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ORIGINAL RESEARCH

New Users of Herbal Medicine Containing Aristolochic Acids and the Risk of Dementia in the Elderly: A Nationwide, Population-Based Study in Taiwan

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Background: Herbal medicine containing aristolochic acids (HMCAA) was used for inflammatory and infectious diseases. This study aimed to investigate the association between the usage of HMCAA and the risk of dementia.

Methods: A total of 199 new users of HMCAA were enrolled, along with 597 controls without the usage of HMCAA, at a ratio of 1:3 – matched by age, sex, and comorbidity, between 2000 and 2003 – from the National Health Research Institutes Database (NHRID) of Taiwan, which contains two million randomly sampled subjects, in this cohort study. We used Fine and Gray's survival analysis (competing with mortality) to compare the risk of developing dementia during a 15-year follow-up period (2000–2015).

Results: In general, HMCAA was not significantly associated with dementia (adjusted subdistribution hazard ratio [SHR] = 0.861, 95% confidence interval [CI] = 0.484–1.532, $p = 0.611$) for the HMCAA-cohort, although differential risk was observed among the groups at risk. The patients with usage of HMCAA aged ≧ 85 years were associated with a higher risk in dementia (adjusted SHR: 6.243, 95% CI=1.258–21.084, $p = 0.001$), in comparison to those aged 50–54 years. Furthermore, the patients with usage of HMCAA that had cerebrovascular accidents were associated with an increased risk of dementia.

Conclusion: The usage of HMCAA was associated with the risk of developing dementia in the patients aged ≧ 85 years.

Keywords: herbal medicine containing aristolochic acids, traditional Chinese herbal medicines, dementia

Introduction

Dementia is a global public health problem,[1] and it has been estimated that the prevalence was of 2–5% for the population aged ≥65 years in Taiwan's community studies.[2–4] Dementia causes a significant increase in the cognitive and functional impairment; therefore, it is considered as a heavy burden to the caregivers and the society of these patients.[5–8] Injuries on the brain such as traumatic brain injury,[9] stroke,[10] or carbon monoxide intoxication,[11,12] could also contribute to the development of dementia. Further study is therefore needed to evaluate other toxic chemicals and the risk of dementia.

Herbal medicine containing aristolochic acids (HMCAA) have been widely used in traditional Chinese medicine.[13–15] However, the Committee on Chinese Medicine and

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the Pharmacy of the Department of Health in Taiwan has banned HMCAA since 2003,[14] because of its nephrotoxicity.[16–18] HMCAA is an inhibitor of phospholipase A2, and even an apoptosis inducer.[19] In addition, phospholipases serve as mediators of the amyloid-beta peptide neurotoxicity, as an early event contributing to the neurodegeneration characteristic of Alzheimer's disease.[20] On the other hand, previous studies have found that other traditional medicines, such as Jia-Wei-Xiao-Yao-San, were associated with a lower risk of dementia.[21,22] However, the association between HMCAA and dementia has not, as yet, been studied. We have therefore conducted this study to investigate as to whether HMCAA was associated with the risk of dementia, by using a nationwide, population-based database in Taiwan, the National Health Insurance Research Database (NHIRD).

Methods

Data Sources

We used the Longitudinal Health Insurance Database (LHID), a subset of two million randomly sampled patients from the NHIRD, during a 15-year period (2000–2015) in this study. Taiwan's National Health Insurance (NHI) Program was launched in 1995, and had contracts with 97% of the medical providers and enrolled more than 99% of the 23 million population, as of June, 2009.[23] The details of the program have been documented in previous studies.[24–36]

Ethics Approval

This study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). This study was approved by the Institutional Review Board (IRB) of the Tri-Service General Hospital (TSGH). The TSGH IRB waived the need of individual consents since all the identification data were encrypted in the NHIRD (IRB No. 2-107-05-026).

Study Design and Participants

The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)[37] diagnostic codes were used in the NHIRD. Each diagnosis of dementia was made by a board-certified psychiatrist or neurologist according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), and its Text-revised edition (DSM-IV-TR).[38,39] The records of ambulatory care visits and inpatient claims by the NHI Administration are randomly reviewed, to verify the accuracy of the diagnoses.[40] Therefore, using the NHIRD is considered as being suitable to study the association between HMCAA and the risk of development of dementia.

This is a retrospective cohort study. Patients who first started to use HMCAA from January 1, 2000, to December 31, 2003, were identified. The exclusion criteria were those using HMCAA before 2000, those diagnosed with dementia before 2000, and patients with kidney disease, liver disease, and hepatoma. A total of 199 patients who used HMCAA were enrolled, and another 597 patients who had not used HMCAA were enrolled as the control group, at a ratio of 1:3, propensity score-matched by age, sex, and index year, from the NHRID (Figure 1).

