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Chinese herbal medicine may reduce major adverse cardiovascular events in patients with dialysis hypotension: A taiwan nationwide cohort study

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ABSTRACT

Background: The association between Chinese herbal medicine (CHM) and the risk of developing major adverse cardiovascular events (MACEs) in patients with dialysis hypotension is unclear and has not yet been investigated. This study aimed to determine whether CMH intervention could reduce the risk of MACEs in patients with dialysis hypotension.

Methods: The study data from the Taiwan National Health Insurance Research Database were analyzed to clarify this association. For this study, a case-control design with a cohort of patients who received hemodialysis (HD) from 2008 to 2018, 20 295 HD patients who had received blood pressure (BP) raising drugs were identified. After 1:1 frequency-matching, 730 patients were identified as CHM users and CHM non-users. Vascular access revision/reconstruction and MACEs were observed as the main outcomes during the follow-up period.

Results: The occurrence of vascular access revision/reconstruction in HD patients receiving BP raising drugs was associated with a 0.34-fold lower risk in CHM users than in CHM non-users [adjusted hazard ratio (aHR) = 0.34, 95% confidence interval (CI) = 0.26, 0.45]. The occurrences of MACEs in HD patients receiving BP raising drugs was associated with a 0.41-fold lower risk in CHM users than in CHM non-users (aHR = 0.41, 95% CI = 0.33, 0.51). A markedly predominant effect was observed in those receiving CHM for more than 180 days (aHR = 0.32; 95% CI = 0.22, 0.45).

Conclusion: The findings revealed lower vascular access dysfunction and MACEs risk correlated with the use of CHM treatment among HD patients who received BP raising drugs.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the general population in the United States and worldwide. The median age-adjusted cardiovascular (CV) mortality rate was found to be 272.6 per 100 000 residents over a 20-year study period (2000–2019).[1] CVD also accounts for the majority of deaths in patients with end-stage renal disease (ESRD). Compared with the general population, patients with ESRD exhibit a pronounced risk (10–20 times greater) of CVD.[2,3] In addition to CV mortality, CV morbidity and major adverse cardiovascular events (MACEs) are frequently observed in patients with ESRD. In dialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS), the overall prevalences of coronary artery disease (CAD), congestive heart failure (HF), peripheral artery disease, and cerebrovascular accident (CVA) range from 15% to 35% in different regions.[4] In

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Abbreviations

aHR	adjusted hazard ratio
BP	blood pressure
CAD	coronary artery disease
CCI	Charlson comorbidity index
CHF	congestive heart failure
CHM	Chinese herbal medicine
CI	confidence interval
CKD	chronic kidney disease
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
ESRD	end-stage renal disease
HD	hemodialysis
IR	incidence rate
HR	hazard ratio
MI	myocardial infarction
NHIRD	National Health Insurance Research Database
ICD	International Classification of Disease
SD	standardized difference
95% CI	95% confidence interval
MACEs	major adverse cardiovascular events
MOST	Ministry of Science and Technology
NHI	national health insurance
TCM	Traditional Chinese medicine
PS	propensity matched
RCIPD	Registry for Catastrophic Illness Patient Database

addition, the mortality rate following acute myocardial infarction (MI) in hemodialysis (HD) patients greatly increases over time (59% and 73% at 1 and 2 years, respectively).[5]

The growing incidence of metabolic risk factors for CVD such as diabetes, hypertension, and dyslipidemia, as well as risk factors due to deterioration of kidney function, are to blame for the high prevalence of CV morbidity and mortality in the dialysis population.[6,7] Moreover, CV insults related to repeated HD could increase the probability of subsequent MACEs, including volume overload before each HD session, asymptomatic myocardial ischemia during dialysis, and imbalance between calcium and phosphorus (Ca/P).[8–10]

Among HD-related CV morbidities, intradialytic hypotension (IDH) is also regarded as a risk factor,[11] as it occurs in 8%–40% of all HD sessions.[12] One possible explanation is that the transient coronary hypoperfusion decline in systolic blood pressure (BP) during the dialysis procedure may result in myocardial stunning,[13,14] which thus gradually leads to adverse outcomes.[15] A number of strategies have been used to prevent IDH, including the modulation of ultrafiltration, adjustments of dialysate composition, and low dialysate temperature; however, all of these have had limited effects.[16] No consistently effective approach has been suggested to address IDH except using vasopressors such as midodrine, desmopressin acetate (DDAVP), or etilefrine.[17,18] However, a previous report of an association between midodrine and high mortality raises concerns about its safety.[19]

Traditional Chinese medicine (TCM) is an important part of the healthcare system in Taiwan. Chinese herbal medicine (CHM) products are concentrated from decoctions into powders through standard Good Manufacturing Practice pharmaceutical technology, so CHM products are consistent in quality and convenient to use for patients.[20] As the Taiwan National Health Insurance (NHI) program fully reimburses patients for CHM products, copious amounts of data on the insured population's use of CHM and Western medical (WM) treatments are available for analysis.[21] However, scientific reports on the effects of co-administration of CHM and WM in ESRD patients remain rare. Recently, one preprint showed that lower vasopressor use among HD patients was correlated with the use of CHM treatments.[22]

Our previous report showed that CHM treatment could reduce vasopressor use in IDH patients.[22] The purpose of the current study was to use data from the National Health Insurance Research Database (NHIRD) to investigate whether CHM can subsequently decrease the risk of MACEs in IDH patients.

