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The effectiveness of Fuzi in combination with routine heart failure treatment on chronic heart failure patients

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ABSTRACT

Ethnopharmacological relevance: Fuzi, Aconiti Lateralis Radix Praeparata, is widely used in Traditional Chinese Medicine (TCM) for the treatment of acute heart failure (HF) for 2000 years. However, the clinical evidence of Fuzi in the treatment of chronic HF is limited, especially when used in combination with Western medications.
Materials and methods: This population-based propensity score (PS)-matched cohort study aimed to evaluate the effectiveness of Fuzi on the chronic HF. From 4753 chronic HF patients who had used TCM herbal medicine, we performed 1:1 PS matching and selected target patients with (n = 921) and without (n = 921) Fuzi use for further analysis. The primary outcomes were all-cause mortality and composite cardiovascular (CV) outcomes. Hazard ratio (HR) was calculated by Cox proportional hazard regression and the competing risk analysis. The dose-response relationship and the association between the initiation of TCM herbal medicine and the primary outcomes were evaluated by restricted cubic spline (RCS) functions.
Results: There was no difference in all-cause mortality (HR, 0.99; 95% confidence interval [CI], 0.76–1.27) and composite CV outcomes (HR, 0.96; 95% CI, 0.84–1.11) between the Fuzi user and non-user groups. For CV safety issue, the result showed that Fuzi use was not associated with a higher risk of cardiac arrhythmias (HR, 1.03; 95% CI, 0.83–1.29). The dose-response relationship showed that Fuzi cumulative dose (≥150g) was associated with lower composite CV risk (HR, 0.76; 95% CI, 0.59–0.99). In addition, the RCS model showed that late initiation (≥2.5 years) of TCM herbal drugs in chronic HF patients had a higher risk of all-cause mortality (HR, 1.81; 95%CI, 1.07–3.08).
Conclusions: This study is the first real-world evidence to demonstrate the effect of Fuzi combined with routine HF treatment. Importantly, the result indicated that long-term Fuzi use had a significant benefit in preventing

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cardiovascular events. The late initiation of TCM herbal drugs was associated with a higher risk of all-cause mortality. Further clinical trials are needed to support or undermine the assumption of using Fuzi and current Western medications to treat chronic HF.

Abbreviations:

AF	atrial fibrillation
AFL	atrial flutter
BNP	B-type natriuretic peptide
CD	cumulative dose
CI	confidence interval
CV	cardiovascular
HF	heart failure
HR	hazard ratio
ICU	intensive care unit
NYHA	New York Heart Association
LVEF	left ventricular ejection fraction
PS	propensity score
RCS	restricted cubic spline
SHR	subdistribution hazard ratio
TCM	traditional Chinese medicine.

1. Introduction

In clinical practice, combination usage of Traditional Chinese Medicine (TCM) and Western medications are common in Asia. More and more clinical trials are exploring the benefits of combining Chinese and Western medicines (He et al., 2019). Fuzi, Aconiti Lateralis Radix Praeparata, is prescribed by TCM doctors to manage life-threatening situations such as cold extremities and weak pulse, and this practice started at least 2000 years ago (Nyirimigabo et al., 2015; Singhuber et al., 2009). TCM Fuzi decoction served as a life-saving prescription at that time when no Western medicine was available to treat diseases. Currently, Fuzi is also used to treat several clinical conditions such as neuralgia, polyuria, poor circulation, heart failure (HF), impotence, diabetes mellitus (DM), and arthritis (Tai et al., 2015). However, because of its potential toxicity, the application of Fuzi is still limited (Lu et al., 2010).

A systematic review and meta-analysis showed limited evidence of the efficacy and additional benefits of Fuzi formulas on HF (Yang et al., 2019). However, the study collected 1490 participants in twelve randomized controlled trials (RCT), in which the case numbers were limited, and the study design and endpoint of each RCT were different. According to our review (Tai et al., 2015), Fuzi related prescriptions are distributed as modern dosage forms such as botanical pills, capsules, and injections in China. For example, Qili-qiangxin capsules contain Fuzi and Astragali radix as the principal active components in addition to 11 other TCM herbs (Tao et al., 2013). Shenfu injection is another modern formula prepared by Fuzi and Ginseng. Both of these formulas were found to significantly improve the New York Heart Association (NYHA) classifications, reduce the serum level of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and left ventricular ejection fraction (LVEF) in HF patients as demonstrated by a randomized controlled trial (Li et al., 2013), and a meta-analysis study (Song et al., 2012). We noticed that the duration of drug treatment was less than one month, and the follow-up period was mostly less than six months in previous investigations. Therefore, the long-term effect of Qili-qiangxin capsules and Shenfu injection for HF patients remains unclear. Different from ancient times, the majority of HF patients are treated with β-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), diuretics, or digoxin in current clinical practice. The effect of Fuzi and Fuzi formulas in combination with Western medicine for HF patients also remains unclear.

In the United States and Europe, Fuzi is used as processed slices. In Taiwan, Fuzi and Fuzi-based formulas such as Sini Tang (Aconiti Lateralis Radix Praeparata, Zingiberis Rhizoma, and Glycyrrhizae Radix et Rhizoma*)* and Fuzi-Lizhong Tang (Aconiti Lateralis Radix Praeparata, Ginseng Radix, Zingiberis Rhizoma, Atractylodis Macrocephalae Rhizoma, and Glycyrrhizae Radix et Rhizoma) are produced as standardized commercial powders based on Taiwan's herbal pharmacopeia (Chiu et al., 2013; Tai et al., 2015). The total concentration of diester-diterpenoid alkaloids (DAs), including aconitine, mesaconitine, and hypaconitine should not be above 0.020% in crude Fuzi materials. On the other hand, the total concentration of monoester-diterpenoid alkaloids (MAs), including benzoylaconine, benzoylmesaconine, and benzoylhypaconine, the less toxic alkaloids, should be over 0.010%. The standard ensured the concentration of active components of Fuzi and avoided the possible toxicity.

