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ORIGINAL ARTICLE

Association between Aortic Aneurysm and Ulcerative Colitis: A Nationwide Taiwanese Retrospective Cohort Study

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Background: Ulcerative colitis (UC) is an immune-mediated inflammatory disease that is associated with an increased incidence of cardiovascular events. Several inflammatory mechanisms associated with the pathogenesis of UC are involved in the initiation and progression of aortic aneurysms (AAs). We aimed to evaluate whether patients with UC have an increased risk of AA. **Methods:** We conducted a retrospective cohort study using data extracted from Taiwan's National Health Insurance Research Database. All medical conditions for each case and control subject were categorized using the International Classification of Diseases, 9th Revision. Hazard ratios and 95% confidence intervals for associations between UC and AA were estimated using the Cox regression adjusted for comorbidities. **Results:** Our analyses included 7256 UC patients and propensity score-matched controls. Compared to the controls, UC patients exhibited a significantly increased risk of developing an AA (adjusted odds ratio = 3.154, $P < 0.001$). **Conclusion:** UC patients have an increased risk of developing an AA, and healthcare professionals should be aware of this risk when treating UC patients. Aortic surveillance may be required for UC patients.

Key words: Ulcerative colitis, aortic aneurysm, inflammatory bowel disease

INTRODUCTION

Ulcerative colitis (UC) is a chronic, nonspecific inflammatory disease of the colonic mucosa with an unclear etiology. Pathologically, UC is characterized by ulceration in the mucosal and submucosal areas, and degradation of the extracellular matrix is one of the major events that occur during this process. The incidence rates of UC worldwide vary between 0.5 and 24.5 per 100,000 inhabitants.[1] Between 2000 and 2010, the overall incidence rates of UC were 0.208 and 0.838 per 100,000 person-years in Taiwan.[2] UC can affect patients at any age; however, its onset typically follows a bimodal pattern with one peak at 15–25 years and a smaller peak at 55–65 years. UC is slightly more common in women than in men.[3] Aortic aneurysms (AAs) are often diagnosed accidentally. Enlarged aneurysms can result in rupture and are a common cause of sudden death. The incidence of AA ranges from six cases per 100,000 persons to 9.1 per 100,000 among women and 16.3 per 100,000 among men annually based on studies performed in England and Sweden.[4,5] Among the Asian population, the average annual incidence of AA is 5.6 per 100,000 persons in Taiwan, and the prevalence is 19.9 per 100,000 persons, with a predominance noted among men 50–54 years of age (27.3 per 100,000 persons per year).[6]

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Previous studies have demonstrated that AA is more prevalent in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) than in the general population.[7] Several studies have suggested that UC is associated with an increased incidence of cardiovascular events, including arterial stiffening, atherosclerosis, and ischemic heart disease due to systemic inflammation, which leads to oxidative stress and phenotypic changes in smooth muscle cells.[8-10]

We hypothesized that UC patients may have an increased risk of AA due to UC-related cardiovascular risks and shared molecular mechanisms. AA has been reported to be a rare complication of UC.[11,12] However, the association between UC and AA has not been thoroughly evaluated in large-scale studies. Therefore, we aimed to determine whether UC patients exhibit an increased risk of AA using a national healthcare insurance claim database.

METHODS

Data source

The national health insurance program was launched in Taiwan in 1995, and 97% of medical providers and more than 99% of the entire population (approximately 23 million beneficiaries) are included in it. The national health insurance research database (NHIRD) is used for national population-based retrospective cohort studies. A subgroup database of the NHIRD, the longitudinal health insurance database (LHID), which provides information on medical service utilization using a randomly selected sample of one million people receiving benefits (representing approximately 5% of Taiwan's population), was used to study the association between AA and UC. The accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases (e.g. acute coronary syndrome and stroke), has previously been confirmed.[13,14] The LHID consists of "deidentified" secondary data. International classification of diseases, 9th revision, clinical modification (ICD-9-CM) diagnostic and procedure codes (up to five each), genders, ages, patient identification numbers, dates of admission and discharge, and outcomes are coded. In addition, information regarding the medical institutions that served the patients was obtained. We used encoded personal identification to prevent ethical violations related to individual information. Our study followed the Declaration of Helsinki and other relevant guidelines. The Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, permitted this study (TSGH IRB No. 2-105-05-082).