The HMCAA Medications

The records of HMCAA were retrieved from the NHIRD. We also calculated the estimated cumulative dosage of aristolochic acid for each subject using an estimated average dosage of aristolochic acid per 1 g. For Guan Mu Tong, Guang Fang Ji, Ma Dou Ling, Qing Mu Xiang, Tian Xian Teng, and Xi Xin, this was 2.59, 2.04, 0.63, 0.009, 0.026, and 0.042 mg, respectively, with the reference from one previous study on HMCAA.[41] We also analyzed the cumulative dosage as 1–250, 251–500, 501–1000, >1000 mg of HMCAA and the risk of dementia.

Covariates

Covariates included sex, age (50–54, 55–64, 65–74, 75–84, ≧85), geographical area of residence (northern, central, southern, and eastern Taiwan), urbanization level (levels 1 to 4, as described below), seasons for medical help, monthly insured premiums (in New Taiwan dollars (NT$): <18,000, 18,000–34,999, ≥35,000), and levels of medical care (medical center, regional hospital, and local hospital). For indexing comorbidity, we used the Charlson comorbidity index (CCI, scores of 0, 1, 2, 3, ≧4), which is the most widely used comorbidity index in the literature.[13,42] Other comorbidities were diabetes mellitus, hypertension, hyperlipidemia, obesity, chronic kidney disease (CKD), atrial fibrillation, and cerebrovascular accidents (CVA). We also included the common indications of the usage of HMCAA as hepatitis, UTI, dysuria, urolithiasis, vaginitis, scrotum swelling, inguinal hernia, dysmenorrhea, oral ulcer, upper respiratory tract infection (URI), bronchitis, pneumonia, cough, allergy, eczema, headache, arthralgia, pain, neuralgia, heart failure, edema, CVA (Table S1). [41]

Major Outcome

All of the study participants were followed from the index year until the onset of dementia, death, withdrawal from the NHI program, or the end of 2015. Patients with dementia were identified by the ICD-9-CM codes of 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0, and the types of dementia are grouped as follows: Alzheimer dementia (AD), vascular dementia (VaD), and other dementia (Table S1).

Statistical Analysis

All analyses were performed using the SPSS software version 22.0 for Windows (IBM Corp., Armonk, NY). χ^2 and *t*-tests were used to evaluate the distribution of the categorical and continuous variables between the patients who did and did not use HMCAA. In addition, the Fisher exact test for categorical variables was used to statistically examine the differences between the two cohorts, while the sample size was < 5. For the analysis of the non-normally distributed variables between the cohorts, the *U*-test was used. Fine and Gray's survival analysis and regression analysis were used to determine the risk of dementia (competing with mortality), and the results were presented as a subdistribution hazard ratio (SHR) with a 95% confidence interval (CI).[43] The Value-added module, including the Competing Risks Survival Analysis, in the SPSS, was used to conduct the Fine and Gray's survival analysis (https://www.asia-analytics.com.tw/en/product/p-asia-analytics-2.jsp). Differences in the risk of dementia between the two groups were estimated using the Kaplan–Meier method with the Log-rank test. A 2-tailed p value <0.05 was considered to be statistically significant.

Results

Baseline Characteristics of the Study Population

Table 1 depicts the baseline characteristics of the study population. There were 199 subjects in the HMCAA usage group and 597 in the non-HMCAA controls, with a similar

