

Association Between Silymarin Use and Age-related Macular Degeneration in Patients With Chronic Hepatic Diseases: a Population-based Retrospective Cohort Study

Mu-Ming Chien

Taipei Medical University

Hsiu-Chen Lin

Taipei Medical University

Li-Fen Lee

Taipei Medical University

Joseph Jordan Keller

Ohio State University

Li-Hsuan Wang (✉ shiuhan@tmu.edu.tw)

Taipei Medical University

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Abstract

Silymarin is a bioflavonoid compound mostly used in patients with chronic hepatic diseases (CHDs). It has been shown to inhibit retinal angiogenesis in in vitro and in vivo animal studies. Age-related macular degeneration (AMD) is a leading cause of vision impairment worldwide, and no definite preventive measures for AMD exist at present. Through this study, we aimed to investigate whether the use of silymarin affects the risk of AMD in patients with CHDs. Cox proportional hazard models were used to assess the hazard ratio (HR) of AMD in this population-based retrospective cohort study. The CHDs was associated with a higher risk of AMD (adjusted hazard ratio (aHR): 1.33, 95% CI 1.22–1.46), and the use of silymarin reduced the risk of AMD among patients with CHDs (aHR: 0.76, 95% CI: 0.67–0.87). A higher accumulative dose (defined daily dose [DDD] < 631 mg) of silymarin was associated with a lower risk of AMD, but the difference was nonsignificant. In conclusion, CHDs were associated with a higher incidence of AMD, and the use of silymarin was associated with a reduced risk of AMD in patients with CHDs. However, a higher accumulative DDD of silymarin did not reduce the risk of AMD.

Introduction

Age-related macular degeneration (AMD) is a disease that affects the macular region of the retina, causing the progressive loss of central vision. It is currently the third leading cause of vision impairment worldwide, and the number of individuals with AMD is expected to reach approximately 200 million by 2020, posing a global health burden^{1,2}. AMD is a disease of the aging eye, with multiple factors including genetics and environmental factors affecting its course^{1,3}. Among these factors, oxidative stress had attracted much interest. Large randomized controlled trials have shown beneficial effects of the use of high-dose oral antioxidant vitamins in slowing the progress of AMD, leading to their inclusion in the treatment of AMD by some authorities^{4–6}. Other nutrients with antioxidant effects, such as anthocyanins and selenium, were also investigated⁷.

Silymarin, a bioflavonoid, is a natural compound extracted from *Silybum marianum*, or milk thistle⁸. Silymarin has been used as a traditional Chinese herbal medicine for more than 2,000 years, mostly in patients with chronic hepatic diseases (CHDs) such as viral hepatitis, nonalcoholic fatty liver disease, and cirrhosis⁸. It was found to have multiple potential pharmacological properties, such as antioxidant, anti-inflammatory, and hepatoprotective effects⁹. An in vitro study found that silibinin, the main bioactive component of silymarin, inhibited the secretion of vascular endothelial growth factor (VEGF) from retinal pigment epithelium cells¹⁰. In a rat model of AMD, it inhibited retinal edema and angiogenesis caused by VEGF and hypoxia conditions¹⁰. However, whether these results can be extrapolated to humans is still unknown. Thus, through this study, we aimed to investigate the effect of silymarin on the risk of AMD by using a nationwide health insurance database. Because silymarin is usually used in patients with CHDs, this specific population was analyzed.

Materials And Methods

Data source

This population-based, retrospective claim database study utilized the Longitudinal Health and Welfare Database (LHWD) provided by the Health and Welfare Data Science Center (HWDC) of Taiwan. This sampled database is derived from Taiwan's National Health Insurance database, which covers 99.9% of Taiwan's population as of 2014¹¹. The HWDC established and verified the sampled database.