2. Materials and method

2.1. Study design and data source

This retrospective cohort study used data extracted from the Taiwan NHIRD, which includes health claim data on nearly 99% of Taiwan's population from 1995 to present. The Registry for Catastrophic Illness Patient Database (RCIPD), a sub-dataset of the NHIRD, includes all patients who meet the criteria of the Bureau of National Health Insurance for a catastrophic illness certificate. Catastrophic illnesses are defined as severe illnesses requiring advanced health care, such as ESRD. Before 2016, the NHIRD identified diseases according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and since 2016, it has done so according to the ICD-10-CM. All medical records in the NHIRD are linked using unique, encrypted identification numbers to protect personal privacy. This study was approved by the Institutional Review Board of the Research Ethics Committee of China Medical University Hospital (CMUH110-REC1-038 (CR-2)).

2.2. Study population

The study cohort included patients with ESRD (ICD-9: 585.x, ICD-10: N18.4, N18.5, N18.6, N18.9) aged 40 years and above who received HD for at least 90 days from 2008 to 2018. HD patients who received BP raising drugs were included in the study population. The exclusion criteria of this study included patients who were aged less than 40 years, received peritoneal dialysis or kidney transplant before HD, had a follow-up time less than one month after the index date, or had missing data on sex or age. Patients who used CHM for more than 30 days were defined as CHM users, and those who used CHM for fewer than 30 days were considered CHM non-users as a non-matching design cohort.[23] A CHM cohort and a propensity matched (PS) non-CHM cohort with the PS-matching design were established. Logistic regression analysis was used to calculate the propensity score for each person by estimating the probability of the treatment assignment. Baseline variables used in the calculation of propensity scores included gender, age, the year of dialysis initiation, monthly income, residential area, baseline score on the Charlson comorbidity index (CCI), and drug used (including midodrine, etilefrine, and DDAVP) (Fig. 1).

2.3. Main outcome

The study outcome measures were the number of first diagnoses for vascular access revision/reconstruction, MACEs (including MI, HF, CVA, cardiac arrhythmia), and mortality after the index date. Both cohorts were observed from the index date to the date of hospitalization for vascular access revision/reconstruction (treatment codes 69032 B, 69032C, 69034C), myocardial infarction (ICD-9: 410; ICD-10: I21, I22), heart failure (ICD9 428; ICD10 I50), cerebrovascular disease (ICD-9: 430–438; ICD-10: I60–I69), cardiac arrhythmia (ICD-9: 427; ICD-10: I46–I49), death, withdrawal from the insurance system, or the end of the follow-up period (December 31, 2019).

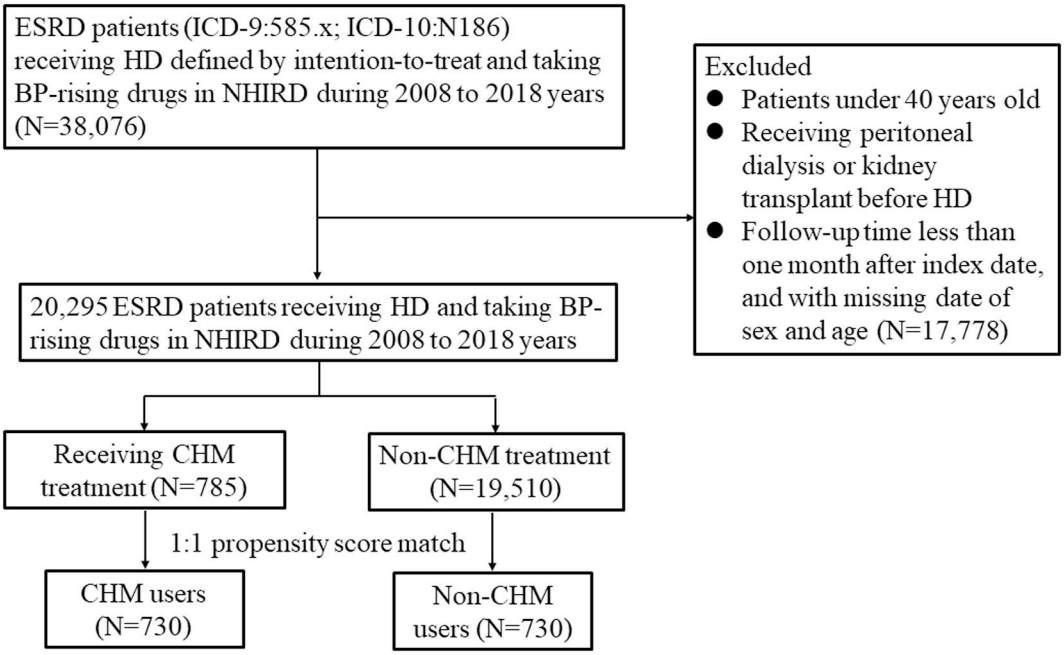

Fig. 1. Flowchart of the study participant selection process.

