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Cholangitis in patients with atrial fibrillation

A retrospective cohort study in Taiwan

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Abstract

The purpose of this study is to investigate whether atrial fibrillation (AF) and cholangitis is associated.

This is a propensity-matched retrospective cohort report from the Taiwan National Health Insurance Research Database. We included patients who had AF but didn't have cholangitis, and matched controls between January 1, 2000 and December 31, 2012. The AF cohort comprised 114,572 patients and the comparison cohort comprised 114,572 subjects. All participants were followed up until developing cholangitis, death, or December 31, 2013, whichever came first. The cox model was used to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for comparing the risk of cholangitis in the AF cohort and non-AF cohort.

The incidence of cholangitis was higher in patients with AF than in those without AF [4.2 and 2.54 per 1000 person–years; adjusted HR (95%CI), 1.92(1.54, 2.41)]. Comparing to subjects without AF, patients with AF had higher risk of cholangitis in the subgroup of ≥65 years (adjusted HR = 1.76, 95%CI = 1.40–2.21), female (adjusted HR = 2.51, 95%CI = 1.74–3.63), male (adjusted HR = 1.60, 95%CI = 1.19–2.14), without comorbidities (adjusted HR = 1.79, 95%CI = 1.23–2.61), and with comorbidities (adjusted HR = 1.85, 95%CI = 1.73–1.99).

AF is associated with a higher incidence of cholangitis. The need of further investigations is mandatory because of the inherent limitations of observational study.

Keywords: atrial fibrillation, cholangitis, cohort

1. Introduction

Impact of atrial fibrillation (AF) on lifespan is well established, mostly through the effect of cardiovascular disease.[1–3] Indeed, research on AF is increasingly growing and remains a hot issue. However, compared to the AF-associated cardiovascular effect, the impact of AF on noncardiovascular disorders has gain few attentions.[4–8] Cholangitis, although it was once thought to be a localized gastrointestinal disorder, has been reported to be associated with cardiovascular disease and diabetes mellitus.[9–11] It would appear interesting and novel to exam whether the association between AF and cholangitis exists. Hence, with a huge population data acquired from the Taiwan National Health Insurance Research Database and consisted of 114,572 AF patients and 114,572 controls, we conducted the observational cohort secondary data analysis study to explore this issue that are currently not available in medical literature.

2. Methods

2.1. Data source

We used inpatients files of the National Health Insurance Research Database which built by Taiwan National Health Research Institute.[12] This study has been approved by the Research Ethics Committee at China Medical University Hospital (CMUH104-REC2–115-AR-4). International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used in this study.

2.2. Sample participants

We designed a national population-based study to analyze all inpatient patients, and we survey the AF (ICD-9-CM code 427.31) patients whether they had higher risk of cholangitis. Our study cohort included patients with a diagnosis of AF for the first time between January 1, 2000 and December 31, 2012. Each patient's date of first diagnosis of AF from the hospital was considered as the index date. Those who had a diagnosis of

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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cholangitis before index date, a diagnosis of heart failure before endpoint, and incomplete age or sex information were excluded. The comparison cohort were selected subjects without a diagnosis of AF during the same study period. Selected comparison individuals with a history of cholangitis before the index date, with incomplete age or sex information were excluded. The risk rates of cholangitis in the two cohort were evaluate and compared, and two cohorts were propensity-score matched at a ratio of 1:1 based on the baseline characteristics of the patients including age, sex, AF diagnosis year, and comorbidities of chronic kidney disease, end stage renal disease, gallbladder stone disease, hyperlipidemia, obesity, diabetes, alcoholism, chronic hepatitis B virus infection, chronic hepatitis C virus infection, hypertension, coronary artery disease, chronic obstructive pulmonary disease, peripheral artery occlusive disease, gout, stroke, pancreatitis, rheumatic disease, cancer, and inflammatory bowel disease. A total of 114,572 AF patients and 114,572 controls without AF were enrolled in our study. Mortality rates were considered when comparing risk rates to eliminate the influence of death on the calculated risk of cholangitis. All participants were followed up until developing cholangitis, death, or December 31, 2013, whichever came first (Fig. 1).