Study design and patient selection criteria

The study period was from 2001 to 2014, and our patient enrollment period was from 2001 to 2009. The study flowchart is depicted in Figure 1. The International Classification of Diseases, ninth revision (ICD-9) code 571.X was used for the confirmation of CHD diagnoses, and codes 362.50, 362.51, and 362.52 were used for the diagnosis of AMD. Patients diagnosed as having CHDs twice from January 1, 2001 to December 31, 2009 were enrolled. Those aged < 40 years were excluded. The diagnosis date was defined as the date of the first diagnosis of CHDs, and the index date was defined as the date of the first recorded use of silymarin for Study Group I.

Among the patients diagnosed as having CHDs, Study Group I included patients with silymarin use and excluded patients who had used silymarin before the diagnosis date, those who had used silymarin for fewer than 90 days within 1 year after index date, those who had AMD before the diagnosis date, and those who were diagnosed as having AMD within 1 year after the index date. Among patients diagnosed as having CHDs who did not use silymarin, those diagnosed as having AMD before the diagnosis date were excluded, and those remaining were grouped into Study Group II.

From patients without CHDs or silymarin use, we randomly selected a group of patients and assigned them to the Comparison Group, which was 1:1 matched with Study Group II by age, sex, and year of diagnosis date. Because the patients in the Comparison Group were not diagnosed as having CHDs, the date used for matching was called the reference date in the Comparison Group. Patients from the Comparison Group who were diagnosed as having AMD before the reference date were excluded.

This study was approved by Ethics Committee of Taipei Medical University (TMU-JIRB, No.: N201610012). Because all NHIRD data are delinked and deidentified, the requirement for obtaining informed consent was waived. We confirm that all methods were performed in accordance with the relevant guidelines and regulations and the study had been performed in accordance with the Declaration of Helsinki.

Risk factors and confounding factors

The potential risk factors for AMD, including hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular diseases, coronary artery diseases, heart failure, peripheral vascular diseases, gastrointestinal disorders, dementia, obesity, tobacco use disorder, and alcohol abuse were identified in the patients. The potential confounding factors of medication use, including that of lipid-lowering agents

(statin, fibrate), antihypertensive agents (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers), and aspirin, were also evaluated.

Outcome measurement

Because we aimed to investigate the long-term use of silymarin in patients with CHDs, only those who had used silymarin for more than 90 days per year were included. We evaluated the occurrence of AMD in each group as the primary outcome. For the evaluation of the dose-response as the secondary outcome, the Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) system was used¹². Owing to lack of data regarding silymarin DDD in World Health Organization suggestions, we set its DDD to 420 mg according to the package insert¹³.

Statistical analysis

Among the different patient groups, means with standard deviations were used to describe age, and proportions were used to describe all other variables (including sex, comorbidities, and co-medication). Student's *t* test and Pearson's chi-squared test were performed to evaluate the differences in all the other baseline characteristics. The Cox proportional hazards regression model was used to analyze the risk of AMD between the groups. The potential risk factors mentioned in the previous section were included in the model.

Two-tailed hypothesis tests were used in all analyses, and $p < 0.05$ indicated statistical significance. SAS (version 9.4; SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Baseline characteristics

The LHWD database consisted of 113,387 patients aged > 40 years and diagnosed as having CHDs at least twice from 2001 to 2009. Among them, 14,579 were enrolled into Study Group I (patients with CHDs who used silymarin) and 54,866 were enrolled into Study Group II (patients with CHDs who did not use silymarin). The Comparison Group (the 1:1 matched control group, patients without CHDs or silymarin use) consisted of 53,320 patients. The baseline patient characteristics are shown in Table 1. All characteristics other than obesity significantly differed between Study Groups I and II. Between Study Group II and the Comparison Group, all characteristics other than sex significantly differed.