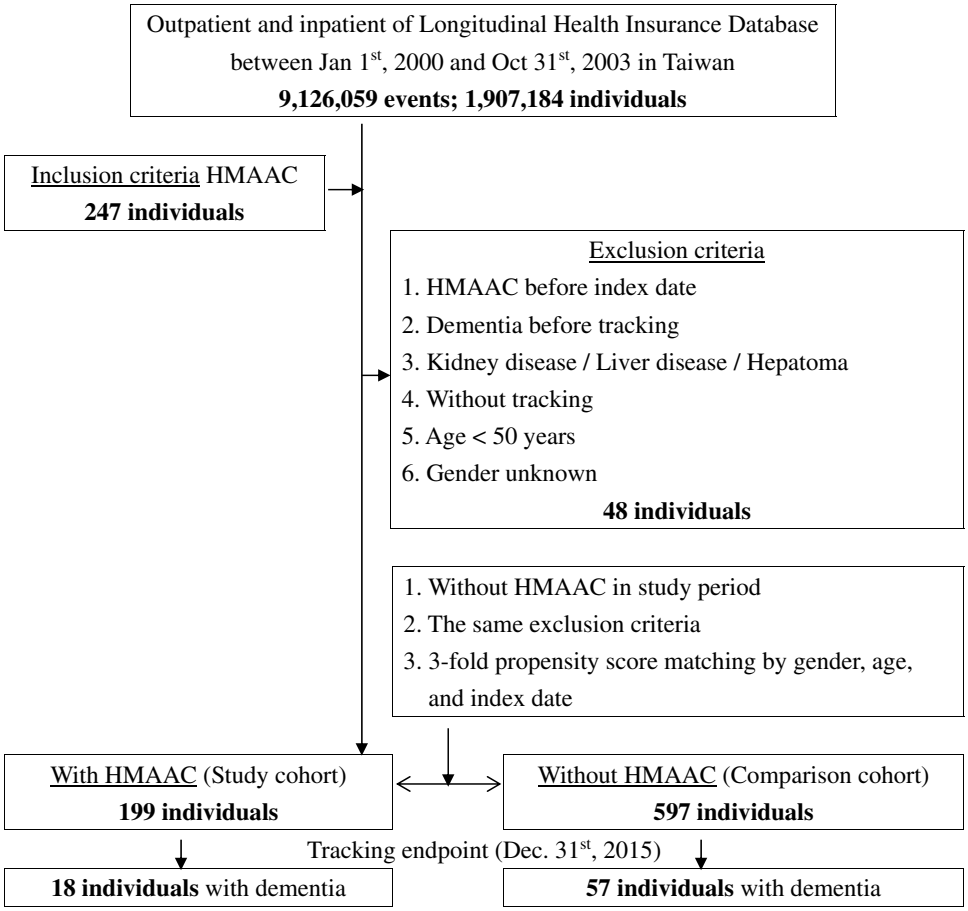

Figure 1 The flowchart of study sample selection.

Table 1 Characteristics of Study at the Baseline

Variables	HMAAC	With		Without		P
		n	%	n	%	
Total		199	25.00	597	75.00	
Gender						0.999
Male		104	52.26	312	52.26	
Female		95	47.74	285	47.74	
Age (years)		67.23 ± 9.78		67.04 ± 9.20		0.816
Age group (years)						0.999
50–54		26	13.07	78	13.07	
55–64		53	26.63	159	26.63	
65–74		71	35.68	213	35.68	
75–84		49	24.62	147	24.62	
≧85		0	0.00	0	0.00	
Insured premium (NT$)						0.605
<18,000		196	98.49	591	98.99	
18,000–34,999		3	1.51	5	0.84	
≧35,000		0	0.00	1	0.17	
Diabetes mellitus		33	16.58	103	17.25	0.913
Hypertension		48	24.12	122	20.44	0.273
Hyperlipidemia		9	4.52	20	3.35	0.512
Obesity		0	0.00	0	0.00	–
Chronic kidney disease		0	0.00	0	0.00	–
Atrial fibrillation		6	3.02	9	1.51	0.224
Cerebrovascular accidents		16	8.04	63	10.55	0.340
Hepatitis		0	0.00	0	0.00	–
Urinary tract infection		14	7.04	39	6.53	0.870
Dysuria		1	0.50	0	0.00	0.250
Urolithiasis		0	0.00	0	0.00	–
Vaginitis		1	0.50	0	0.00	0.250
Scrotum swelling		0	0.00	0	0.00	–
Inguinal hernia		6	3.02	8	1.34	0.127
Dysmenorrhea		0	0.00	0	0.00	
Oral ulcer		0	0.00	0	0.00	–
Upper respiratory infection		2	1.01	7	1.17	0.847
Bronchitis		11	5.53	28	4.69	0.704
Pneumonia		10	5.03	32	5.36	0.855
Cough		0	0.00	1	0.17	0.563
Allergy		0	0.00	0	0.00	–
Eczema		0	0.00	0	0.00	–
Headache		0	0.00	0	0.00	–
Arthralgia		0	0.00	2	0.34	0.414
Pain		0	0.00	0	0.00	–
Neuralgia		0	0.00	0	0.00	–
Heart failure		7	3.52	17	2.85	0.635
Edema		1	0.50	1	0.17	0.438
CCI_R group						0.906
0		165	82.91	500	83.75	
1		16	8.04	37	6.20	
2		3	1.51	10	1.68	
3		12	6.03	38	6.37	
≧4		3	1.51	12	2.01	
Season						0.969
Spring (Mar–May)		59	29.65	166	27.81	
Summer (Jun–Aug)		40	20.10	123	20.60	
Autumn (Sep–Nov)		41	20.60	126	21.11	
Winter (Dec–Feb)		59	29.65	182	30.49	
Location						0.398
Northern Taiwan		75	37.69	236	39.53	
Middle Taiwan		50	25.13	151	25.29	
Southern Taiwan		61	30.65	159	26.63	
Eastern Taiwan		13	6.53	42	7.04	
Outlets islands		0	0.00	9	1.51	
Urbanization level						0.410
1 (The highest)		77	38.69	196	32.83	
2		80	40.20	258	43.22	
3		14	7.04	39	6.53	
4 (The lowest)		28	14.07	104	17.42	
Level of care						0.567
Hospital center		61	30.65	205	34.34	
Regional hospital		63	31.66	188	31.49	
Local hospital		75	37.69	204	34.17	