2.3. Outcome and comorbidity

The major outcome in this study was cholangitis (ICD-9-CM code 576.1). Associated comorbidities were also considered as potential confounding factors in this study, such as chronic kidney disease, end stage renal disease, gallbladder stone disease, hyperlipidemia, obesity, diabetes mellitus, alcoholism, chronic hepatitis B virus infection, chronic hepatitis C virus infection, hypertension, coronary artery disease, chronic obstructive pulmonary disease, peripheral arterial occlusive disease, gout, stroke, pancreatitis, rheumatic disease, cancer, inflammatory bowel disease.

2.4. Statistical analysis

For each AF patient, a matched control was assigned using the propensity score matching technique to account for baseline differences between AF and non-AF subjects. The propensity score was assigned based on the probability that an individual would be a case of AF and estimated by a multivariable logistic

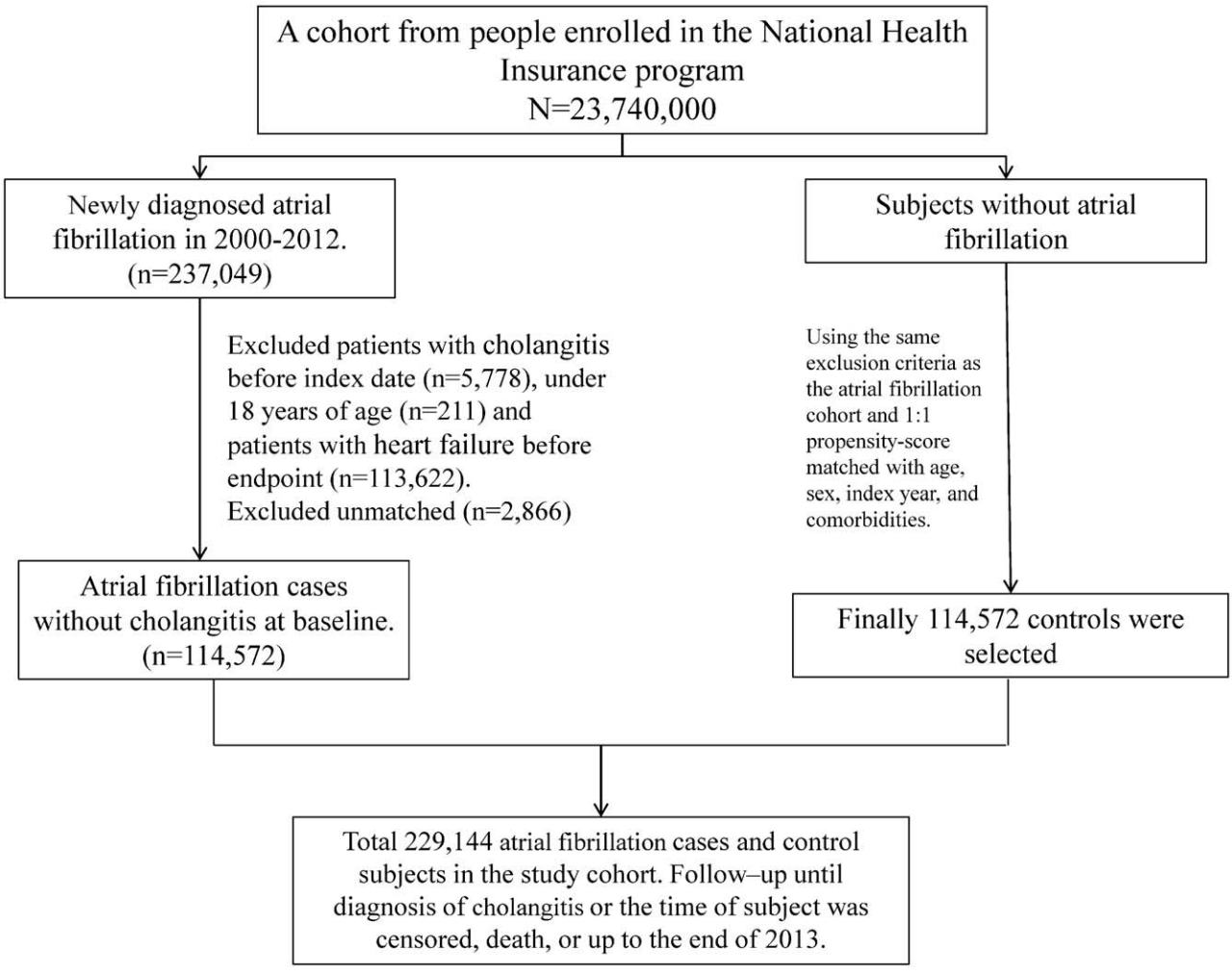

Figure 1. The flow diagram of this study.