TCM products are commonly prescribed through the Taiwanese healthcare system. The TCM prescriptions and Western medical records are all documented in the Taiwan National Health Insurance (NHI) Database, which provides a unique opportunity to evaluate the combination of TCM and Western medications. Therefore, this study aimed to evaluate for the first time the long-term effect of Fuzi combined with routine HF treatment among chronic HF patients using the Taiwan NHI Database.

2. Materials and methods

2.1. Data source

This retrospective cohort study was conducted using a longitudinal cohort of Taiwan NHI Database, which comprises a randomly sampled representative database of one million people from the entire NHI enrollees who were alive in 2000 (National Health Insurance Administration and Taiwan, 2014). The single-payer NHI program enrolled more than 99% of the 23 million people of Taiwan's population, and it was launched in 1995 (Huang et al., 2016). The Taiwan NHI Database contains claim records of the beneficiaries, such as the demographic data, inpatient records, outpatient prescriptions, and expenditure of the healthcare services. The study was approved by the Institutional Review Board of Antai Medical Care Cooperation Antai-Tian-Sheng Memorial Hospital (protocol number: 18-015-C; approval date: Feb. 21st, 2018).

2.2. Study design

We included patients with chronic HF between January 1, 2000 and December 31, 2010, who were identified by the International Classification of Diseases Revision, Ninth Revision, Clinical Modification (ICD-9-CM) code (Fig. 1). Out of 10,348 patients with chronic HF, we excluded 776 patients who were diagnosed with cancer before HF. To minimize the confounding by indication (Kyriacou and Lewis, 2016), we firstly identified chronic HF patients who had TCM herbal prescriptions after the HF diagnosis (n = 4947). The initiation of TCM or Fuzi prescriptions was the index date (Fig. 2). The end-of-follow-up date was defined as the earliest date of the following: 90 days after the last prescription of the TCM herbal or Fuzi prescriptions, date of death, and the last day of the cohort.

To enhance the internal validity, we excluded 194 participants whose dose of TCM prescriptions in the NHI database were missing (Fig. 1). Further, we searched for Fuzi as a single component and Fuzi-

based formulas from outpatient medical claims of NHIRD with the corresponding drug code of Fuzi. There were four Fuzi-based formulas used in the Taiwan NHI system, including Sini Tang, Fuzi-Lizhong Tang, Jenwu Tang (Aconiti Lateralis Radix Praeparata, Poria, Paeoniae Rubra Radix, Zingiberis Rhizoma, and Atractylodis Macrocephalae Rhizoma), and Mahuang-Fuzi-Hsihsin Tang (Ephedra Herba, Aconiti Lateralis Radix Praeparata, and Asari Radix et Rhizoma) (Tai et al., 2021a). All candidates were divided into the Fuzi user (n = 930) and non-user (n = 3823) groups (Fig. 1).

2.3. Matching strategy

To minimize confounding factors, we performed complete matching by sex and 1:1 propensity-score (PS) matching by age, first HF diagnosis date, time interval, medical comorbidities, and baseline Western medications (Tai et al., 2021b) (Fig. 2). The medical comorbidities included atrial fibrillation (AF)/atrial flutter (AFL), hypertension, diabetes mellitus (DM), cerebrovascular, ischemic heart, chronic obstructive pulmonary disease (COPD), hyperlipidemia, chronic kidney (CKD), and chronic liver diseases. The corresponding ICD-9-CM codes selected these comorbidities in outpatient medical claims before the index date (Fig. 2). The baseline medications were also considered as confounding covariates, including aspirin, clopidogrel, warfarin, digoxin, β-blockers, xanthine oxidase inhibitors, uricosuric agents, colchicine, amiodarone, calcium channel blockers (CCBs), diuretics, lipid-lowering agents (statins and other lipid-lowering agents), and ACEI/ARBs. The direct and PS matching were conducted using the PSMATCH procedure provided by SAS (SAS Institute Inc., Cary, NC, USA). Standardized mean differences were calculated to compare the distribution of baseline covariates between the ULT and the non-ULT groups after PS matching (Austin, 2009). A previous study suggested that a standardized mean difference above 0.1 denoted meaningful imbalance in the baseline covariates.

2.4. Outcome measures

The primary outcomes comprised all-cause mortality and composite CV outcomes, including CV death and admission due to HF, myocardial infarction (MI), stroke, and arrhythmias. All-cause mortality was identified by in-hospital death in the in-patient medical claims. The secondary outcomes were intensive care unit (ICU) admission and admission due to individual MI, HF, stroke, and arrhythmias. The specific admission code identified ICU admission.

2.5. Statistical analyses

All analyses were conducted using SAS version 9.4. The PS matching was carried out by the PSMATCH procedure. Baseline characteristics are described as mean ± standard deviation for continuous variables and number and percentage for categorical variables. The HR and 95% confidence intervals (CIs) of the all-cause mortality were calculated by the Cox proportional hazard model. The Kaplan–Meier method was used to compare the two groups for time-to-event analysis (Tai et al., 2021b).

Death was considered a competing risk because its occurrence could not be treated as independent censoring when analyzing the time of events (Tai et al., 2021b). Therefore, we conducted the proportional subdistribution hazard regression to calculate the HR of composited CV outcomes and secondary outcomes adjusted for the competing event of death. The SAS macros %CIF and %PSHREG were used for the competing risk analyses (Kohl et al., 2015).

Taking into account the continuous exposure in regression models was an important issue (Steenland and Deddens, 2004). Especially, sometimes the association between a dependent variable and the independent variable was not linear. To evaluate the dose-response relationship and the association between the initiation of TCM herbal medicine and the primary outcomes, we quantified the association using the restricted cubic spline (RCS) functions (Desquilbet and Mariotti, 2010). By RCS model, we did not have to categorize the exposure that several limitations had already been pointed out (Greenland, 1995).