Notes: Age of dementia (yrs): 75.70 ± 8.96 (overall), 76.11 ± 6.64 (HMAAC group), 75.57 ± 9.63 (non-HMAAC group).

Abbreviations: HMAAC, herbal medicine containing aristolochic acid; *P*, Chi-square/Fisher exact test on category variables and Mann–Whitney *U*-test on continuous variables.

distribution of sex, age, insured premiums, CCI scores, comorbidities, medical indications, seasons, geographical area of residence, urbanization levels, and levels of medical care.

The Association Between HMCAA and Dementia in the Patients Aged ≧ 85 Years

Of the HMCAA usage group, 18 (674.29 per 100,000 person-years) developed dementia when compared to 57 (706.82 per 100,000 person-years) in the control group, after the 15-year follow-up. The Kaplan–Meier analysis was used for the dementia-free survival in the HMCAA-users and user controls

(Log-rank test, $p = 0.909$) in Figure 2. In addition, the overall mean ages at the beginning of the dementia were: 75.70 (Standard deviations [SD] ± 8.96) years for), 76.11 (SD ± 6.64) years for the HMAAC group, and 75.57 (SD± 9.63) years for the non-HMAAC group.

Table 2 depicts that Fine and Gray's survival analysis revealed that the adjusted SHR for dementia was 0.861 (95% CI = 0.484–1.532, p = 0.611), when compared with the controls, after adjusting for age, sex, CCI scores, and all the covariates. There were multicollinearities between the urbanization levels and regions, thus we only analyzed the urbanization levels. The adjusted SHR for patients aged ≧85 years was adjusted SHR: was 6.243 (95% CI=1.258–21.084, p = 0.001) in contrast to patients with age 50–55. Furthermore, the patients with usage of HMCAA with cerebrovascular accidents were associated with the risk of dementia (adjusted SHR as 6.096, 95% CI=3.466–9.720, p<0.001). But the patients with medical help from the medical center (adjusted SHR as 0.562, 95% CI=0.262–0.996, p=0.044) and the regional hospital were associated with a lower risk of dementia (adjusted SHR as 0.534 as 95% CI=0.290–0.984, p<0.039).

Table S2 depicts that the Cox regression model revealed that the adjusted HR for dementia was 0.929 (95% CI = 0.528–1.634, p = 0.797), when compared with the controls, after adjusting for age, sex, CCI scores, and all the covariates. There were multicollinearities between the urbanization levels and regions, thus, we only analyzed the urbanization levels. The adjusted HR for the patients aged ≧85 years was 8.996 (95% CI=1.813–31.020, p = 0.001) in contrast to the patients aged 50–55 years. Furthermore, the patients with usage of HMCAA with urinary tract infection (adjusted HR as 6.157, 95% CI=3.563–10.640, p<0.001) were associated with the risk of dementia. The patients who resided in the urbanization level 1 area (adjusted HR as 1.990, 95% CI=1.032–3.835, p=0.040) were also associated with the risk of dementia. But the patients with the CCI 1 (adjusted HR as 0.128, 95% CI=0.017–0.968, p=0.046) were associated with a lower risk of dementia.