Table 1
Baseline characteristics of the study and comparison groups

Patients with CHDs					
Variables	With silymarin use (Study Group I) N = 14,579	Without silymarin use (Study Group II) N = 54,866	Without CHDs or Silymarin use (Comparison Group)	p value ^a	p value ^b
Age, years (mean ± SD)	56.42 ±10.49	56.11 ± 11.17	55.54 ± 10.70	0.0017	<0.0001
Sex/Male (n, %)	8486 (58.2)	27,311 (49.8)	26,465 (49.6)	<0.0001	0.6373
Hypertension (n, %)	6499 (44.6)	18,106 (33.0)	12,834 (24.1)	<0.0001	<0.0001
DM (n, %)	4344 (29.8)	11,352 (20.7)	6399 (12.0)	<0.0001	<0.0001
Hyperlipidemia (n, %)	4944 (33.9)	14,080 (25.7)	6967 (13.1)	<0.0001	<0.0001
Cerebrovascular disease (n, %)	1753 (12.0)	5579 (10.2)	4014 (7.5)	<0.0001	<0.0001
CAD (n, %)	3181 (21.8)	10,537 (19.2)	6074 (11.4)	<0.0001	<0.0001
Heart failure (n, %)	757 (5.2)	2406 (4.4)	1377 (2.6)	<0.0001	<0.0001
Peripheral vascular disease (n, %)	469 (3.2)	1354 (2.5)	809 (1.5)	<0.0001	<0.0001
GI disorder (n, %)	10,016 (68.7)	35,126 (64.0)	24,402 (45.8)	<0.0001	<0.0001
Dementia (n, %)	147 (1.0)	690 (1.3)	497 (0.9)	0.009	<0.0001
Obesity (n, %)	155 (1.1)	630 (1.2)	274 (0.5)	0.3773	<0.0001
Tobacco use disorder (n, %)	140 (1.0)	398 (0.7)	250 (0.5)	0.008	<0.0001

CHDs, chronic hepatic diseases; DM, diabetes mellitus; CAD, coronary artery disease; GI, gastrointestinal; CCB, calcium channel blocker; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; SD, standard deviation; GI, gastrointestinal

^aPatients with CHD in Study Group I vs. Study Group II; ^bPatients with CHD in Study Group II vs. Comparison Group

Patients with CHDs					
Alcohol abuse (n, %)	76 (0.5)	125 (0.2)	36 (0.1)	<0.0001	<0.0001
Statins (n, %)	2051 (14.1)	5909 (10.8)	3179 (6.0)	<0.0001	<0.0001
Fibrate (n, %)	1642 (11.3)	4018 (7.3)	2140 (4.0)	<0.0001	<0.0001
Aspirin (n, %)	456 (3.1)	1406 (2.6)	1228 (2.3)	0.0004	0.0056
CCB (n, %)	5939 (40.7)	16,173 (29.5)	11,473 (21.5)	<0.0001	<0.0001
ACEI (n, %)	3952 (27.1)	10,132 (18.5)	7347 (13.8)	<0.0001	<0.0001
ARB (n, %)	2174 (14.9)	5743 (10.5)	3630 (6.8)	<0.0001	<0.0001
CHDs, chronic hepatic diseases; DM, diabetes mellitus; CAD, coronary artery disease; GI, gastrointestinal; CCB, calcium channel blocker; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; SD, standard deviation; GI, gastrointestinal					
^a Patients with CHD in Study Group I vs. Study Group II; ^b Patients with CHD in Study Group II vs. Comparison Group					

Risk of AMD in patients with CHDs, with or without silymarin use

The risk of AMD in the different groups is shown in Table 2. Among patients with CHDs (Study Groups I and II), use of silymarin reduced the risk of AMD; the adjusted hazard ratio (aHR) was 0.76 (95% CI: 0.67–0.87). Among patients without silymarin use (Study Group II and Comparison Group), the diagnosis of CHDs was associated with a significantly higher risk of AMD (aHR 1.33, 95% CI 1.22–1.46). The results revealed that although patients with CHD were associated with a higher rate of AMD, silymarin use was associated with a reduction in the occurrence of AMD.

