Bidirectional association between aortic dissection and atrial fibrillation: Findings from a huge national database

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Abstract
Objective: To explore the link between aortic dissection (AD) and atrial fibrillation (AF).
Methods: Using the National Health Insurance Research Database (NHIRD), cohorts were constructed for evaluating the incidence of AF in patients with AD (study 1) and the incident AD among AF patients (study 2) based on propensity matching analysis. Cox proportion hazard regression models were used to examine the effect of AD on the risk of AF, shown as hazard ratios (HRs) with 95% confidence intervals (CIs). Similar statistical procedures were used for study 2.
Results: The study 1 consisted of 11,813 patients in the AD cohort and 11,813 controls in the non-AD cohort and the study 2 consisted of 190,494 patients in the AF cohort and 190,494 controls in the non-AF cohort. The overall incidence density of AF was 1.32-fold higher in the AD cohort than in the non-AD cohort (11.1 and 8.3 per 1000 person-years), with an adjusted HR (aHR) of 1.74 (95% CI = 1.53-1.98). The AF cohort had 1.18-fold higher incidence of AD than the non-AF cohort (0.55 vs 0.47 per 1000 person-years), with an aHR of 1.24 (95% CI = 1.07-1.44).
Conclusions: Bidirectional association between AD and AF was shown for the first time in this study.

KEYWORDS
aortic dissection, atrial fibrillation, cohort

1 | INTRODUCTION

Aortic dissection (AD) is a life threatening disease once left undiagnosed or untreated.1,2 The phenomenon of AD presenting with atrial fibrillation (AF) has indeed been discussed previously3-9; in case of subclinical AD, AF may occur and be a sign of alert. For clinicians who care for patients with AF, it is well known that stroke, heart failure, and death are common AF complications.10-12 To date, whether there is an increased risk of AD in patients with AF remained unknown.

To provide additional evidence linking AD and AF from the viewpoint of clinical aspect, investigation on the relationship between AF and AD might be thoughtful. Hence, we sought to utilize the Taiwanese national dataset to describe the incidence of AF in patients with AD and the incidence of AD in patients with AF, using propensity score methods, multivariate controlling and combining a large number of comorbidities in our analysis to explore the link between AD and AF.

2 | METHODS

2.1 | Data source

We used the National Health Insurance Research Database (NHIRD) of the National Health Insurance (NHI) program in Taiwan to conduct this retrospective nationwide cohort study. The NHI program was established...
by the Taiwanese government on March 1, 1995, and it covered more than 99% of the 23.74 million residents in Taiwan. In this retrospective cohort study, the history of disease diagnosis was obtained from inpatient files, with data available from 1996 to 2011. The diagnoses in Taiwan NHI were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115-R3).

2.2 | Sampled participants

For study 1, we identified patients aged 18 or older years with AD diagnosed between 2000 and 2010 (ICD-9-CM codes 441.0) and control individuals without AD. The index date for control patients was randomly appointed a month and day with the same index year of the matched AD cases. We defined the diagnosed date of AD as the index date for each patient. We excluded patients with a diagnosis of AF (ICD-9-CM codes 427.31) at baseline and those with incomplete medical records information. Patients in the AD and non-AD cohorts were selected by 1:1 matching based on a propensity score. The propensity score was calculated using a logistic regression model to estimate the probability of the AD status assignment, based on the baseline variables including year of AD diagnosis, sex, age, and comorbidities of hypertension, diabetes mellitus (DM), hyperlipidemia, coronary heart disease (CHD), heart failure (HF), chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), chronic kidney disease (CKD), hyperthyroidism, sleep disorders, gout, cerebrovascular disease, chronic liver disease, cancer, asthma, peptic ulcer disease, and valvular heart disease (VHD). For study 2, patients aged 18 or older