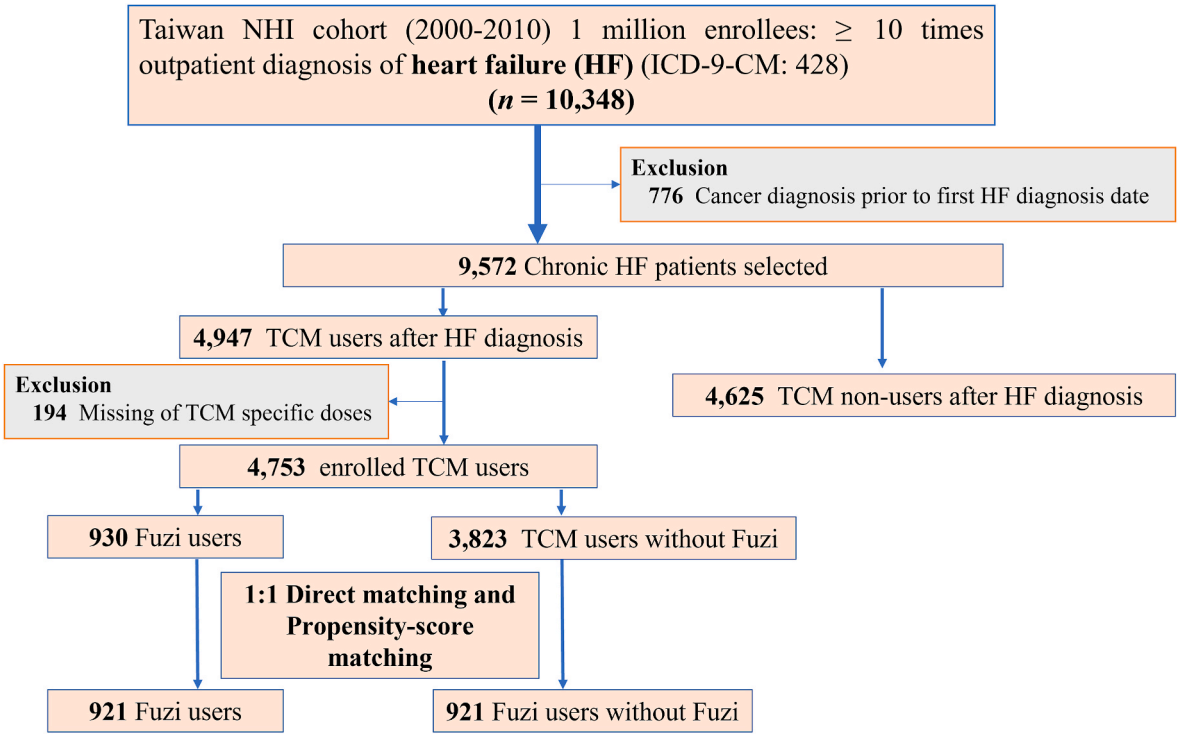

Fig. 1. Study flow chart. TCM, traditional Chinese medicine.

3. Results

3.1. Baseline characteristics

Before matching, the Fuzi user group was female predominant (70.4% *vs*. 69.7%), had a longer time interval between the first date of HF diagnosis and the index date (3.1 ± 2.6 vs. 1.9 ± 2.1 years), and had a higher rate of ischemic heart disease (41.6% *vs*. 35.3%), cerebrovascular disease (35.3% *vs*. 27.1%), COPD (62.0% vs. 52.5%), and chronic liver disease (34.1% *vs*. 27.4%) compared with the Fuzi non-user group (Table 1). The usage of routine HF treatment and related CV medications was not similar between the two groups, especially for the use of *β*-blockers (74.5% *vs*. 61.2%), CCBs (71.9% vs. 64.6%), diuretics (80.2% vs. 77.1%) were more frequent in the Fuzi user group.

After 1:1 PS matching by criteria, there were 921 patients in the Fuzi user group and 921 patients in the Fuzi non-user group. The time interval between the date of HF first diagnosis and index date was 3.0 ± 2.6 years. The mean follow-up was 1.4 ± 2.0 years. The mean age of the Fuzi user and non-user groups was 68.4 ± 13.4 *vs*. 67.9 ± 13.8 years, respectively. The CV-related covariates were well-balanced after PS matching (Table 1), with standardized mean difference below 0.1.

3.2. Outcomes

The risk of all-cause mortality was similar between the Fuzi user and non-user groups (HR, 0.99; 95% CI, 0.76–1.27) (Table 2). The Kaplan-Meier survival curve (Log-rank test, $p = 0.91$) also showed no difference between the two groups (Fig. 3A). Competing risk analysis showed no statistical difference of composite CV risks between the two groups (HR, 0.96; 95% CI, 0.84–1.11) while considering the competing risk of death (Table 2). The cumulative incidence function curves (Grey's test, $p = 0.60$) between the two groups showed no significant separation (Fig. 3B). The risk of ICU admission and admission due to HF, MI, and stroke were similar between the Fuzi user and non-user groups (Table 2). For CV safety issue, the result showed that Fuzi use was not associated with a higher risk of cardiac arrhythmias (HR, 1.03; 95% CI, 0.83–1.29).

3.3. Trend analysis

The median of Fuzi cumulative dose was 36 g (25th percentile, 15; 75th percentile, 99.4). To quantify the association between Fuzi cumulative doses and the outcomes, we set the median of Fuzi cumulative dose as the reference value and evaluated the risk by Cox regression in the RCS function. The result showed that Fuzi cumulative dose was not associated with the all-cause mortality (Table 3 and Fig. 4A). The RCS curve showed that the risk of CV events decreased with increasing Fuzi cumulative doses (Fig. 4B). Importantly, Fuzi users with cumulative doses >150g (HR, 0.76; 95% CI, 0.59–0.99) began to have a lower risk of CV events than Fuzi users with the median dose (Table 3). Fuzi cumulative doses >200g did not show additional protective effect. The results supposed that Fuzi cumulative doses reached 150–200g was enough to prevent CV events.