Table 2

Crude hazard ratios (HRs) and adjusted HRs for the risk of age-related macular degeneration (AMD) between the study and comparison groups

Patients with CHDs			
Results	With Silymarin use (Study Group I) N = 14,579	Without Silymarin use (Study Group II) N = 54,866	Without CHDs or Silymarin use (Comparison Group) N = 53,320
AMD (n, %)	292 (2.00)	1,394 (2.54)	864 (1.62)
Crude HR (95% CI)	0.79 (0.69–0.89) ^{***}	1	-
Adjusted HR (95% CI)	0.76 (0.67–0.87) ^{***}	1	-
Crude HR (95% CI)		1.58 (1.45–1.72) ^{***}	1
Adjusted HR (95% CI)		1.33 (1.22–1.46) ^{***}	1
CHDs, chronic hepatic diseases; AMD, age-related macular degeneration; HR, hazard ratio; CI, confidence interval; SD, standard deviation			
Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, cerebrovascular disease, coronary artery disease, heart failure, peripheral vascular disease, gastrointestinal disorder, dementia, obesity, tobacco use disorder, alcohol abuse, statin, fibrate, aspirin, calcium channel blocker, angiotensin-converting-enzyme inhibitor, and angiotensin II receptor blocker			
***p < 0.001, **p < 0.01, *p < 0.05			

Relation between risk of AMD and silymarin dose

Patients in Study Group I were further categorized into five subgroups according to the total exposure dose accumulation of silymarin (Table 3). Compared with Study Group II, the risk of AMD decreased as the total exposure dose accumulation of silymarin increased; however, the difference was not statistically significant (p for trend > 0.05). The aHRs in the <90, >90–270, >270–450, and >450–630 mg DDD groups were 0.78 (95% CI: 0.62–0.97), 0.78 (95% CI: 0.64–0.94), 0.69 (95% CI: 0.50–0.96), and 0.59 (95% CI: 0.35–0.98), respectively. However, the risk of AMD in patients with total silymarin exposure of more than 630 mg DDD was not significantly different from that in patients in Study Group II (aHR 0.86, 95% CI: 0.63–1.16).

Table 3

Dose-effect analysis of the risk of age-related macular degeneration in patients with chronic hepatic diseases who used silymarin

Results	Patients with CHDs and without silymarin use (Study Group II) N = 54,866	Patients with CHDs and silymarin use (Study Group I)				
		< 90 mg DDD N = 3,620	90–270 mg DDD N = 5,714	271–450 mg DDD N = 2,088	451–630 mg DDD N = 1,088	>631 mg DDD N = 2,069
AMD (n, %)	1,394 (2.54)	79 (2.18)	118 (2.07)	37 (1.77)	15 (1.38)	43 (2.08)
Crude HR	1	0.86	0.81	0.70	0.54	0.82
(95% CI)		(0.68–1.07)	(0.67–0.98)*	(0.50–0.96)*	(0.32–0.90)*	(0.60–1.10)
Adjusted HR	1	0.78	0.78	0.69	0.59	0.86
(95% CI)		(0.62–0.97)*	(0.64–0.94)**	(0.50–0.96)*	(0.35–0.98)*	(0.63–1.16)
CHDs, chronic hepatic diseases; AMD, age-related macular degeneration; HR, hazard ratio; CI, confidence interval; SD, standard deviation; DDD, defined daily dose						
Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, cerebrovascular disease, coronary artery disease, heart failure, peripheral vascular disease, gastrointestinal disorder, dementia, obesity, tobacco use disorder, alcohol abuse, statin, fibrate, aspirin, calcium channel blocker, angiotensin-converting-enzyme inhibitor, and angiotensin II receptor blocker						
**p < 0.01, *p < 0.05						

Discussion

In this study, we compared the incidence of AMD among three groups of patients by using a nationwide database: those with CHDs who used silymarin (Study Group I), those with CHDs who did not use silymarin (Study Group II), and those without CHDs or silymarin use (Comparison Group).