Table 1

Demographic characteristics and comorbidities of patients with and without atrial fibrillation.

	Atrial fibrillation					
	Yes (N = 114,572)		No (N = 114,572)			
	n	%	n	%	Standardized mean differences	*P*-value
Age, yr						<.001
≤64	28,582	25.0	26,971	23.5	0.03	
≥65	85,990	75.1	87,601	76.5	0.03	
Mean (SD)*	72.3	13.2	72.3	12.8	0.000	.82
Gender						.12
Female	47,072	41.1	46,703	40.8	0.01	
Male	67,500	58.9	67,869	59.2	0.01	
Comorbidity						
CKD	6808	5.94	6949	6.07	0.01	.22
ESRD	3857	3.37	3926	3.43	0.003	.43
GB stone disease	9491	8.28	9722	8.49	0.01	.08
Hyperlipidemia	18,681	16.3	19,256	16.8	0.01	.001
Obesity	94	0.08	104	0.09	0.003	.48
Diabetes	35,675	31.1	36,225	31.6	0.01	.01
Alcoholism	1983	1.73	1978	1.73	0.000	.94
Chronic HBV infection	2894	2.53	2977	2.60	0.01	.27
Chronic HCV infection	3096	2.70	3151	2.75	0.003	.48
Hypertension	76,706	67.0	77,242	67.4	0.01	.02
CAD	44,114	38.5	44,643	39.0	0.01	.02
COPD	26,774	23.4	26,944	23.5	0.004	.40
PAOD	7026	6.13	7317	6.39	0.01	.01
Gout	9883	8.63	10,074	8.79	0.01	.16
Stroke	49,499	43.2	50,313	43.9	0.01	.001
Pancreatitis	2631	2.30	2647	2.31	0.001	.82
Rheumatic disease	1397	1.22	1437	1.25	0.003	.45
Cancer	18,356	16.0	18,675	16.3	0.01	.07
Inflammatory bowel disease	327	0.29	333	0.29	0.001	.82

Chi-square test.

* *t* test.

CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ESRD = end stage renal disease, GB = gallbladder, HBV = hepatitis B virus, HCV = hepatitis C virus, PAOD = peripheral artery occlusive disease, SD = standard deviation.

regression model adjusting for observed covariates. All the confounders such as age, gender and comorbidities were included in the propensity-score model. Demographic characteristics and the prevalence of comorbidities were compared by standardized mean difference in which values ≤0.10 indicated a negligible difference between the two cohorts. We estimated the cumulative incidences of cholangitis for the AF and comparison cohorts with Kaplan–Meier method, and we examined the difference between the two curves by log-rank test. Multivariate models were simultaneously adjusted for age, gender, and comorbidities. The cox model was used to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for comparing the risk of cholangitis in the AF cohort relative to the non-AF cohort. The Fine and Gray model, which extended the univariate and multivariate cox proportional-hazard regression model, were used to estimate the subhazard ratios of cholangitis by considering death as a competing risk. We used SAS software (version 9.4 for Windows; SAS Institute, Cary, NC) for all statistical analyses and Kaplan-Meier survival curves plot. A 2-sided *P*-value less than .05 was considered statistically significant.

3. Results

After propensity-score matching, our study cohort consisted of 229,144 patients (93775 women and 135,369 men). The AF cohort comprised 114,572 patients and the comparison cohort comprised 114,572 subjects. The matched baseline characteristics and comorbidities of all participants are listed in Table 1. Among the study subjects, male gender and age ≥65 years were dominant. The matched pairs were similar with respect to all covariates, including age, sex, and all comorbidities (all standardized mean difference ≤0.10).