We also evaluated the effect of early or late initiation of TCM herbal drugs in relation to all-cause mortality and CV outcomes. We set one year of the time interval between first HF diagnosis and the index date as the reference value. The RCS curve showed that the late initiation of TCM herbal drugs (longer time interval) increased all-cause mortality risk (Fig. 5A). The time interval >2.5 years (HR, 1.81; 95% CI, 1.07–3.08) and >3.0 years (HR, 2.06; 95% CI, 1.23–3.47) had significantly increased risks of all-cause mortality (Table 4). In contrast, the risk of CV events did not increase with longer time intervals (Table 4 and Fig. 5B).

4. Discussion

4.1. Main findings

To the best of our knowledge, the current study is the first real-world evidence to demonstrate the long-term effect of Fuzi on chronic HF patients. In general, Fuzi was not associated with lower risk of all-cause mortality and CV risks compared to other TCM herbal drugs (Table 2). Dive into details, Fuzi only had an additional benefit on CV outcomes when Fuzi cumulative dose was between 150 and 200g in the trend analysis (Fig. 4B and Table 3). However, increased cumulative doses of Fuzi did not reduce the risk of all-cause mortality (Fig. 4A and Table 3). It indicated that, the effect of Fuzi did not strong enough to prevent death especially under additional TCM use. The result showed that Fuzi was an appropriate candidate among TCM herbal drugs for chronic HF patients to prevent cardiovascular outcomes on top of routine Western HF medications. Importantly, our result also demonstrated that the long-term usage of Fuzi did not increase the incidence of CV adverse events such as cardiac arrhythmias compared to the use of other TCM herbal drugs in chronic HF patients (Table 2).

The late initiation of TCM herbal drugs increased all-cause mortality risk in the trend analysis (Fig. 5A). The longer interval indicated that patients had longer HF courses, which might be related to the severity of HF. Therefore, the result could be interpreted in the two points of view as follows. One was that TCM herbal drugs might not be effective in the later stage of chronic HF. The other was that early initiation of TCM might bring benefits to chronic HF management. However, further clinical trials are needed to support or undermine these assumptions of using TCM herbal drugs on top of Western medications to treat chronic

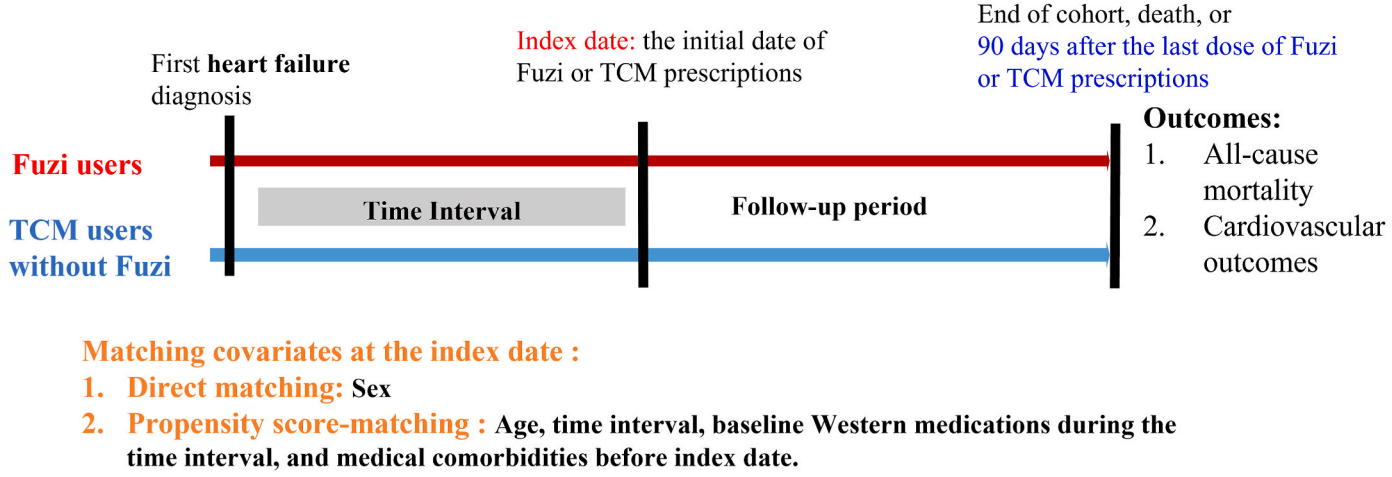

Fig. 2. Study design and matching covariates.

Table 1
Clinical demographics of chronic heart failure patients with traditional Chinese Medicine (TCM) herbal drugs with or without Fuzi before and after 1:1 propensity score (PS)-matching.