The study had stringent criteria; the included patients were required to have been diagnosed as having CHDs on at least two different occasions. To better evaluate the effect of silymarin on the occurrence of AMD, we included only patients with long-term silymarin use after the diagnosis of CHDs. Those who had AMD before using silymarin or within 1 year after initiating silymarin were excluded.

We found that patients with CHDs who did not use silymarin had a higher risk of AMD, with an aHR of 1.33 (95% CI, 1.22–1.46). Among patients with CHDs, use of silymarin was associated with a lower risk of AMD (aHR 0.76, 95% CI 0.67–0.87); however, no significant dose-dependent response was observed.

AMD is classified into two forms, a nonneovascular or “dry” form and a neovascular “wet” form. Anti-VEGF agents have shown to be an effective treatment for neovascular AMD, but no effective preventive measures exist¹⁴. Antioxidant vitamin supplements may slow the progression of AMD; however, a meta-analysis suggested that they do not prevent or delay the onset of AMD [^{15,16}]. Various other nutrients have been tested for their possible preventive effects against AMD, and the findings of the current study add silymarin to the list⁷.

Pretreatment of retinal pigmented epithelial cells with silibinin, the main component of silymarin, was shown to inhibit the hypoxia-induced pathway in a previous study, reducing VEGF secretion, thereby preventing hypoxia-induced angiogenesis in a rat model of AMD¹⁰. Other than AMD, in vitro studies have shown that silibinin can protect retinal ganglion cells from blue light-induced injury¹⁷ and prevent hyperpermeability induced by diabetic conditions in human retinal endothelial cells¹⁸. Further human studies are warranted to confirm the efficacy of silibinin in preventing these eye conditions.

The risk factors of AMD include age, genetics, smoking status, and diet¹. Liver disease was previously not considered a risk factor for AMD, but some case series have reported that retinopathy occurs in approximately 15% of patients with liver cirrhosis and 32% of patients with chronic hepatitis C^{19,20}. The authors of the aforementioned studies have suggested that loss of synthetic function of the liver and hemodynamic effects of portal hypertension in patients with cirrhosis might contribute to retinopathy, and immune-mediated ischemic retinopathy might be the pathogenesis underlying chronic C hepatitis - associated retinopathy^{19,21}. Pathologic angiogenesis is closely related to the fibrogenic progression of CHDs, with hypoxia and hypoxia-inducible factors playing a major role, and in vitro study has shown that antiangiogenic therapy is highly effective in significantly reducing fibrogenic progression²². We suggested that this pathologic angiogenesis also occurs in the retina, leading to a higher incidence of AMD in patients with CHDs, and can be suppressed with silymarin use.

The current study had some limitations. Because this was a retrospective study based on information from the health insurance database, the type of AMD that occurred, the type of CHD that was more related to the higher risk of AMD, and the type of AMD whose incidence was reduced by silymarin were difficult to discriminate. Further prospective trials with silymarin are warranted to answer these questions and help elucidate its mechanism.

In conclusion, CHDs were associated with a higher incidence of AMD, and the use of silymarin was associated with a reduced risk of AMD in patients with CHDs. However, a higher dose of silymarin was not associated with a significantly lower risk of AMD.

Declarations

Author contributions:

Mu-Ming Chien and Hsiu-Chen Lin contributed to conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. Li-Fen Lee contributed to conception and design, analysis and interpretation of data, and final approval of the version to be published. Joseph Jordan Keller partly contributed to acquisition of data, analysis and interpretation of data, revising it critically for important intellectual content and final approval of the version to be published. Li-Hsuan Wang contributed to conception and design, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published.

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Conflict of interest:

All authors have no conflict of interest, financial or otherwise.