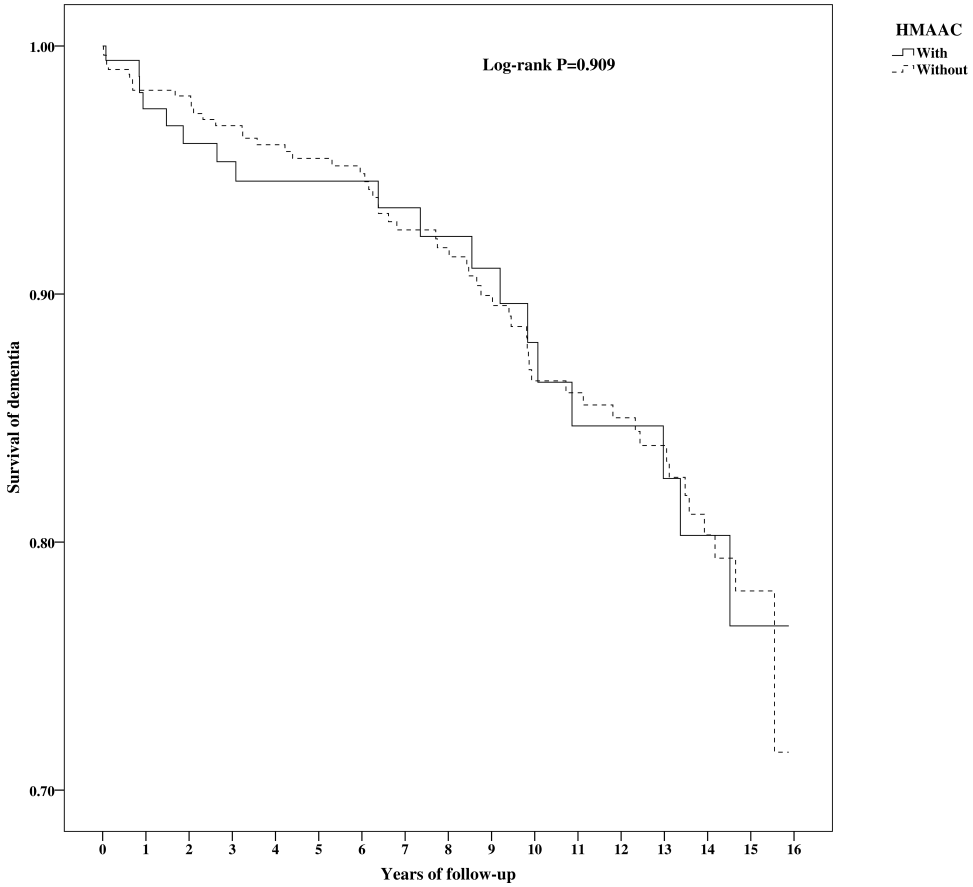

Figure 2 Dementia-free survival for patients with HMCAA users and non-users during the 15-year follow-up period in Taiwan from the index year.

Table 2 Factors of Dementia by Using Cox Regression

Variables	Competing Risk in the Model							
	Crude HR	95% CI	95% CI	P	Adjusted HR	95% CI	95% CI	P
HMAAC (reference: without)	0.960	0.565	1.631	0.881	0.861	0.484	1.532	0.611
Male (reference: female)	1.008	0.640	1.586	0.974	1.328	0.783	2.254	0.292
Age 55–64 (reference: Age 50–54)	0.679	0.323	1.429	0.308	0.650	0.215	1.356	0.456
Age 65–74 (reference: Age 50–54)	1.016	0.514	2.006	0.964	1.009	0.479	1.996	0.664
Age 75–84 (reference: Age 50–54)	1.641	0.671	4.016	0.278	1.477	0.590	3.925	0.146
Age≧85 (reference: Age 50–54)	7.247	1.340	35.233	0.013	6.243	1.258	21.084	0.001
Insurance premium (NT$)18,000–34,999 (reference: <18,000)	0.653	0.091	4.702	0.672	0.423	0.051	3.491	0.424
Insurance premium (NT$)≧35,000(reference: <18,000)	0.000	–	–	0.989	0.000	–	–	0.996
Diabetes mellitus (reference: without)	0.929	0.547	1.579	0.785	1.067	0.549	1.702	0.908
Hypertension (reference: without)	0.741	0.457	1.201	0.224	0.480	0.169	1.059	0.063
Hyperlipidemia (reference: without)	0.593	0.145	2.422	0.467	0.527	0.117	2.379	0.405
Atrial fibrillation (reference: without)	0.610	0.150	2.485	0.490	0.648	0.151	2.791	0.561
Cerebrovascular accidents (reference: without)	4.764	3.006	7.550	<0.001	6.096	3.466	9.720	<0.001
Urinary tract infection (reference: without)	2.543	1.511	4.280	<0.001	1.715	0.935	3.147	0.081
Upper respiratory tract infection (reference: without)	0.000	–	–	0.992	0.000	–	–	0.996
Bronchitis (reference: without)	1.104	0.348	3.506	0.867	1.356	0.371	4.953	0.645
Pneumonia (reference: without)	0.640	0.278	1.477	0.296	1.041	0.778	1.694	0.078
Heart failure (reference: without)	0.181	0.025	1.301	0.089	0.145	0.018	1.136	0.066
CCI_R 1 (reference: CCI_R 0)	0.799	0.251	2.549	0.705	0.678	0.201	2.291	0.532
CCI_R 2 (reference: CCI_R 0)	2.293	0.719	7.315	0.161	1.848	0.512	6.664	0.348
CCI_R 3 (reference: CCI_R 0)	0.868	0.346	2.161	0.761	0.705	0.273	1.819	0.470
CCI_R≧4 (reference: CCI_R 0)	0.300	0.045	2.614	0.232	0.314	0.042	2.347	0.259
Summer (reference: Spring)	0.570	0.278	1.167	0.124	0.758	0.355	1.615	0.472
Autumn (reference: Spring)	0.706	0.362	1.376	0.306	0.859	0.433	1.850	0.765
Winter (reference: Spring)	1.555	0.833	2.905	0.166	1.758	0.902	3.426	0.098
Urbanization level 1 (reference: Urbanization level 4)	1.170	0.608	2.255	0.638	1.527	0.674	3.458	0.310
Urbanization level 2 (reference: Urbanization level 4)	1.190	0.638	2.221	0.585	1.251	0.617	2.538	0.534
Urbanization level 3 (reference: Urbanization level 4)	0.608	0.138	2.679	0.511	0.483	0.103	2.263	0.356
Medical center (reference: Local hospital)	0.537	0.302	0.955	0.034	0.562	0.262	0.996	0.044
Regional hospital (reference: Local hospital)	0.575	0.337	0.981	0.042	0.534	0.290	0.984	0.039