Sampled patients

This study had a retrospective, matched cohort design. Using the LHID, we selected adult patients aged ≥20 years who were newly diagnosed with UC (ICD-9-CM 710.2) and who were followed up between 2000 and 2013. We excluded patients who were diagnosed with AA (ICD-9-CM 441.0-441.9), Turner syndrome (ICD-9-CM 758.6), aortic coarctation (ICD-9-CM 747.10), a bicuspid aortic valve (ICD-9-CM 746.4), Marfan syndrome (ICD-9-CM 759.82), and Ehlers–Danlos syndrome (ICD-9-CM 756.83). Patients were monitored for <6 months. The date of UC diagnosis was used as the index date. Control candidate sampling comparisons were selected from individuals in the LHID with no history of UC. The patient and control cohorts were selected by 1:1 matching according to the following baseline variables: age; sex; comorbidities including hypertension (ICD-9-CM 401-405), diabetes mellitus (DM) (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272.0-272.4), Behcet's disease (ICD-9-CM 136.1), giant cell arteritis (ICD-9-CM 446.5), RA and other inflammatory polyarthropathies (ICD-9-CM 714), relapsing polychondritis (ICD-9-CM 733.99), and Takayasu's arteritis (ICD-9-CM 446.7); chronic obstructive pulmonary disease (COPD) (ICD-9-CM 490-496); and medication history including use of a β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, diuretic, steroid, or other immunosuppressant drug. The index dates for control patients were the same as the corresponding dates for patients with AA. The study outcome was a diagnosis of an AA during the 14-year follow-up period. AAs were identified using ICD-9 codes. The end point of the follow-up period was December 31, 2013, the time at which an AA event occurred, or when the patient died.

Statistical analysis

All data analyses were conducted using SPSS software version 22 (SPSS Inc., Chicago, IL, USA). Chi-square and *t*-tests were used to evaluate the distributions of categorical and continuous variables, respectively. The primary goal of the study was to determine whether UC patients exhibit an increased risk of developing an AA. The association between the outcomes (prognoses) and clinical characteristics was investigated using the Cox regression. The results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). A two-tailed $P < 0.05$ was considered to indicate the statistical significance.

RESULTS

A flow diagram of our patient enrollment scheme is depicted in Figure 1. A total of 7256 patients diagnosed with UC were

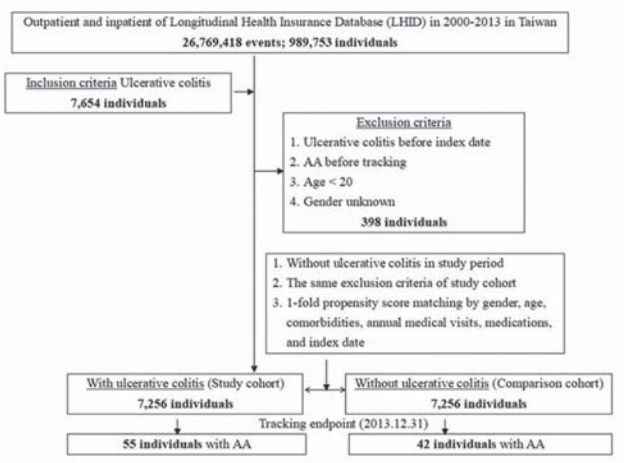

Figure 1: Patient selection flowchart

identified in the NHIRD, which contains a total of 989,753 individuals. An additional 7256 age-matched, gender-matched, comorbidity-matched, and medication-matched patients were designated controls. As shown in Table 1, no significant differences in gender; age; comorbidities including DM, hypertension, hyperlipidemia, cancer, congestive heart failure, RA, SLE, chronic kidney disease, and COPD; or medication use were noted between the two groups after matching. Table 2 presents the incidences of AA during the 10-year follow-up period. At the end of the follow-up period, UC patients exhibited a significantly increased incidence of AA (0.76% vs. 0.58%, $P = 0.045$). Patients with UC exhibited a significantly increased cumulative risk of developing an AA in subsequent years compared to patients without UC [log-rank test <0.001, Figure 2]. Regarding the Cox regression analysis, independent of the effects of gender, age, comorbidities and medication use, and patients with UC also exhibited a significantly increased risk of developing an AA compared to patients without UC [adjusted HR = 3.154, 95% CI = 2.073–4.798, $P < 0.001$, Table 3 and Supplemental Table 1].