Table 1: Demographic characteristics and comorbidities in patients with and without aortic dissection

| Variables                | Aortic dissection |                   |                   | Standardized mean differences\(^a\) |
|--------------------------|-------------------|-------------------|-------------------|-----------------------------------|
|                          | No (N=11813)      | Yes (N=11813)     |                   |                                   |
|                          | n | %      | n | %      |                                   |
| Sex                      |   |        |   |        |                                   |
| Female                   | 3797 | 32.1  | 3375 | 28.6  | 0.08                             |
| Male                     | 8016 | 67.9  | 8438 | 71.4  | 0.08                             |
| Age, years               |   |        |   |        |                                   |
| 20–49                    | 1488 | 12.6  | 2201 | 18.6  | 0.17                             |
| 50–64                    | 3015 | 25.5  | 3683 | 31.2  | 0.13                             |
| ≥ 65                     | 7310 | 61.9  | 5929 | 50.2  | 0.24                             |
| Mean (SD)\(^†\)         | 67.5 | 14.5  | 63.9 | 14.6  | 0.25                             |
| Comorbidity              |   |        |   |        |                                   |
| Hypertension             | 8598 | 72.8  | 8357 | 70.7  | 0.05                             |
| Diabetes mellitus        | 1964 | 16.6  | 1505 | 12.7  | 0.05                             |
| Hyperlipidemia           | 1330 | 11.3  | 1149 | 9.73  | 0.05                             |
| CHD                      | 2994 | 25.3  | 3078 | 26.1  | 0.02                             |
| Heart failure            | 1048 | 8.87  | 1141 | 9.66  | 0.03                             |
| COPD                     | 1205 | 10.2  | 1138 | 9.63  | 0.02                             |
| PAD                      | 332  | 2.81  | 426  | 3.61  | 0.05                             |
| CKD                      | 457  | 3.87  | 416  | 3.52  | 0.02                             |
| Hyperthyroidism          | 90   | 0.76  | 50   | 0.42  | 0.04                             |
| Sleep disorders          | 337  | 2.85  | 279  | 2.36  | 0.03                             |
| Gout                     | 1013 | 8.58  | 979  | 8.29  | 0.01                             |
| Cerebrovascular disease  | 2328 | 19.7  | 2290 | 19.4  | 0.01                             |
| Chronic liver disease    | 987  | 8.36  | 716  | 6.06  | 0.09                             |
| Cancer                   | 764  | 6.47  | 509  | 4.31  | 0.10                             |
| Asthma                   | 735  | 6.22  | 607  | 5.14  | 0.05                             |
| Peptic ulcer disease     | 2345 | 19.9  | 1907 | 16.1  | 0.10                             |
| VHD                      | 1207 | 10.2  | 1581 | 13.4  | 0.10                             |

\(^a\) A standardized mean difference of ≤0.10 indicates a negligible difference between the two cohorts.

CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PAD, peripheral artery disease; VHD, valvular heart disease.
years with AF diagnosed between 2000 and 2010 and control individuals without AF were identified. Patients suffering from AD at the baseline and those with missing medical records information were excluded. For each AF identified, controls were selected and matched by propensity score under the same exclusion criteria. The propensity score was calculated using a logistic regression model to estimate the probability of the AF status assignment, based on the baseline variables including year of AF diagnosis, sex, age, and comorbidities of hypertension, DM, hyperlipidemia, CHD, HF, COPD, PAD, CKD, hyperthyroidism, sleep disorders, gout, cerebrovascular disease, chronic liver disease, cancer, asthma, peptic ulcer disease, and VHD.

2.3 | Outcome

Subjects in the study 1 were followed until the diagnosis of AF or until withdrawal from the NHI program or death, or December 31, 2011. Subjects in the study 2 were followed until the diagnosis of AD or until withdrawal from the NHI program or death, or December 31, 2011.