Notes: Interaction term (Age × HMAAC): $P = 0.013$.

Abbreviations: HMAAC, herbal medicine containing aristolochic acid; adjusted HR, adjusted hazard ratio: adjusted for the variables listed in Table 1; CI, confidence interval.

Table S3 reveals that the other type of dementia was found to be proportionately higher than AD and VaD, in both HMCAA and non-HMCAA groups. For example, there were 11.11% of AD in the HMCAA group. In addition, the adjusted SHR of AD, VaD, and other dementia were 2.601 (p = 0.189), 0.606 (p = 0.772), and 0.834 (p = 0.420), respectively.

Table S4 reveals the mortality information of this study, including the mean age of mortality and the leading causes of mortality in the HMCAA-users or non-user controls. The mean ages of the mortality of the HMCAA users were 75.99 (SD ± 7.72) years and 76.37 (SD ± 9.55) years. Table S5 depicts the sensitivity analysis for the risk of dementia by excluding the dementia diagnosis in the first, first two, and first 5 years.

Table S6 shows the subgroup analysis for the factors of dementia using the Cox regression and Fine and Gray's competing risk model. The p-values of the interaction term analysis of Age × HMAAC were 0.019 in the non-competing risk model and0.013 in the competing risk model.

For the adjustment of the different covariates, we conducted all the seven models, from no adjustment (Model 0) to adjustment with all the covariates (Model 6). All the

models of adjustment were not statistically significant (Table S7).

The Cumulative Dosage of HMCAA and the Risk of Dementia

The HMCAA was not associated with the increased risk of dementia in different cumulative dosages. After 2005, no usage of HMCAA was found in the participants from this study (Table 3).

Discussion

The Association Between HMCAA and the Risk of Dementia

After adjusting for the covariates, the overall adjusted SHR was 0.861 (95% CI = 0.484–1.532, p = 0.611), when compared with the controls. HMCAA was not significantly associated with the risk of different types of dementia. The Kaplan-Meier analysis revealed that the 15-year cumulative incidence rate between the HMCAA-cohort and the controls was not significant (p=0.909). The adjusted SHR for patients aged ≧ 85 years was 6.243 (95% CI=1.258–21.084, p = 0.001), in contrast to the patients aged 50–55 years. In other words, the patients in the HMCAA-cohort aged ≧ 85 years had a nearly sixfold increased risk of developing dementia. In addition, the Fine and Gray's model benefits from the use of the inclusion of the actual mortality data to study the usage of HMCAA as a risk factor for dementia.[44,45]

To our best knowledge, this is the first study on the topic of the association between the usage of HMCAA and the risk of dementia. Since HMCAA was widely used in Taiwan before 2003, the long-term effects could not be overlooked. Several countries have banned the usage of HMCAA,[14,46] and the Food and Drug Administration (FDA) has issued a warning about consuming HMCAA.[47] However, this fact does not detract from the relevance of the results for clinical practice: HMCAA-containing herbal medicine are still used in several countries such as China,[48] Korea,[49] and some Asian and Balkan countries.[50] In addition, HMCAA could also be detected in some raw herbal medicine.[51] This finding could serve as a reminder for the clinicians caring for those exposed to HMCAA, as to the potential risk of dementia in the elderly.

