoepidemiology of CAA.

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Author contributions

Chein-Tang Fang, Yaw-Bin Huang, and Chung-Yu Chen designed the data collection instruments, conceptualized and designed the study, drafted the initial manuscript and approved the final manuscript as submitted. Chen-Chun Kuo, Chein-Tang Fang, Yi-Ping Fang and Chung-Yu Chen carried out the initial analyses, critically reviewed the manuscript, and all authors approved the final manuscript as submitted.

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Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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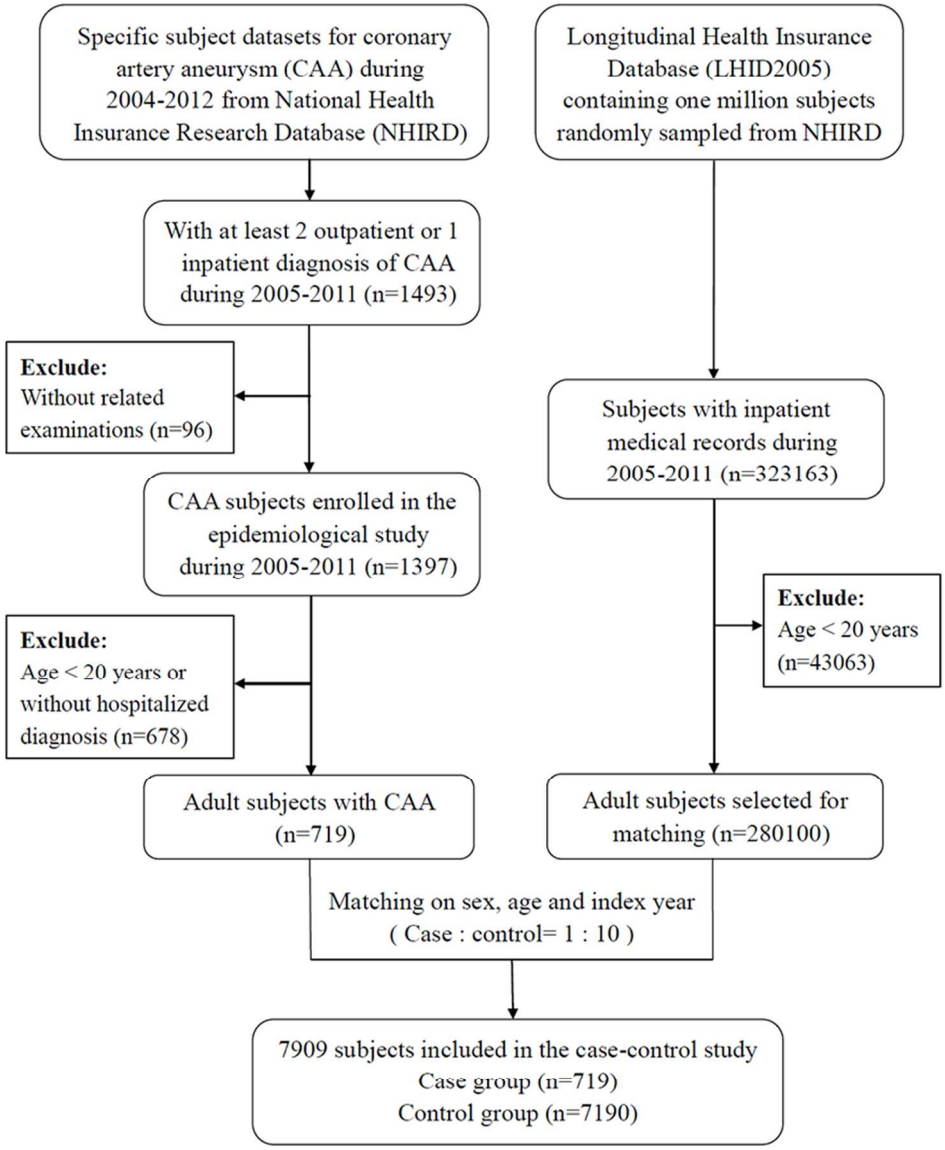
Figure Legends

Figure 1. Flow chart of the study population.

Figure 2. Age distribution of the CAA population

Figure 3. (a) Incidence rate of CAA population during 2005-2011. (b) Mortality rate of CAA population during 2005-2011