2.4 | Statistical analysis

For study 1, the distributions of the sex, age, and comorbidities were compared between the AD cohort and the non-AD cohort, and the differences were examined using the standardized mean difference (SMD). A SMD of ≤0.10 indicates a negligible difference between the two cohorts. The overall, sex-, age-, comorbidity-specific, and follow-up period incidence densities rate of AF (per 1000 person-years, PY) were measured for each cohort. Univariable and multivariable Cox proportion hazard regression models were used to examine the effect of AD on the risk of AF, shown as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariable-adjusted models included covariates that were not adequately balanced in Tables 1 and 3 (standardized difference > 0.1). The cumulative incidence curve of AF was computed using the Kaplan-Meier method and the differences between both cohorts were examined using the log-rank test. Similar data analysis procedures were performed to calculate the incidence density rates of AD (per 1000 person-years, PY) and HRs (95% CIs) for the AF and non-AF cohorts in the study 2. Data analyses were conducted using statistical package SAS (Version 9.4, SAS Institute Inc., Carey, North Carolina). A two-tailed P value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study 1

The study 1 consisted of 11,813 patients in the AD cohort and 11,813 controls in the non-AD cohort (Table 1). Men represented the majority of the study cohorts (71.4% vs 67.9%) and over a half of study population were more than 65 years old. The AD cohort were slightly younger than the non-AD cohort. The average follow-up duration was 3.71 ± 3.19 years for the AD cohort and 4.85 ± 2.99 years for the non-AD cohort. Figure 1A shows that the cumulative incidence of AF was higher in the AD cohort than in the non-AD cohort (the log-rank test P < .001) after 12 years of follow-up.

The overall incidence density of AF was 1.32-fold higher in the AD cohort than in the non-AD cohort (11.1 and 8.3 per 1000 person-years, respectively). The differences in incidence densities of AF between both cohorts were examined using the log-rank test. Similar data analysis procedures were performed to calculate the incidence density rates of AD (per 1000 person-years, PY) and HRs (95% CIs) for the AF and non-AF cohorts in the study 2. Data analyses were conducted using statistical package SAS (Version 9.4, SAS Institute Inc., Carey, North Carolina). A two-tailed P value < .05 was considered statistically significant.

![Graph A](image1.png) A, Cumulative incidence of atrial fibrillation (AF) for patients with (solid line) and without (dashed line) aortic dissection. B, Cumulative incidence of aortic dissection for patients with (solid line) and without (dashed line) AF.
The incidence density and risk of AF were compared in the AD cohort and the non-AD cohort regarding several variables including sex, age, with or without comorbidity, individual comorbidity and follow-up period. The risk of AF in AD patients was also significantly higher than that of the non-AD cohort in most stratified analysis (except for with comorbidity of