Table 2 shows that the incidence and hazard ratio of cholangitis in AF patients compared to those without AF. The incidence of cholangitis was higher in patients with AF than in those without AF [4.2 and 2.54 per 1000 person–years; adjusted HR (95%CI), 1.92(1.54, 2.41)]. After controlling for potential confounding factors, comparing to subjects without AF, patients with AF had a higher risk of cholangitis in the subgroup of age ≥65 years (adjusted HR = 1.76, 95%CI = 1.40–2.21), female (adjusted HR = 2.51, 95%CI = 1.74–3.63), male (adjusted HR = 1.60, 95%CI = 1.19–2.14), without comorbidities (adjusted HR = 1.79, 95%CI = 1.23–2.61), and with comorbidities (adjusted HR = 1.85, 95%CI = 1.73–1.99).

The competing risk regression model which considered the competing risk of death is shown in Table 3. After adjustment for confounding factors in the competing risk regression model, the risk of cholangitis remained significantly increased in the AF cohort (adjusted subhazard ratio = 1.43, 95%CI 1.15–1.76, $P < .001$).

Table 2

Comparison of incidence and hazard ratio of cholangitis stratified by age, gender, and comorbidity between patients with and without AF.

	Atrial fibrillation							
	Yes			No				
Variable	Event	PY	Rate†	Event	PY	Rate†	Crude HR (95%CI)	Adjusted HR§ (95%CI)
All	1799	428,376	4.2	1533	604,385	2.54	1.64 (1.53, 1.76)***	1.92 (1.54, 2.41)***
Age, yr								
≤64	250	156,639	1.60	161	171,043	0.94	1.69 (1.39, 2.06)***	2.27 (0.66, 7.84)
≥65	1549	271,737	5.70	1372	433,342	3.17	1.80 (1.67, 1.94)***	1.76 (1.40, 2.21)***
Gender								
Female	704	174,788	4.03	594	248,439	2.39	1.66 (1.49, 1.86)***	.2.51 (1.74, 3.63)***
Male	1095	253,588	4.32	939	355,945	2.64	1.63 (1.49, 1.78)***	1.60 (1.19, 2.14)***
Comorbidity‡								
No	54	42,007	1.29	63	54,831	1.15	1.10 (0.76, 1.58)	1.79 (1.23, 2.61)***
Yes	1745	386,369	4.52	1470	549,554	2.67	1.68 (1.57, 1.80)***	1.85 (1.73, 1.99)***

AF = atrial fibrillation, CAD = coronary artery disease, CI = confidence intervals, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ESRD = end stage renal disease, GB = gallbladder, HBV = hepatitis B virus, HCV = hepatitis C virus, HR = hazard ratio, PAOD = peripheral artery occlusive disease, PY = person–years.

† Rate, incidence rate per 1000 person-years; Crude HR, relative hazard ratio.

‡ Comorbidity: Patients with any one of the comorbidities were classified as the comorbidity group: CKD, ESRD, GB stone disease, hyperlipidemia, obesity, diabetes, alcoholism, chronic HBV infection, chronic HCV infection, hypertension, CAD, COPD, PAOD, gout, stroke, pancreatitis, rheumatic disease, cancer, and inflammatory bowel disease.

§ Model was mutually adjusted for age, sex, and comorbidities of CKD, ESRD, GB stone disease, hyperlipidemia, obesity, diabetes, alcoholism, chronic HBV infection, chronic HCV infection, hypertension, CAD, COPD, PAOD, gout, stroke, pancreatitis, rheumatic disease, cancer, and inflammatory bowel disease.

*** $P < .001$.

Figure 2 shows the cumulative incidence curves of cholangitis for groups with and without AF. From the first year of follow-up to the end of the study period, the incidence of cholangitis events in the AF cohort was higher than in the comparison cohort.

4. Discussion

In this study, we found a significant increase in cholangitis in the AF cohort as compared to the controls. Interestingly, this association was much more profound in the subgroup of ≥65 years, women and with comorbid medical illness.

Strengths of the manuscript include: evaluation of a clinically important issue; large cohort of patients extracted from the impressive database; and appropriate statistical techniques for analysis, especially matching for age, sex and comorbidities in both groups as per Table 1.

It is well established that AF is associated with stroke, heart failure, and mortality.[1–3] Some might be bewildered on which bases would the authors come up with the hypothesis that AF would constitute a direct or indirect risk for developing a cholangitis since AF could lead to thromboembolic events or cause a heart failure over the years but both are difficult to bring in relation to a cholangitis. Known predisposing risk factors for a cholangitis being rather hepatic or bile duct diseases, gallstones etc. As such, some might argue that it seems that this is rather a coincidental byproduct of a statistical exercise. Indeed, the association between AF and gastrointestinal complications are limited.[13,14] However, it has been adequately shown in this

Table 3

Incidence and subhazard ratio (SHR) of cholangitis in propensity score (PS)-matched cohorts, using the univariable and multivariable competing-risks regression models.