	Before PS Matching		*P*-Value	1:1 PS-matching		Standardized Mean Difference [a]
	Fuzi (+) $n = 930$	Fuzi (−) $n = 3823$		Fuzi (+) $n = 921$	Fuzi (−) $n = 921$	
Age, years	68.3 ± 13.4	68.5 ± 13.0	0.67	68.4 ± 13.4	67.9 ± 13.8	0.038
Female	655 (70.4%)	2665 (69.7%)	0.67	649 (70.5%)	649 (70.5%)	<.001
Intervals	3.1 ± 2.6	1.9 ± 2.1	<.001*	3.1 ± 2.6	3.0 ± 2.6	0.036
Comorbidities						
AF/AFL	147 (15.8%)	527 (13.8%)	0.11	144 (15.6%)	148 (16.1%)	0.012
Ischemic heart disease	387 (41.6%)	1348 (35.3%)	<.001†	383 (41.6%)	388 (42.1%)	0.011
Hypertension	743 (79.9%)	3052 (79.8%)	0.97	734 (79.7%)	764 (80.7%)	0.024
Diabetes mellitus	373 (40.1%)	1415 (37.0%)	0.08	369 (40.1%)	384 (41.7%)	0.033
Cerebrovascular disease	328 (35.3%)	1037 (27.1%)	<.001†	321 (34.9%)	329 (35.7%)	0.019
COPD	577 (62.0%)	2008 (52.5%)	<.001†	569 (61.8%)	574 (62.3%)	0.011
Hyperlipidemia	403 (43.3%)	1543 (40.4%)	0.10	399 (43.3%)	391 (42.5%)	0.018
Chronic kidney disease	122 (13.1%)	411 (10.8%)	0.04†	119 (12.9%)	129 (14.0%)	0.034
Chronic liver disease	317 (34.1%)	1048 (27.4%)	<.001†	313 (34.0%)	315 (34.2%)	0.005
Baseline medications						
Aspirin	621 (66.8%)	2230 (58.3%)	<.001†	613 (66.6%)	608 (66.2%)	0.011
Clopidogrel	137 (14.7%)	351 (9.2%)	<.001†	135 (14.7%)	123 (13.4%)	0.040
Warfarin	102 (11.0%)	336 (8.8%)	0.04†	101 (11.0%)	102 (11.1%)	0.004
Digoxin	397 (42.7%)	1456 (38.1%)	0.01†	391 (42.5%)	409 (44.4%)	0.040
β-blockers	693 (74.5%)	2338 (61.2%)	<.001†	684 (74.3%)	689 (74.8%)	0.012
XOI	137 (14.7%)	463 (12.1%)	0.03†	136 (14.8%)	141 (15.3%)	0.016
Uricosuric agents	187 (20.1%)	654 (17.1%)	0.03†	185 (20.1%)	170 (18.5%)	0.042
Colchicine	160 (17.2%)	572 (15.0%)	0.09	159 (17.3%)	163 (17.7%)	0.012
Amiodarone	105 (11.3%)	323 (8.5%)	0.007†	103 (11.2%)	101 (11.0%)	0.007
CCBs	669 (71.9%)	2471 (64.6%)	<.001†	661 (71.8%)	662 (71.9%)	0.002
Diuretics	746 (80.2%)	2949 (77.1%)	0.03†	738 (80.1%)	755 (82.0%)	0.045
Statin	313 (33.7%)	932 (24.4%)	<.001†	307 (33.3%)	294 (31.9%)	0.031
Other lipid lowering agents	146 (15.7%)	455 (11.9%)	0.002†	145 (15.7%)	141 (15.3%)	0.012
ACEI/ARBs	719 (77.3%)	2776 (72.6%)	0.004†	710 (77.1%)	714 (77.5%)	0.010

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; XOI, xanthine oxidase inhibitors.
* Independent *t*-test: *p*-value < 0.05. † Chi-square test: *p*-value < 0.05.
[a] The Standardized mean difference above 0.1 might denote meaningful imbalance in the baseline covariates.

Table 2
All-cause mortality and cardiovascular outcomes of chronic heart failure patients with traditional Chinese Medicine (TCM) herbal drugs with or without Fuzi.

	Fuzi (+) $n = 921$	Fuzi (−) $n = 921$	HR [a] (95% CI)	*P*-Value
Primary outcomes				
All-cause mortality	98 (10.6%)	153 (16.6%)	0.99 (0.76–1.27)	0.91
Composite CV outcomes	339 (36.8%)	466 (50.6%)	0.96 (0.84–1.11)	0.60
Secondary outcomes				
ICU hospitalization	160 (17.4%)	249 (27.0%)	0.96 (0.78–1.18)	0.71
Heart failure hospitalization	187 (20.3%)	266 (28.9%)	1.01 (0.84–1.22)	0.92
MI hospitalization	104 (11.3%)	169 (18.4%)	0.93 (0.72–1.19)	0.54
Stroke hospitalization	129 (14.0%)	194 (21.1%)	1.01 (0.80–1.26)	0.96
CV safety outcome				
Cardiac arrhythmias hospitalization	140 (15.2%)	204 (22.2%)	1.03 (0.83–1.29)	0.77

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; ICU, intensive care unit.
[a] HR of all-cause mortality was calculated by multivariable Cox proportional hazards regression; HR of composite CV outcomes and secondary outcomes were calculated by multivariable proportional subdistribution hazard regression. HRs were adjusted for age, sex, interval, comorbidities, and baseline medications listed in Table 1.

HF.

4.2. The pharmacological activity of Fuzi in the treatment of HF

Fuzi, combined with other TCM herbs in formulations, is frequently utilized to treat different CV diseases, including HF (Tai et al., 2021a). Since Fuzi was the main active component of these products, the clinical efficacy is mostly related to the bioactivities of its constituents. Importantly, the traditional way of Fuzi processing remarkably changes the phytochemical profile of the drug. *Aconitum* species, including *A. carmichaelii* are rich sources of C19-diterpenoid alkaloids and C20-diterpenoid alkaloids. Among these compounds, primarily DAs are responsible for the CV and central nervous system bioactivities of the crude drug, whereas MAs and unesterified diterpenoid alkaloids (UAs) possess less remarkable activities. However, during processing, the amount of DAs decreases, and the amount of long-chain fatty acid-bearing lipo-alkaloids and unesterified alkaloids increases (Csupor et al., 2009; Lai et al., 2019).