| Variables            | Aortic dissection |            |            |            |            |            |            |            |            |
|----------------------|-------------------|------------|------------|------------|------------|------------|------------|------------|------------|
|                      | Event person-years| Rate#      | Event Person-years | Rate#      | Crude HR (95% CI) | Age-adjusted HR (95% CI) |
| Total                | 475               | 57 237     | 8.3        | 485        | 43 870      | 11.1       | 1.32 (1.17, 1.50)** | 1.74 (1.53, 1.98)*** |
| Sex                  |                   |            |            |            |            |            |            |            |            |
| Female               | 165               | 18 081     | 9.13       | 161        | 12 147      | 13.3       | 1.44 (1.16, 1.79)** | 1.76 (1.42, 2.20)*** |
| Male                 | 310               | 39 157     | 7.92       | 324        | 31 723      | 10.2       | 1.29 (1.10, 1.50)** | 1.73 (1.48, 2.03)*** |
| Age, years           |                   |            |            |            |            |            |            |            |            |
| 20-49                | 9                 | 8347       | 1.08       | 34         | 10 282      | 3.31       | 3.06 (1.47, 6.39)**  |            |
| 50-64                | 55                | 16 269     | 3.38       | 90         | 15 555      | 5.79       | 1.71 (1.22, 2.39)**  |            |
| ≥65                  | 411               | 32 620     | 12.6       | 361        | 18 033      | 20.0       | 1.59 (1.38, 1.83)*** |            |
| Comorbiditya         |                   |            |            |            |            |            |            |            |            |
| No                   | 34                | 6528       | 5.21       | 40         | 4820        | 8.30       | 1.59 (1.01, 2.52)*   | 3.44 (2.11, 5.59)*** |
| Yes                  | 441               | 50 709     | 8.70       | 445        | 39 050      | 11.4       | 1.30 (1.14, 1.49)*** | 1.64 (1.43, 1.87)*** |
| Hypertension         | 383               | 39 955     | 9.59       | 349        | 31 726      | 11.0       | 1.14 (0.99, 1.32)    | 1.51 (1.30, 1.74)*** |
| DM                   | 96                | 8260       | 11.6       | 75         | 4733        | 15.9       | 1.35 (1.00, 1.83)    | 1.51 (1.11, 2.04)**  |
| Hyperlipidemia       | 56                | 6134       | 9.13       | 54         | 4182        | 12.9       | 1.39 (0.96, 2.02)    | 1.51 (1.04, 2.20)*   |
| CHD                  | 180               | 13 295     | 13.5       | 184        | 10 628      | 17.3       | 1.27 (1.03, 1.56)*   | 1.51 (1.23, 1.85)*** |
| Heart failure        | 86                | 3622       | 23.7       | 96         | 2861        | 33.6       | 1.41 (1.05, 1.88)*   | 1.74 (1.29, 2.33)*** |
| COPD                 | 95                | 4700       | 20.2       | 80         | 3056        | 26.2       | 1.28 (0.95, 1.73)    | 1.32 (0.98, 1.78)    |
| PAD                  | 19                | 1257       | 15.1       | 23         | 1203        | 19.1       | 1.23 (0.67, 2.26)    | 1.49 (0.80, 2.76)    |
| CKD                  | 22                | 1632       | 13.5       | 23         | 1171        | 19.7       | 1.45 (0.81, 2.61)    | 1.61 (0.90, 2.90)    |
| Hyperthyroidism      | 5                 | 480        | 10.4       | 4          | 181         | 22.1       | 1.96 (0.52, 7.36)    | 1.58 (0.40, 6.22)    |
| Sleep disorders      | 11                | 1345       | 8.18       | 14         | 994         | 14.1       | 1.73 (0.78, 3.81)    | 1.99 (0.90, 4.40)    |
| Gout                 | 53                | 4344       | 12.2       | 52         | 3369        | 15.4       | 1.23 (0.84, 1.81)    | 1.45 (0.98, 2.13)    |
| Cerebrovascular disease | 101             | 9646       | 10.5       | 116        | 6449        | 18.0       | 1.70 (1.30, 2.22)*** | 2.00 (1.53, 2.61)*** |
| Chronic liver disease | 38                | 4336       | 8.76       | 32         | 2236        | 14.3       | 1.64 (1.02, 2.63)*   | 1.63 (1.02, 2.61)*   |
| Cancer               | 26                | 2771       | 9.38       | 23         | 1315        | 17.5       | 1.87 (1.07, 3.28)*   | 1.80 (1.02, 3.16)*   |
| Asthma               | 54                | 3129       | 17.3       | 49         | 1870        | 26.2       | 1.48 (1.00, 2.18)*   | 1.41 (0.95, 2.07)    |
| Peptic ulcer disease | 99                | 10 366     | 9.55       | 98         | 6068        | 16.2       | 1.67 (1.26, 2.21)*** | 1.78 (1.34, 2.35)*** |
| VHD                  | 85                | 5139       | 16.5       | 96         | 5856        | 16.4       | 1.00 (0.75, 1.34)    | 1.52 (1.13, 2.06)*** |