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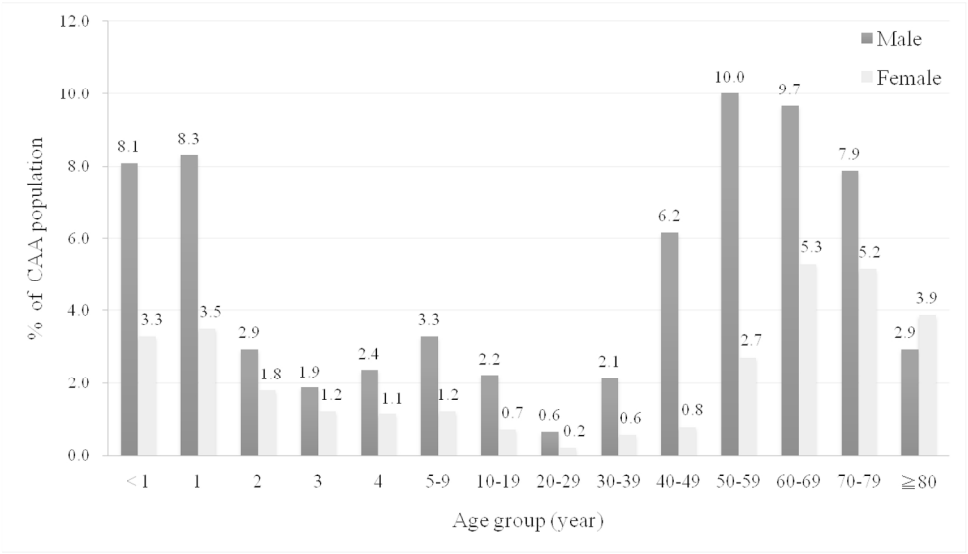

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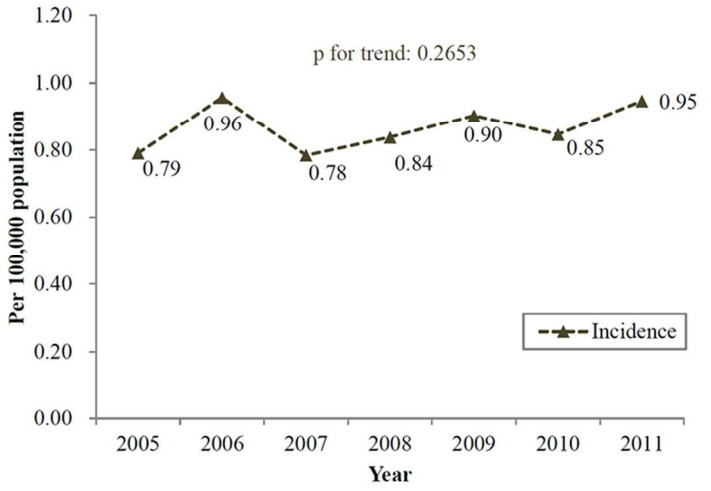
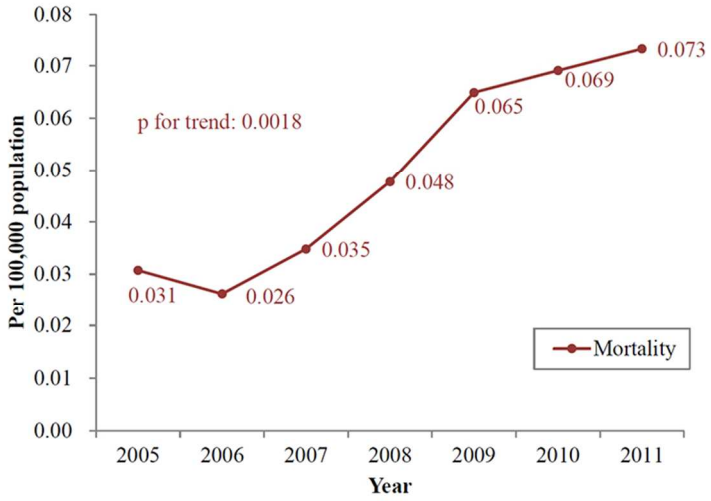


(a)



(b)

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Supplementary

eTable 1. Spearman correlation coefficients among risk factors

		DM	CVD	PVD	VV	AD	AA	SLE	RA	IBD
CAS	r	0.103*	0.036*	0.023*	0.002	0.030*	0.021	0.010	0.015	-0.011
	p	**<0.0001**	**<0.05**	**<0.05**	0.873	**<0.05**	0.068	0.397	0.176	0.342
HTN	r	0.284*	0.198*	0.028*	-0.008	0.035*	0.040*	0.016	0.019	0.007
	p	**<0.0001**	**<0.0001**	**<0.05**	0.483	**<0.05**	**<0.001**	0.149	0.092	0.549
Lipid	r	0.267*	0.015	0.036*	-0.012	-0.007	0.010	0.002	0.007	-0.025*
	p	**<0.0001**	0.178	**<0.05**	0.301	0.515	0.375	0.831	0.532	**<0.05**

r, Spearman correlation coefficient; * $p < 0.05$;

CAS, coronary atherosclerosis; HTN, hypertension; Lipid, Dyslipidemia; DM, diabetes mellitus; CVD, cerebrovascular disease; PVD, peripheral vascular disease; VV, varicose vein; AD, aortic dissection; AA, aortic aneurysm; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; IBD, inflammatory bowel disease.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-14
		(b) Give reasons for non-participation at each stage	8-14
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-14
		(*b*) Report category boundaries when continuous variables were categorized	8-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.