Table 1: Characteristics of study in the baseline

Ulcerative colitis	Total, *n* (%)	With, *n* (%)	Without, *n* (%)	*P*
Total	14,512	7256 (50.00)	7256 (50.00)	
Gender				
Male	7786 (53.65)	3893 (53.65)	3893 (53.65)	0.999
Female	6726 (46.35)	3363 (46.35)	3363 (46.35)	
Age (years)	55.27±17.45	55.40±17.67	55.13±17.23	0.351
DM	1383 (9.53)	701 (9.66)	682 (9.40)	0.611
Hypertension	1734 (11.95)	863 (11.89)	871 (12.00)	0.858
Hyperlipidemia	143 (0.99)	75 (1.03)	68 (0.94)	0.614
Cancer	989 (6.82)	500 (6.89)	489 (6.74)	0.742
CHF	164 (1.13)	78 (1.07)	86 (1.19)	0.583
Rheumatic arthritis	41 (0.28)	20 (0.28)	21 (0.29)	0.877
SLE	29 (0.20)	18 (0.25)	11 (0.15)	0.265
CKD	570 (3.93)	281 (3.87)	289 (3.98)	0.765
COPD	496 (3.42)	243 (3.35)	253 (3.49)	0.681
Steroid	3282 (22.62)	1645 (22.67)	1637 (22.56)	0.890
β blockers	2581 (17.79)	1284 (17.70)	1297 (17.87)	0.794
CCB	2401 (16.54)	1196 (16.48)	1205 (16.61)	0.858
ACEI	2532 (17.45)	1274 (17.56)	1258 (17.34)	0.743
ARB	2610 (17.,99)	1314 (18.11)	1296 (17.86)	0.713
Diuretic	2378 (16.39)	1188 (16.37)	1190 (16.40)	0.982
Statin	2516 (17.34)	1245 (17.16)	1271 (17.52)	0.584

P-value (category variable: Chi-square/Fisher's exact test; continue variable: *t*-test). DM=Diabetes mellitus; CHF=Congestive heart failure; SLE=Systemic lupus erythematosus; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; CCB=Calcium channel blocker; ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blockers

DISCUSSION

Our cohort study revealed the novel finding that UC is associated with an increased incidence of AA development compared to a control cohort. After adjusting for comorbidities and medications used, we found that the HR for subsequent AAs among UC patients was 3.154 times that of the control subjects.

Patients with rheumatologic diseases have an increased risk of cardiovascular disease.[15] Therefore, the regular follow-up care for cardiovascular disease has been suggested for these patients. Although the prevalence of traditional cardiovascular risk factors, including hypertension, DM, hyperlipidemia, and obesity, is lower in UC patients than in the general population, UC patients have an increased risk of venous thromboembolism,[16] arterial stiffness,[17] coronary artery disease,[9] and stroke.[18]

The pathophysiological association between UC and AA remains unclear. Several molecular mechanisms, including inflammatory cytokines (interleukin [IL]-1 and tumor necrosis factor [TNF]-α) and matrix metalloproteinase (MMP) activation, are associated with the pathogenesis of UC.[19,20] These molecular mechanisms also actively participate in the initiation and progression of AAs. Systemic inflammation in

Table 2: Incidences of aortic aneurysm and dissection and other characteristics during the 10-year follow-up period

Ulcerative colitis	Total, *n* (%)	With, *n* (%)	Without, *n* (%)	*P*
Total	14,512	7256 (50.00)	7256 (50.00)	
Aortic aneurysm	97 (0.67)	55 (0.76)	42 (0.58)	0.045
Gender				
Male	7786 (53.65)	3893 (53.65)	3893 (53.65)	0.999
Female	6726 (46.35)	3363 (46.35)	3363 (46.35)	
Age (years)	66.40±19.39	66.49±19.45	66.30±19.33	0.555
DM	1912 (13.18)	827 (11.40)	1085 (14.95)	<0.001
Hypertension	2279 (15.70)	1094 (15.08)	1185 (16.33)	0.040
Hyperlipidemia	283 (1.95)	119 (1.64)	164 (2.26)	0.008
Cancer	1720 (11.85)	790 (10.89)	930 (12.82)	<0.001
CHF	542 (3.73)	224 (3.09)	318 (4.38)	<0.001
Rheumatic arthritis	41 (0.28)	25 (0.34)	16 (0.22)	0.164
SLE	27 (0.19)	16 (0.22)	11 (0.15)	0.441
CKD	1000 (6.89)	447 (6.16)	553 (7.62)	<0.001
COPD	985 (6.79)	411 (5.66)	574 (7.91)	0.004
Steroid	3490 (24.05)	1789 (24.66)	1701 (23.44)	0.091
β blockers	2656 (18.30)	1345 (18.54)	1311 (18.07)	0.479
CCB	2582 (17.79)	1298 (17.89)	1284 (17.70)	0.778
ACEI	2747 (18.93)	1377 (18.98)	1370 (18.88)	0.899
ARB	2477 (17.07)	1264 (17.42)	1213 (16.72)	0.270
Diuretic	2616 (18.03)	1305 (17.99)	1311 (18.07)	0.914
Statin	2799 (19.29)	1398 (19.27)	1401 (19.31)	0.966