Follow-up year

|         | Event person-years | Rate# | Event Person-years | Rate# | Crude HR (95% CI) | Age-adjusted HR (95% CI) |
|---------|--------------------|-------|--------------------|-------|-------------------|--------------------------|
| ≤1      | 86                 | 11 454 | 7.51               | 144   | 9468              | 15.2                     | 1.98 (1.52, 2.59)*** | 2.44 (1.86, 3.20)*** |
| 2-3     | 168                | 19 105 | 8.79               | 134   | 14 666            | 9.14                     | 1.04 (0.83, 1.31)    | 1.41 (1.12, 1.78)*** |
| 4-5     | 106                | 12 684 | 8.36               | 94    | 9584              | 9.81                     | 1.17 (0.89, 1.55)    | 1.58 (1.19, 2.09)**  |
| >5      | 115                | 13 994 | 8.22               | 113   | 10 152           | 11.1                     | 1.36 (1.05, 1.76)*   | 1.82 (1.40, 2.37)*** |

Rate#, incidence rate per 1000 person-years;  
Abbreviations: CHD, coronary heart disease; CI; confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HR, hazard ratio; PAD, peripheral artery disease; VHD, valvular heart disease.  
*Patients with any comorbidity of hypertension, diabetes mellitus, hyperlipidemia, CHD, heart failure, COPD, PAD, CKD, hyperthyroidism, sleep disorders, gout, cerebrovascular disease, chronic liver disease, cancer, asthma, peptic ulcer disease, and VHD were defined as the comorbidity group.  
P < .05; **P < .01; ***P < .001.

years), with an adjusted HR (aHR) of 1.74 (95% CI = 1.53-1.98) after controlling for age (Table 2).
COPD, PAD, CKD, hyperthyroidism, sleep disorders, gout, and asthma).

3.2 | Study 2

The study 2 consisted of 190,494 patients in the AF cohort and 190,494 controls in the non-AF cohort (Table 3). Both cohorts had more men (54.9% vs 55.3%) and more than 75% of the study population were aged ≥ 65 years. The average follow-up duration was 3.47 years for the AF cohort and 4.19 years for the non-AF cohort.

Figure 1B shows that the cumulative incidence of AD was higher in the AF cohort than in the non-AF cohort (the log-rank test \( P = .01 \)) after 12 years of follow-up. The AF cohort had 1.18-fold higher incidence of AD than the non-AF cohort (0.55 vs 0.47 per 1000 person-years), with an aHR of 1.24 (95% CI = 1.07-1.44) (Table 4). The sex-specific AD risk for the AF cohort relative to the non-AF cohort was significantly higher for women (aHR = 1.37; 95% CI = 1.08-1.75). The age-specific AD risk for the AF cohort relative to the non-AF cohort was higher for the aged 50 to 64 group (aHR = 1.56; 95% CI = 1.06-2.28) and for the aged ≥65 group (aHR = 1.19; 95% CI = 1.01-1.40). Among the comorbid subjects, patients with AF had a higher risk of AD compared to the non-AF cohort (aHR = 1.20 for hypertension; aHR = 1.47 for diabetes mellitus; aHR = 1.67 for chronic liver disease; aHR = 1.37 for peptic ulcer disease). In the first year of follow-up, the AF cohort had a higher risk of AD compared with the non-AF cohort (aHR = 1.78, 95% CI = 1.34-2.36).

4 | DISCUSSION

Using Taiwan national cohort claims data, the authors addressed for the first time the bidirectional association between AD and AF. Considering that there is no previous large scale report on the association between