The putative cardiotonic effect might partly explain the efficacy of Fuzi in HF treatment. This activity was confirmed in various models (on the isolated heart and on different animal species *in vivo*) and was shown to be more pronounced under the condition of cardiac insufficiency (Zhou et al., 2015). It may be related to the release of catecholamines and the excitement of *β*-receptors, and the increase of intracellular calcium concentration (Zhao et al., 2012). The active constituents responsible for these effects are not known. However, (partly) unesterified diterpene alkaloids (benzoylmesaconine, mesaconine, hypaconine), non-diterpenoid alkaloids such as salsolinol (Wen et al., 2019), coryneine (Kimura et al., 1995), and neutral compounds (fuzinoside) might be involved. Moreover, Fuzi possesses a cardioprotective effect by preventing cardiomyocytes from hypoxia-reoxygenation injury. From this aspect, the polysaccharide fraction of Fuzi was studied. The

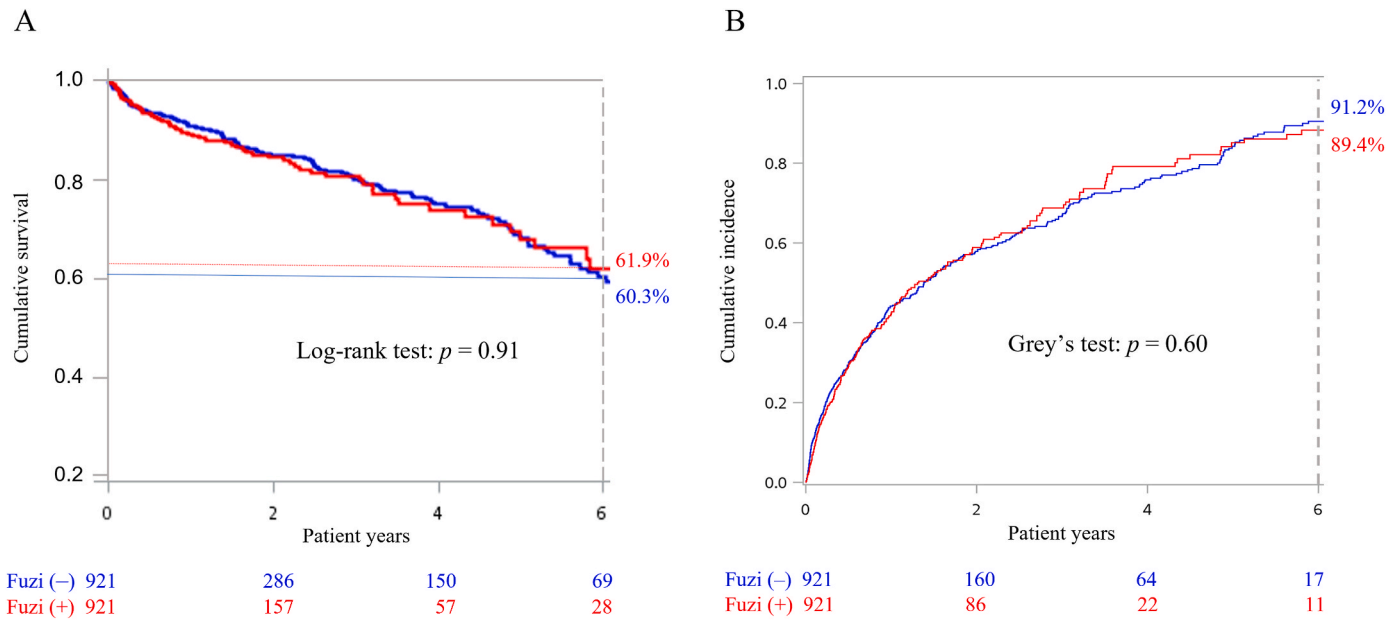

Fig. 3. (A) Kaplan-Meier analysis of all-cause mortality between Fuzi user and non-user groups. (B) Competing risk analysis of cardiovascular outcomes between the Fuzi user and non-user groups.

Table 3
Estimates of Cox regression investigating associations between Fuzi cumulative doses and death or cardiovascular events using restricted cubic spline function.

Fuzi cumulative doses (g)	All-cause mortality		Cardiovascular events [a]	
	HR	95% CI	HR	95% CI
15 g	0.88	0.59–1.32	0.95	0.78–1.16
36 g	1.00	–	1.00	–
100 g	1.07	0.79–1.46	0.84	0.71–1.00
150 g	1.06	0.65–1.70	0.76	0.59–0.99
200 g	1.05	0.64–1.75	0.55	0.57–0.98

CI, confidence interval; HR, hazard ratio.
We used the median of Fuzi cumulative doses (36g) as the reference value.
[a] Cardiovascular events included intensive care unit hospitalization, and hospitalization due to myocardial infarction, heart failure, stroke, and cardiac arrhythmias.

protective effects can be explained by maintaining physiological intracellular calcium concentration, thereby lessening the mitochondria injury by scavenging reactive oxygen species, and thus protecting cells from apoptosis (Yan et al., 2018). The anti-arrhythmic effect of Fuzi also contributes to its overall clinical effect in HF. It was confirmed that the DA-free aqueous extract of Fuzi prevents and treats the arrhythmia induced by aconitine (Khan et al., 2018).

4.3. Suggestions for further clinical study and translational research

Fuzi has firstly introduced in Shennong Ben Chiu et al., 2013) years ago, and it was used in critical conditions such as shock (Tai et al., 2015). Most of the Fuzi-based formulas in Shang Han Lun, which was one of the most important TCM textbooks, focused on the management of acute symptoms. For chronically ill patients without corresponding symptoms listed in Shang Han Lun, Fuzi was not considered as a long-term TCM herb to maintain physical functions because of its potential toxicity (Lin et al., 2004). As we mentioned, Shenfu injection and Qili-qiangxin capsules tended to be used in HF patients with acute exacerbation or with poorer NYHA classification. In this situation, Fuzi might have greater benefits on HF-related symptoms while included in the routine HF treatment.

From the Western medicine perspective, physicians applied the treatment mainly based on the classification of disease rather than the symptoms during long-term follow-up. In the current HF treatment guideline, a combination of HF medications is usually used, such as digoxin, β-blockers, CCBs, diuretics, and ACEI/ARBs (van der Meer et al., 2019). These combinations provided effective management for most chronic HF patients. Therefore, it was difficult to find additional benefits for new drug candidates such as Fuzi during the long-term management of HF.