P-value (category variable: Chi-square/Fisher's exact test; continue variable: *t*-test). DM=Diabetes mellitus; CHF=Congestive heart failure; SLE=Systemic lupus erythematosus; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; CCB=Calcium channel blocker; ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blockers

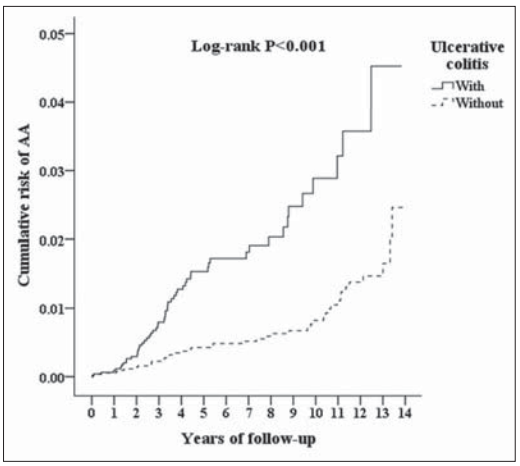

Figure 2: Kaplan–Meier curve of the cumulative risk of aortic aneurysm due to ulcerative colitis

UC patients elevates levels of inflammatory cytokines, such as TNF-α and IL-1, which might trigger phenotypic changes in vascular smooth muscle cells and further lead to the expression of osteoblast markers, resulting in medial calcification, and reduced vessel elasticity.[21] Calcification and bony metaplasia are common pathological findings for AAs. Many studies have revealed aberrantly increased expression of MMPs in intestinal biopsy tissue from patients with active UC including MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-12, and MMP-13.[22-24] MMP-9 is among the most abundantly expressed MMPs in the bowel mucosa of active UC patients, and it correlates with disease activity. However, MMPs are responsible for vessel-wall remodeling, and MMP-2 and MMP-9 play an important role in the degradation of elastin and collagen in the aortic wall in AA.[25] Defects in intestinal epithelial barrier function are a characteristic feature of UC that can facilitate the translocation of endotoxins and bacterial lipopolysaccharides produced by intestinal microflora into the circulatory system, and the resulting activation of inflammatory responses can lead to atherosclerosis.[26] Gut microbiota has been recognized as one of the essential factors for the development of IBD. Gut microbiota and intestinal epithelial barrier function are altered in patients with IBD.[27] However, many gut microbes have been identified within atherosclerotic arteries and nonatherosclerotic AAs,[28] which implie that the gut microbiota might contribute to the inflammatory response that leads to aneurysm formation.

Corticosteroids may be used to treat symptoms of UC. Prolonged or high-dose corticosteroid treatment likely causes disintegration of connective tissue of the media and possibly primary aortic wall involvement and/or vascular damage in patients with autoimmune disorders, which can result in AA enlargement.[29,30] In this study, UC patients and control subjects were matched for steroid use. Therefore, the effect of corticosteroids was controlled.

The main strength of our study is its population-based database design. We accounted for several aneurysm-related confounding factors. Although we adjusted the results extensively using the multivariate logistic regression models, there were several limitations and unmeasured confounders in our study. First, Asia is traditionally considered an area with a relatively low incidence of IBD, ranging from 0.54 to 3.44 per 100,000 individuals with a UC predilection in Asia.[31] Nevertheless, the incidence of UC is rapidly increasing as a Westernized lifestyle becomes more popular. Second, the NHIRD registry cannot provide detailed information on laboratory results, family histories, and health-related lifestyle factors, such as tobacco use, that can increase the risk of AA. These were potential

Table 3: Factors of aortic aneurysm and dissection by using conditional Cox logistic regression