| TABLE 3 | Demographic characteristics and comorbidities in patients with and without atrial fibrillation |
|----------|--------------------------------------------------------------------------------------|
| Variables | Atrial fibrillation                                                                 |
|          | No (N = 190 494) | Yes (N = 190 494) | Standardized mean difference |
| Sex      | n % | n % |
| Female   | 85 117 44.7 | 85 883 45.1 | 0.01 |
| Male     | 105 377 55.3 | 104 611 54.9 | 0.01 |
| Age, years |                |                |                |
| 20-49    | 6981 3.66 | 10 398 5.46 | 0.09 |
| 50-64    | 25 770 13.5 | 29 875 15.7 | 0.06 |
| ≥65      | 157 743 82.8 | 150 221 78.9 | 0.10 |
| Mean (SD) | 74.7 11.6 | 73.5 12.6 | 0.001 |
| Comorbidity |                  |                  |                |
| Hypertension | 126 175 66.2 | 109 709 57.6 | 0.18 |
| DM       | 59 551 31.3 | 50 827 26.7 | 0.18 |
| Hyperlipidemia | 27 603 14.5 | 22 241 11.7 | 0.08 |
| CHD      | 77 171 40.5 | 74 482 39.1 | 0.03 |
| Heart failure | 47 807 25.1 | 63 957 33.6 | 0.19 |
| COPD     | 38 867 20.4 | 39 788 20.9 | 0.01 |
| PAD      | 5222 2.74 | 5536 2.91 | 0.01 |
| CKD      | 10 819 5.68 | 10 466 5.49 | 0.01 |
| Hyperthyroidism | 4267 2.24 | 4222 2.22 | 0.002 |
| Sleep disorders | 6835 3.59 | 5904 3.10 | 0.03 |
| Gout     | 16 735 8.79 | 15 320 8.04 | 0.03 |
| Cerebrovascular disease | 69 200 36.3 | 62 115 32.6 | 0.08 |
| Chronic liver disease | 19 120 10.0 | 15 346 8.06 | 0.07 |
| Cancer   | 16 485 8.65 | 12 524 6.57 | 0.08 |
| Asthma   | 21 261 11.2 | 20 910 11.0 | 0.01 |
| Peptic ulcer disease | 44 930 23.6 | 38 175 20.0 | 0.09 |
| VHD      | 24 981 13.1 | 30 395 16.0 | 0.08 |

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PAD, peripheral artery disease; VHD, valvular heart disease.

*A standardized mean difference of ≤0.10 indicates a negligible difference between the two cohorts.*
AD and AF to date, this is indeed data that could be helpful in the understanding and management of the growing population of adults with AD and AF.

The topic of secondary AF has received increasing attention as prior anecdotal beliefs that AF resolved after resolution of acute illness triggers have yielded to evidence suggesting high AF recurrence.

### TABLE 4

Incidence and hazard ratios of aortic dissection for atrial fibrillation (AF) cohort compared to non-AF cohort by demographic characteristics, comorbidity and follow-up year