We suggest further studies to fully reveal the benefits of adding Fuzi to the routine HF drug combination. First, researchers should evaluate the potential benefits of Fuzi TCM pair such as Fuzi-Ginseng in Shenfu injection and Fuzi-Astragali in Qili-qiangxin capsules. In our previous study, Ganjiang (Zingiberis Rhizoma), Baizhu (Atractylodis Macrocephalae Rhizoma), Dahuang (Rhei Radix et Rhizoma), Fuling (Poria), Quizhi (Cinnamomi Ramulus), Danshen (Salviae Miltiorrhizae Radix et Rhizoma), Rouqui (Cinnamomi Cortex), and Dangqui (Angelicae Sinensis Radix) were potential candidates combined with Fuzi in the treatment of chronic CV diseases (Tai et al., 2021a). For example, a previous study showed that Fuzi–Ganjiang combination had a synergistic effect on acute HF (Zhang et al., 2017). The pharmacological effect and mechanism of these combinations were mostly unknown to researchers. Second, investigators should determine the specific indications and targets for the proposed drug combinations (Tseng and Chang, 2019). For example, sacubitril, a specific inhibitor of the neutral endopeptidase (NEP) that degrades vasoactive peptides, combined with valsartan, an ARB, showed a 20% reduction of CV death in patients with HF and hypotension (Scardovi and Boccanelli, 2019). In the future, it will be interesting to evaluate the efficacy of active components extracted from Fuzi combined with certain medications such as β-blockers, CCBs, diuretics, and ACEI/ARBs in HF patients. Third, physicians should try to replace certain medications with undesirable side effects or narrow therapeutic windows such as digoxin. It will be interesting to design a conclusive comparison between Fuzi and digoxin in chronic HF patients. Finally, researchers should evaluate the effects of Fuzi-based formulas such as Jenwu Tang and Sini Tang in HF patients.

4.4. Strength and limitations

The strength of this study includes the use of a large population-based cohort and taking into consideration the possible confounding

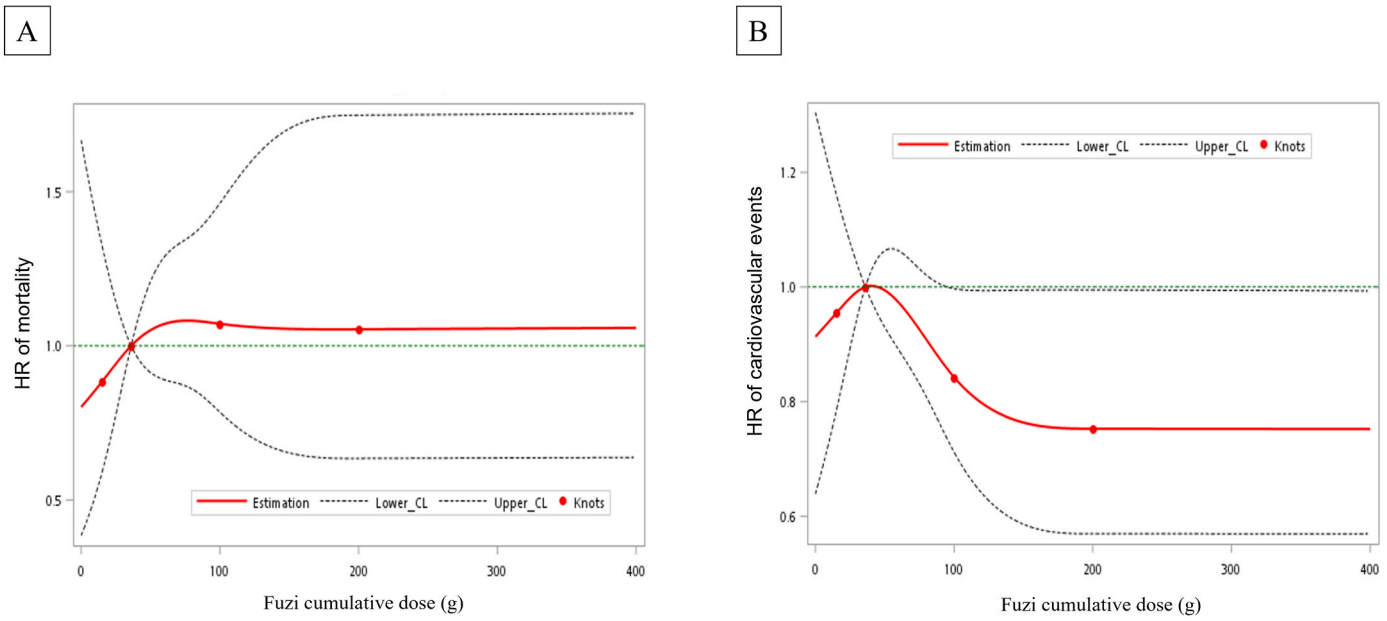

Fig. 4. Restricted cubic splines of the association of Fuzi cumulative doses and the risk of (A) all-cause mortality (B) cardiovascular events. CL, confidence level; HR, hazard ratio.