Variables	Crude HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Ulcerative colitis	2.975	1.898-3.776	<0.001	3.154	2.073-4.798	<0.001
Gender (male)	1.452	1.125-1.599	<0.001	2.045	1.322-3.162	0.001
Age (years)	1.701	0.525-4.120	0.376	1.180	1.002-1.298	0.035
DM	1.452	1.113-1.790	<0.001	1.280	1.128-1.612	<0.001
Hypertension	1.154	1.087-1.665	0.012	1.649	1.060-2.566	0.027
Hyperlipidemia	0.298	0.017-2.118	0.245	0.305	0.042-2.204	0.239
Cancer	1.356	1.155-1.820	0.024	1.622	1.407-1.903	0.001
CHF	1.303	0.626-2.715	0.479	0.598	0.249-0.998	0.049
Rheumatic arthritis	0.000	-	0.906	0.000	-	0.987
SLE	0.000	-	0.895	0.000	-	0.991
CKD	1.074	0.492-2.346	0.857	1.309	1.010-1.598	0.043
COPD	1.124	0.590V2.140	0.722	0.972	0.484-1.998	0.681
Steroid	0.895	0.435-1.012	0.075	0.896	0.528-1.696	0.135
β blockers	1.065	0.854-1.982	0.465	0.965	0.303-1.864	0.645
CCB	1.198	0.450-1.847	0.247	1.128	0.997-1.982	0.783
ACEI	1.045	0.337-1.559	0.386	1.073	0.672-2.015	0.765
ARB	1.006	0.596-1.980	0.813	0.944	0.845-1.423	0.811
Diuretic	0.978	0.312-1.458	0.751	0.837	0.663-1.311	0.672
Statin	0.845	0.670-1.017	0.443	0.739	0.512-1.284	0.582

P-value (category variable: Chi-square/Fisher's exact test; continue variable: *t*-test). DM=Diabetes mellitus; CHF=Congestive heart failure; SLE=Systemic lupus erythematosus; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; CCB=Calcium channel blocker; ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blockers; HR=Hazard ratio; CI=Confidence interval; Adjusted HR=Adjusted variables listed in the table

confounding factors in this study. In this study, we considered the COPD incidence as a proxy variable for tobacco use to eliminate its potential confounding effect.[32] Third, most AAs are asymptomatic unless they dissect or rupture and are therefore diagnosed incidentally when the abdomen is imaged for other indications. Abdominal pain is one of the most common problems for people with UC. Patients with UC are more likely to undergo abdominal imaging than are patients without UC, facilitating incidental identification of AAs but possible inducing selection bias. Although our study identified an association between UC and AA, the cohort study design did not enable determination of a cause-effect relationship. Further prospective follow-up studies, mechanistic studies, and animal experiments should be performed.

CONCLUSION

UC patients have an increased risk of developing an AA, and healthcare professionals should be aware of this risk when treating UC patients. AA is a silent disease; however, it is life-threatening when the aneurysm ruptures. To reduce the incidence of AA rupture, the early detection of AAs in UC patients should be improved. Developing AA prevention strategies might be helpful in limiting the incidence of AA in selected high-risk groups.

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Conflicts of interest

There are no conflicts of interest.

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Supplemental Table 1: Analysis of the locations and the different situation regarding aortic aneurysm according to the international classification of diseases-9 system

Ulcerative colitis		Total, ***n*** (%)	With, ***n*** (%)	Without, ***n*** (%)
ICD-9-CM	AA subgroup			
441	Overall	97	55	42
441.1	Thoracic AA, with ruptured	1 (1.03)	0 (0.00)	1 (2.38)
441.2	Thoracic AA, without ruptured	20 (20.62)	12 (21.82)	8 (19.05)
441.3	Abdominal AA, with ruptured	3 (3.09)	2 (3.64)	1 (2.38)
441.4	Abdominal AA, without ruptured	49 (50.52)	29 (52.73)	20 (47.62)
441.6	Thoracoabdominal AA, with ruptured	0 (0.00)	0 (0.00)	0 (0.00)
441.7	Thoracoabdominal AA, without ruptured	0 (0.00)	0 (0.00)	0 (0.00)
441.5	Unspecified AA, with ruptured	1 (1.03)	0 (0.00)	1 (2.38)
441.9	Unspecified AA, without ruptured	23 (23.71)	12 (21.82)	11 (26.19)

AA=Aortic aneurysms; ICD-9-CM=International Classification of Diseases, 9th Revision, Clinical Modification