| Variables              | Atrial fibrillation |  |  |  |  |
|------------------------|---------------------|---|---|---|---|
|                        | Event person-years  | Rate a | Event person-years  | Rate a | Crude HR (95% CI) | Adjusted HRb (95% CI) |
| Total                  | 373                 | 0.47   | 365                 | 0.55   | 1.18 (1.02, 1.36)** | 1.24 (1.07, 1.44)** |
| Sex                    |                     |        |                     |        |                  |                       |
| Female                 | 130                 | 0.36   | 140                 | 0.47   | 1.30 (1.03, 1.66)* | 1.37 (1.08, 1.75)* |
| Male                   | 243                 | 0.56   | 225                 | 0.61   | 1.11 (0.92, 1.33)  | 1.19 (0.99, 1.44)   |
| Age, years             |                     |        |                     |        |                  |                       |
| 20-49                  | 8                   | 0.22   | 11                  | 0.19   | 0.91 (0.37, 2.27)  | 0.91 (0.36, 2.29)   |
| 50-64                  | 43                  | 0.33   | 70                  | 0.49   | 1.49 (1.02, 2.18)* | 1.56 (1.06, 2.28)* |
| ≥65                    | 322                 | 0.51   | 284                 | 0.61   | 1.19 (1.02, 1.40)* | 1.19 (1.01, 1.40)*  |
| Comorbiditya           |                     |        |                     |        |                  |                       |
| No                     | 22                  | 0.27   | 11                  | 0.20   | 0.76 (0.37, 1.57)  | 1.02 (0.48, 2.19)   |
| Yes                    | 351                 | 0.49   | 354                 | 0.58   | 1.19 (1.02, 1.38)* | 1.23 (1.06, 1.43)** |
| Hypertension           | 291                 | 0.58   | 254                 | 0.71   | 1.23 (1.04, 1.45)* | 1.20 (1.01, 1.42)* |
| DM                     | 74                  | 0.33   | 70                  | 0.46   | 1.38 (1.00, 1.92)  | 1.47 (1.06, 2.05)* |
| Hyperlipidemia         | 64                  | 0.58   | 52                  | 0.66   | 1.15 (0.79, 1.65)  | 1.26 (0.87, 1.82)   |
| CHD                    | 187                 | 0.61   | 176                 | 0.69   | 1.14 (0.93, 1.40)  | 1.19 (0.97, 1.47)   |
| Heart failure          | 102                 | 0.61   | 125                 | 0.65   | 1.06 (0.82, 1.38)  | 1.15 (0.88, 1.50)   |
| COPD                   | 92                  | 0.67   | 79                  | 0.78   | 1.15 (0.85, 1.56)  | 1.16 (0.86, 1.58)   |
| PAD                    | 14                  | 0.82   | 13                  | 0.97   | 1.17 (0.55, 2.49)  | 1.22 (0.56, 2.62)   |
| CKD                    | 17                  | 0.55   | 14                  | 0.61   | 1.13 (0.56, 2.30)  | 1.22 (0.60, 2.49)   |
| Hyperthyroidism        | 8                   | 0.40   | 2                   | 0.11   | 0.28 (0.06, 1.29)  | 0.34 (0.07, 1.64)   |
| Sleep disorders        | 14                  | 0.55   | 13                  | 0.73   | 1.33 (0.62, 2.83)  | 1.40 (0.65, 2.99)   |
| Gout                   | 56                  | 0.89   | 34                  | 0.71   | 0.80 (0.52, 1.22)  | 0.82 (0.54, 1.27)   |
| Cerebrovascular disease| 145                 | 0.55   | 119                 | 0.65   | 1.18 (0.93, 1.51)  | 1.23 (0.97, 1.58)   |
| Chronic liver disease  | 34                  | 0.45   | 32                  | 0.72   | 1.58 (0.98, 2.57)  | 1.67 (1.03, 2.71)* |
| Cancer                 | 22                  | 0.40   | 15                  | 0.57   | 1.40 (0.73, 2.71)  | 1.40 (0.73, 2.71)   |
| Asthma                 | 43                  | 0.54   | 30                  | 0.52   | 0.94 (0.59, 1.51)  | 0.98 (0.61, 1.57)   |
| Peptic ulcer disease   | 104                 | 0.62   | 93                  | 0.87   | 1.37 (1.04, 1.82)  | 1.37 (1.04, 1.82)* |
| VHD                    | 56                  | 0.57   | 78                  | 0.73   | 1.29 (0.91, 1.81)  | 1.34 (0.95, 1.90)   |

| Follow-up year         |  |  |  |  |  |
| ≤1                     | 81                 | 0.45   | 128                 | 0.81   | 1.77 (1.34, 2.34)*** | 1.78 (1.34, 2.36)*** |
| 2-3                    | 153                | 0.54   | 108                 | 0.48   | 0.89 (0.70, 1.14)   | 0.96 (0.75, 1.23)   |
| 4-5                    | 79                 | 0.46   | 65                  | 0.47   | 1.03 (0.74, 1.43)   | 1.11 (0.79, 1.55)   |
| >5                     | 60                 | 0.37   | 64                  | 0.45   | 1.24 (0.87, 1.76)   | 1.36 (0.95, 1.95)   |

Note: Rate a, incidence rate per 1000 person-years. Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HR, hazard ratio; PAD, peripheral artery disease; VHD, valvular heart disease.