	Competing-risks regression models	
	Atrial fibrillation	
Outcome	Yes	No
Crude SHR (95%CI)	1.22 (1.14, 1.31)***	1 (Reference)
Adjusted SHR† (95%CI)	1.43 (1.15, 1.76)***	1 (Reference)

Crude SHR, relative subhazard ratio.

CAD = coronary artery disease, CI = confidence intervals, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ESRD = end stage renal disease, GB = gallbladder, HBV = hepatitis B virus, HCV = hepatitis C virus, PAOD = peripheral artery occlusive disease.

† Model was mutually adjusted for age, sex, and comorbidities of CKD, ESRD, GB stone disease, hyperlipidemia, obesity, diabetes, alcoholism, chronic HBV infection, chronic HCV infection, hypertension, CAD, COPD, PAOD, gout, stroke, pancreatitis, rheumatic disease, cancer, and inflammatory bowel disease.

*** $P < .001$.

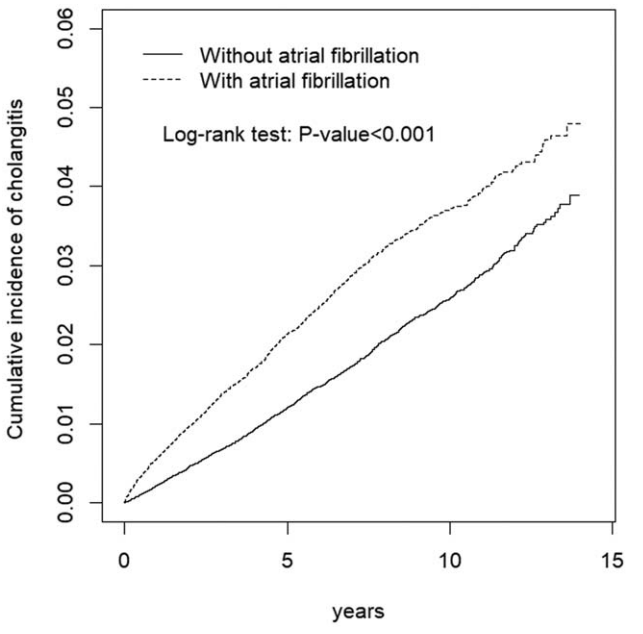

Figure 2. Cumulative incidence of cholangitis for groups with and without atrial fibrillation.

analysis that associations between AF and cholangitis differ according to age, gender and comorbidity status. While the result is statistically significant, and might be an interesting topic which would add to the evidence in this field. It remains an association and the firm conclusion regarding any insight into causality should be interpreted very carefully. Hence, further large scale prospective studies are highly recommended.

Since AF usually occurs in patients who are older and sicker,[15,16] the concept that these factors that contribute to AF causation also make cholangitis more likely. In addition, we found that women with AF are more frequent with incident cholangitis than the comparisons. The underlying expiations for this observation is difficult to conclude due to the nature of the association investigation. Whether it is just an incident finding or it reflects a novel association remained to be determined.

4.1. Limitations

Limitations of the study include: lack of standard robust techniques to detect AF; ascertainment bias, with the likelihood that those with AF have more intense follow up and increasing the probability of diagnosing a cholangitis; retrospective analysis; potential for confounding variables which were not measured and lack of medications in the analysis; use of administrative data for diagnosis of AF, comorbidities, and endpoints; and cause and effect is unclear due to the nature of association studies.

5. Conclusion

A higher incidence of cholangitis among AF patients is found.

Author contributions

Conceptualization: Wei-Syun Hu.
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Investigation: Wei-Syun Hu.
Methodology: Wei-Syun Hu, Cheng-Li Lin.
Project administration: Wei-Syun Hu.
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Supervision: Wei-Syun Hu.
Validation: Wei-Syun Hu.
Visualization: Wei-Syun Hu.
Writing – original draft: Wei-Syun Hu, Cheng-Li Lin.
Writing – review & editing: Wei-Syun Hu, Cheng-Li Lin.

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