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Figures

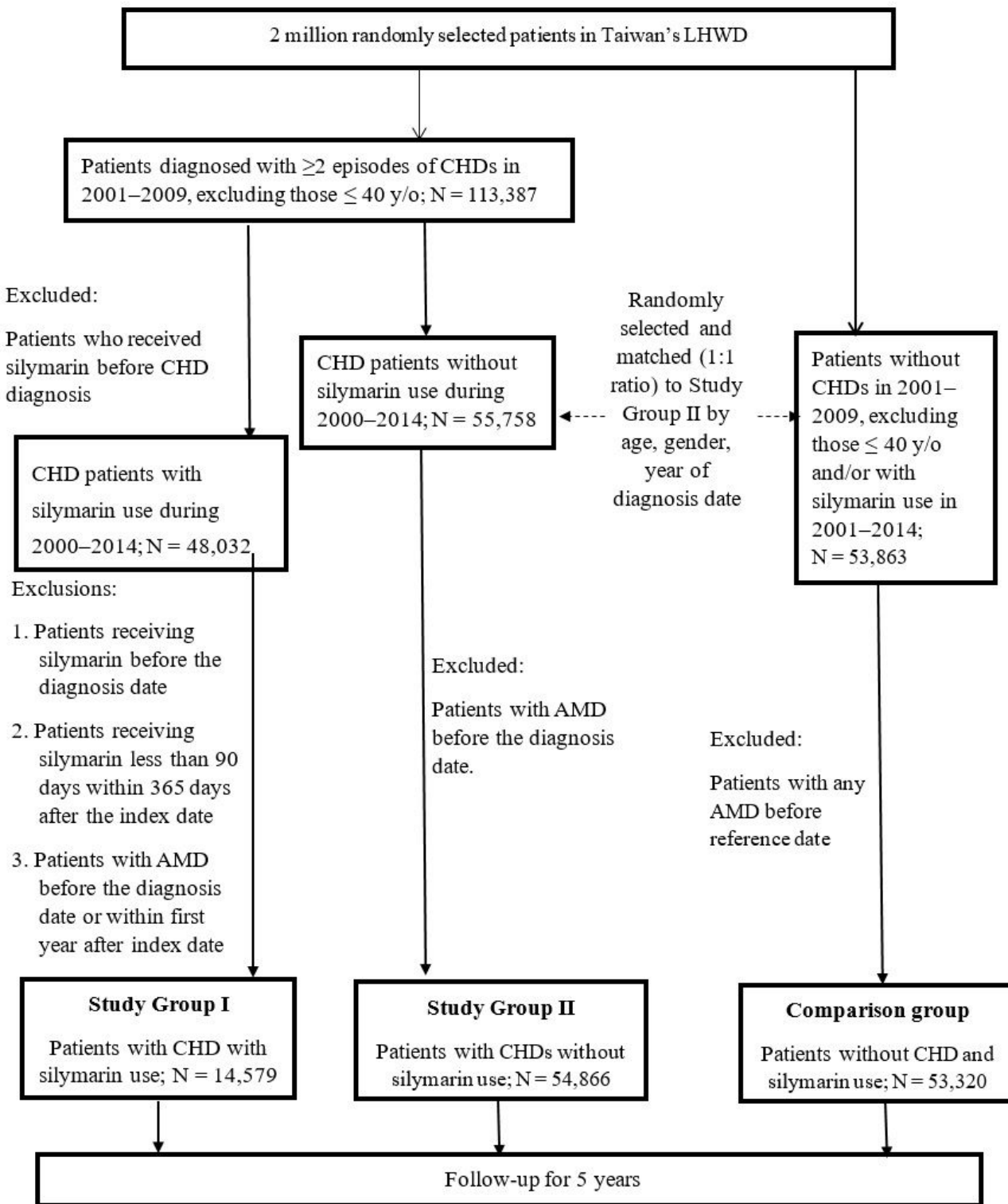


Figure 1

Study flowchart LHW: Longitudinal Health and Welfare Database. Diagnosis Date: the first date of CHDs diagnosis. Index Date: The first date of recorded silymarin use. Reference date of the patient in Comparison Group is the diagnosis date of the matched patient in Study Group II.