Comparison to Previous Literature

Several researchers have found the HMCAA-induced nephrotoxicity since 2002.[16,17,52–55] Some studies have

Table 3 Factors of Dementia in Different Model by Using Cox Regression and Fine and Gray's Competing Risk Model

Model	Subgroups	HMAAC				Non-Competing Risk in the Model				Competing Risk in the Model			
		Populations	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI		P	Adjusted HR	95% CI		P
Model 1	Without	597	57	8064.32	706.82	Reference				Reference			
With/Without	With	199	18	2669.49	674.29	0.929	0.528	1.634	0.797	0.861	0.484	1.532	0.611
Model 2	Without	597	57	8064.32	706.82	Reference				Reference			
Dose	1–100 mg	25	3	303.79	987.52	1.563	0.986	2.101	0.562	1.452	0.926	1.986	0.503
	101–200 mg	13	2	207.12	965.61	1.294	0.811	1.908	0.670	1.209	0.799	1.843	0.614
	201–300 mg	17	2	243.89	820.05	1.012	0.798	1.709	0.684	1.003	0.725	1.675	0.678
	301–400 mg	20	2	291.12	686.99	0.899	0.501	1.445	0.813	0.834	0.496	1.402	0.792
	401–500 mg	23	2	300.12	666.39	0.803	0.426	1.397	0.792	0.798	0.413	1.335	0.711
	>500 mg	101	7	1323.44	528.93	0.724	0.306	1.230	0.861	0.701	0.298	1.184	0.826
Model 3: Dosage	Continuous variables	796	75	10,733.81	698.73	0.921	0.506	1.584	0.629	0.865	0.487	1.539	0.602

Notes: Trend test of Model 2: $P = 0.067$ (non-competing risk in the model), $P = 0.054$ (competing risk in the model).
Abbreviations: HMAAC, herbal medicine containing aristolochic acid; PYs, person-years; adjusted HR, adjusted hazard ratio: adjusted for the variables listed in Table 1; CI, confidence interval.

also found that HMCAA are associated with the risk of urothelial carcinoma,[18,56–58] hepatocellular carcinoma,[41] small intestine cancers,[59] and renal cell carcinoma.[59] Furthermore, Chinese herbalists exposed to HMCAA also were associated with an increased risk of renal failure[60] and urothelial carcinoma.[61] The present study is the first on the topic of the association between HMCAA and the risk of dementia.

Potential Mechanisms for HMCAA and Dementia

Aristolochic acids could inhibit phospholipase A2, and thus, decrease the production of prostaglandins.[62] This mechanism could be a double-edged sword: Previous studies have shown that chemicals from *Aristolochia arcuata*, consisting of HMCAA, have neurotrophic and neuroprotective effects by decreasing the neuroinflammation.[63,64] As some prostaglandins could also be neuroprotective, this mechanism could decrease the levels of these prostaglandins. In addition, there is an aging-shifted prostaglandin profile in the endothelium,[65] and this might also play a role in the brain, and not only in the cardiovascular system. We hypothesize that a decrease of neuroprotective prostaglandins might as well contribute to the risk of dementia in patients, especially in the elderly patients, in the present study. However, the underlying mechanisms for the association between HMCAA and dementia in the elderly needs more detailed studies.

Furthermore, in the present study, patients who used HMCAA with CVA were also associated with the risk of dementia (adjusted SHR as 6.096, 95% CI=3.466–9.720, p<0.001). Previous studies have shown that CVA was also associated with the risk of dementia.[66,67] The association between the patients with medical help from the medical centers (adjusted SHR as 0.562, 95% CI=0.262–0.996, p=0.044) and regional hospital (adjusted SHR as 0.534 as 95% CI=0.290–0.984, p<0.039) and the lower risk of dementia might reflect the impact of socio-economic levels on the risk of dementia.