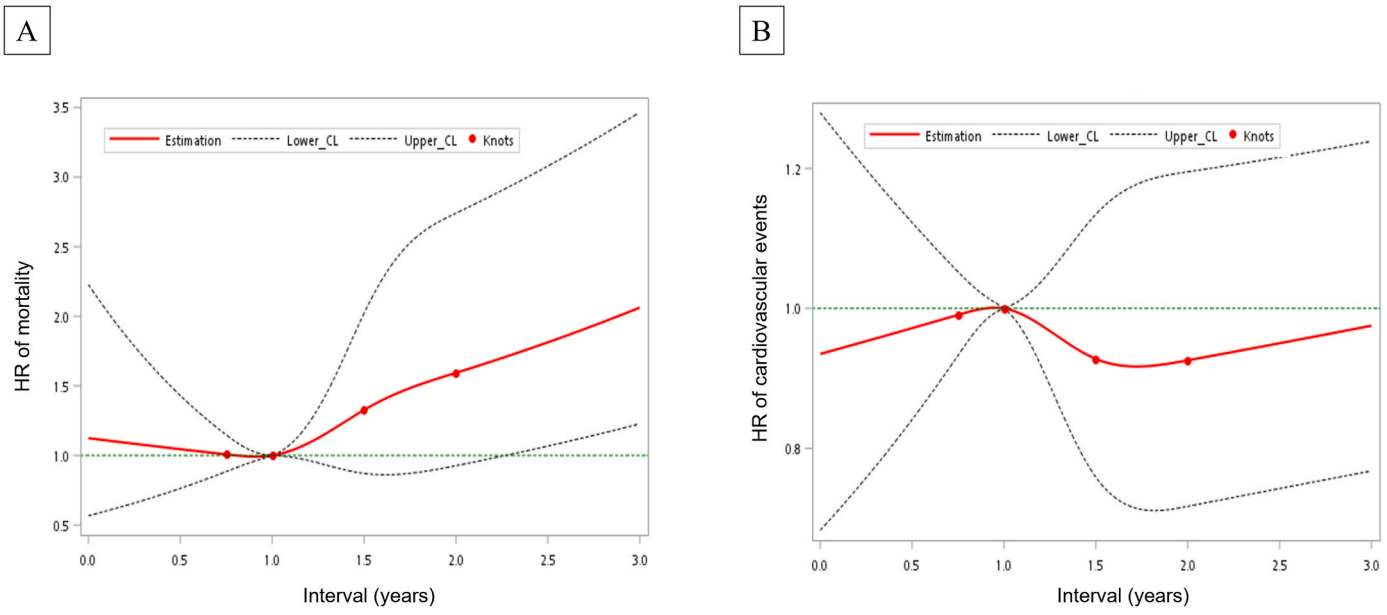

Fig. 5. Restricted cubic splines of the association of time interval between the date of first heart failure diagnosis and index date and the risk of (A) all-cause mortality (B) cardiovascular events. CL, confidence level; HR, hazard ratio.

factors available in the Taiwan NHI Database such as age, sex, time interval, baseline medications, and concomitant comorbidity. Moreover, this study had a longer follow-up than previous studies. Therefore, the results of this study contributed to revealing the role of Fuzi in chronic HF patients based on a real-world setting.

However, our results should be interpreted with the following cautions. Although we used multiple strategies to minimize confounding factors by PS matching, the current observational study might have residual confounding factors and cannot prove causality. Firstly, the effect of the current study might be confounded by socioeconomic status and healthy behaviors. Secondly, some clinical or laboratory data were not available in the Taiwan NHI Database, including LVEF and the cause, type, and severity of HF. To fully reveal the effectiveness of Fuzi combined with routine HF medications among different types of HF, further clinical trials are needed. Thirdly, some possible toxicity of Fuzi in the digestive, developmental, and respiratory systems could not easily be identified in the clinical settings (Sun et al., 2018). On the one hand, the symptoms that occurred in these systems were less serious and urgent. On the other hand, it was more difficult to distinguish whether it was related to Fuzi in the database. Finally, the study cannot evaluate the effect of chronic HF patients without TCM use while considering the confounding by indications. Therefore, the result can only support that Fuzi is a potential candidate for TCM herbal drugs in combination with routine HF Western medications.

Table 4
Estimates of Cox regression investigating associations between time interval and death or cardiovascular events using restricted cubic spline function.

Time interval	All-cause mortality		Cardiovascular events [a]	
	HR	95% CI	HR	95% CI
0.5 year	1.04	0.76–1.43	0.97	0.84–1.12
1 year	1.00	–	1.00	–
1.5 years	1.33	0.87–2.02	0.93	0.76–1.13
2.0 years	1.59	0.93–2.74	0.93	0.72–1.20
2.5 years	1.81	1.07–3.08	0.95	0.74–1.22
3.0 years	2.06	1.23–3.47	0.98	0.77–1.24

CI, confidence interval; HR, hazard ratio.
We used one year of time interval between first date of heart failure diagnosis and the index date as the reference value.
[a] Cardiovascular events included intensive care unit hospitalization, and hospitalization due to myocardial infarction, heart failure, stroke, and cardiac arrhythmias.

5. Conclusions

This study is the first real-world evidence to demonstrate the effect of Fuzi combined with routine HF treatment. This study was also the first to establish the long-term CV safety of Fuzi use. Importantly, the result indicated that Fuzi cumulative doses in the range of 150–200 g had a protective effect on preventing CV events compared to other TCM herbal drugs. It supported that Fuzi as a herbal candidate for HF. However, increased cumulative doses of Fuzi did not reduce the risk of all-cause mortality. Especially, the late initiation of TCM herbal drugs was associated with a higher risk of all-cause mortality. Further clinical trials are needed to support or undermine the assumption of using Fuzi and current Western medications to treat chronic HF.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CRediT authorship contribution statement

Chi-Jung Tai: Conceptualization, Writing – original draft, Formal analysis, Study concept and design, Acquisition, analysis, or interpretation of data, Drafting the manuscript, Statistical analysis. **Mohamed El-Shazly:** Writing – original draft, Drafting the manuscript. **Yi-Hsin Yang:** Conceptualization, Formal analysis, Study concept and design, Acquisition, analysis, or interpretation of data, Statistical analysis. **Yi-Hong Tsai:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis, or interpretation of data. **Dezső Csupor:** Writing – original draft, Drafting the manuscript, Critical revision of the manuscript for important intellectual content. **Judit Hohmann:** Critical revision of the manuscript for important intellectual content, All the listed authors have read and approved the submitted manuscript. **Yang-Chang Wu:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content. **Tzyy-Guey Tseng:** Funding acquisition, Data curation, Acquisition, analysis, or interpretation of data. **Fang-Rong Chang:** Conceptualization, Study concept and design, Critical revision of the manuscript for important intellectual content. **Hui-Chun Wang:** Conceptualization, Writing – original draft, Formal analysis, Study concept and design, Drafting the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis.

Declaration of competing interest

None declared.

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