*Patients with any comorbidity of hypertension, diabetes mellitus, hyperlipidemia, CHD, heart failure, COPD, PAD, CKD, hyperthyroidism, sleep disorders, gout, cerebrovascular disease, chronic liver disease, cancer, asthma, peptic ulcer disease, and VHD were defined as the comorbidity group.

Model was adjusted for age, and comorbidities of hypertension, diabetes mellitus, and heart failure.

*P < .05; **P < .01; ***P < .001.
morbidities, and mortality after secondary AF. Patients with AD complicated AF might have an increased risk of AF-associated adverse events resulting in premature mortality. The two pathologies, AD and AF, are essentially different diseases. It is possible that before the development of AF in AD, there may be several factors that are also considered to be a cause of AD incidence. However, we adopted a propensity score-matching analysis and multivariate adjustment to minimize these biases and the results were statistically true, and we observed that such association was stronger in those without comorbidity, implying that the development of AF in patients with AD might be independent of comorbidities.

Identification of AD is of importance in patients with AF because of high risk of death from AD. The current study showed that the risk ratio was highest among women, old age, and short follow-up times; implying that more attention should be paid to these populations. The potential for higher incidence of AD in patients with AF, although has been corrected for covariates not adequately balanced in Table 3, it could be the case that AF and AD are two potential manifestation of possible variables not considered in the present study, without any pathophysiological relation.

AD, which might involve coronary injury, pericardial involvement, and other direct cardiac effects, could increase the risk of AF. However, there is no argument made in support of an association between AD and subsequent AF although several molecular mechanisms involving the atrial remodeling and weakness of the aortic walls might be possible explanations. Such findings based on this big dataset deserved further investigation.

5 | LIMITATIONS

First, the Taiwanese NHIRD has the power of large numbers, but it does not provide additional physiological insight. Second, diagnoses were retrieved from only inpatient files. This might introduce a bias, as AF patients with concomitant disorders might more often be hospitalized. Third, information about treatment was not collected in this study and this might have influenced the occurrence of both diseases and represents a possible bias in the interpretation of the results. Fourth, although we have used propensity matching and then conducted a multi-variable analysis, it should be mentioned that uncontrolled potential confounders could be an issue in this type of study. Finally, the diagnostic accuracy of the diseases using ICD codes might be potentially the major limitation of the present study. However, this nationwide database has been validated and high accuracy was guaranteed.

6 | CONCLUSION

This is a study evaluating the relationship between the presence of AD and the incidence of AF and vice versa in a large numbers of patients from Taiwan. A positive association for both was found in this study.
favors proteolysis in thoracic aortic aneurysms and dissections. Ann Thorac Surg. 2004;78(6):2106-2110.

17. Diao SL, Xu HP, Zhang B, Ma BX, Liu XL. Associations of MMP-2, BAX, and Bcl-2 mRNA and protein expressions with development of atrial fibrillation. Med Sci Monit. 2016;22:1497-1507.

18. Chen C-L, Huang SKS, Lin J-L, et al. Upregulation of matrix metalloproteinase-9 and tissue inhibitors of metalloproteinases in rapid atrial pacing-induced atrial fibrillation. J Mol Cell Cardiol. 2008;45(6):742-753.

19. Cheng C-L, Kao Y-HY, Lin S-J, Lee C-H, Lai ML. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf. 2011;20:236-242.

20. Ch CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol. 2014;24(6):500-507.

21. Cheng C-L, Chien H-C, Lee C-H, Lin S-J, Yang Y-HK. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. Int J Cardiol. 2015;201:96-101.

22. Sung S-F, Hsieh C-Y, Lin H-J, Chen Y-W, Yang Y-HK, Li C-Y. Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. Int J Cardiol. 2016;215:277-282.

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