Issues on the Validity of Dementia Diagnosis and Prescriptions

In the present study, using a claims database for dementia diagnosis and medications, the missed or wrong classification in the dementia cases and medication users would be a crucial issue. Although there is not yet a study to validate the dementia diagnosis in the NHIRD, previous studies have shown that most of the validated diagnosis codes are for diseases with the modest to high sensitivity and positive predictive values.[68] Among these diseases, high sensitivity and positive predictive values were modest to high in several central nervous diseases, such as acute ischemic stroke[69] (sensitivity as 94.5% and positive predictive values as 97.9%) and epilepsy (sensitivity as 81.4% and positive predictive values as 76.8%).[70] One study have found that the medication dispensing error is 0.01% in Taiwan,[71] which is low and comparable to other developed countries, such as the United States (0.08%),[72] the United Kingdom (0.04),[73] and Slovenia (0.02%).[74] However, further studies are needed to validate the dementia diagnosis and the dispensing error rates in Taiwan's NHIRD and the hospitals or clinics.

Interactions Between Age and the HMCAA Effects

The elder age is also a risk for the development of dementia.[2–4,75] Table S6 revealed that the p-values of the interaction term analysis of Age × HMAAC were 0.019 in the non-competing risk model and 0.013 in the competing risk model for the patients aged ≧ 85 years. Therefore, there was interaction in the age of the HMCAA usage in the patients aged ≧ 85 years.

Limitations

The present study has several limitations that warrant consideration. First, like previous studies using the NHIRD, the data regarding severity, staging, and the caregiver burden of dementia, genetic, psychosocial, laboratory parameters, and environmental factors, were not reported in this claims database. Second, over the counter (OTC) HMCAA for inflammatory diseases was not included in the NHIRD. In addition, HMCAA could also be detected in the dietary supplements used as slimming regimens.[76] However, most of the people would ask for help from the NHI-contracted hospital or clinics for their inflammatory diseases due to the high coverage of medical providers (97%) and beneficiaries (more than 99%) of the NHI system in Taiwan. Furthermore, it is possible that OTC HMCAA could have been used by both groups in this study before the enrollment of the two cohorts. However, it is likely that these two groups, the HMCAA-cohort and the control, have had the same opportunity to have used OTC HMCAA in 2000. Third, there could be differences between the physicians'

prescriptions and the patients' intake, for example, 47.5% of the patients toward hypertension showed non-adherence with antihypertensive medications.[77] However, we could estimate that the patients' intake of medications may well be in a reasonable proportion from the physicians' prescriptions. Fourth, Taiwan's prevalence rate of dementia is 2–5%, which is low compared with international estimates, ranging from 4.6% in Central Europe, 8.7% in North Africa and the Middle East, and 5.6% to 7.6%, in other regions.[78] Therefore, there is an under-ascertainment limitation in this study. Fifth, there could be several residual confounding factors in this study, although we have divided as non-modifiable factors, such as sex and age, and modifiable factors, such as comorbidities, geographical area of residence, urbanization level, seasons for medical help, monthly insured premiums, and levels of medical care. Sixth, in our study, other type of dementia was found to be proportionately higher than AD and VaD. However, in Taiwan, several community studies revealed that Alzheimer-type dementia is the most common cause of dementia (40–-60% in all dementias), followed by vascular dementia (20–30% in all dementias), and mixed or other dementias (7–15%).[2,3,79] One possible explanation for this disparity is that some subjects were classified as other degenerative type of dementia, similar to the findings of previous studies.[80,81] Seventh, we failed to identify the factors, such as selective purchase or cultural differences, that could distinguish the HMCAA-users from the non-users by the characteristics at the study baseline (Table 1). Nonetheless, several previous studies have found individuals that are female, aged 35–59 years, in higher socioeconomic levels, with unhealthy lifestyles, and living in the areas of higher density of practicing traditional Chinese herbal medicine physicians, tend to use more Chinese herbal medicine products.[82–84] Eighth, in the present study, the HMCAA users were matched with the non-users by sex, age, and index year, not including other covariates. This could be a limitation in the lack of population-based weights and propensity matching. However, a matching that included all the covariates could result in a problem that there were no enough non-users as the control group with an exact matching. In addition, even a 1:4 case-control ratio is one way to achieve higher statistical power,[85] however, in the present study, we adopted a practical ratio as 1:3 matching, for obtaining enough controls for the study.

Conclusion

In general, the HMCAA-cohort was not associated with the risk of dementia. However, the usage of HMCAA in patients aged ≧ 85 years was associated with a nearly sixfold higher risk of dementia, in comparison to the controls. This finding could serve as a reminder for clinicians in charge of care for the patients who have used HMCAA, as to the potential risk of dementia in patients aged ≧ 85 years.

Data Sharing Statement

Data are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Administration. Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act", data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (http://www.mohw.gov.tw/cht/DOS/DM1.aspx?f_list_no=812).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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