2.4. Statistical analysis

Two matching methods were adopted to compare the risks of clinical outcomes and mortality between the CHM and non-CHM cohorts in both a non-matching design and a PS-matching design. Demographic characteristics, baseline CCI score, and drug used were compared by Chi-squared test for the categorical variables and *t*-test for continuous variables. Univariable and multivariable Cox Proportional Hazards regression models were used to estimate the hazard ratios (HRs) of clinical outcomes (including vascular access revision/reconstruction, MI, HF, CVA, and cardiac arrhythmia) and mortality between CHM users and non-CHM users. The most frequently prescribed single herbs and herbal formulae were described. The Kaplan–Meier method was used to plot the cumulative proportion of the subjects who experienced MACEs

Table 1
Demographic and clinical characteristics of HD patients receiving BP raising drugs before and after matching.

Variable	Chinese Herbal medicine Before matching					Chinese Herbal medicine After matching				
	Users, N = 785		Non-users, N = 19 510		*p*-value	Users, N = 730		Non-users, N = 730		*p*-value
	N	%	N	%		N	%	N	%	
Gender					<0.001					0.87
Female	452	57.6	9978	51.1		421	57.7	418	57.3	
Male	333	42.4	9532	48.9		309	42.3	312	42.7	
Age, y					<0.001					0.83
40-64	353	45.0	6649	34.1		329	45.1	325	44.5	
≥65	432	55.0	12 861	65.9		401	54.9	405	55.5	
Mean ± SD, y[a]	65.6	10.6	69.6	11.7	<0.001	65.6	10.6	67.6	12.0	0.001
HD duration, y					<0.001					0.91
<1	598	76.2	11 923	61.1		552	75.6	550	75.3	
1-5	171	21.8	7077	36.3		162	22.2	166	22.7	
>5	16	2.04	510	2.61		16	2.19	14	1.92	
Monthly income					<0.001					0.99
Low	232	29.6	7326	37.6		219	30.0	217	29.7	
Median	389	49.6	9193	47.1		364	49.9	365	50.0	
High	164	20.9	2991	15.3		147	20.1	148	20.3	
Residential area					0.03					0.76
Rural	109	13.9	3395	17.4		54	7.40	47	6.44	
Suburban	297	37.8	7230	37.1		297	40.7	297	40.7	
Urban	379	48.3	8885	45.5		379	51.9	386	52.9	
Baseline CCI score					<0.001					0.84
≤3	283	36.1	4277	21.9		272	37.3	274	37.5	
4-6	255	32.5	6044	31.0		229	31.4	234	32.1	
7-9	210	26.8	7574	38.8		194	26.6	194	26.6	
>9	37	4.71	1615	8.28		35	4.79	28	3.84	
Drug use										
Midodrine	696	88.7	17 309	88.7	0.96	644	88.2	654	89.6	0.40
Etilefrine	5	0.64	73	0.37	0.24	5	0.68	6	0.82	0.76
DDAVP	228	29.0	5403	27.7	0.41	212	29.0	200	27.4	0.49

Chi-square test; [a] *t*-test. HD, hemodialysis; BP, blood pressure.

during the follow-up period among the three groups, and the log-rank test was used to assess the differences among these curves. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for statistical analyses. A two-sided *p* of <0.05 was considered statistically significant. Further analysis demonstrated a dose response relationship between CHM use and mortality.

3. Results

3.1. Demographic characteristics of study populations

As shown in Table 1, we identified 785 CHM users and 19 510 CHM non-users as the non-matched cohort. In addition, 730 patients in the CHM cohort were matched with 730 patients in the non-CHM cohort according to the PS. In both cohorts, the female patients outnumbered male patients. Most of the patients were aged ≥65, and the mean age of the CHM users (65.6 ± 10.6) was younger than that of the non-CHM cohort (67.6 ± 12.0). There were no significant differences in the distributions of HD duration, monthly income, residential area, or baseline CCI score between the two cohorts. After *PS*-matching, the two cohorts had similar baseline characteristics.

3.2. The incidence rate and hazard ratio of clinical outcomes in HD patients

A total of 234 cases of vascular access revision/reconstruction were identified during the follow-up period. The incidence rates of vascular access revision/reconstruction were 38.8 per 1000 person-years and 107.3 per 1000 person-years for CHM users and CHM non-users, respectively (Table 2). The number of HD patients receiving both CHM and BP raising drugs who later received vascular access revision/reconstruction was 66% lower in the CHM cohort than in the non-CHM cohort [adjusted hazard ratio (aHR) = 0.34, 95% confidence interval (CI) = 0.26, 0.45]. Moreover, the risk of MACEs was significantly lower in CHM users than in CHM non-users (aHR = 0.41, 95% CI = 0.33, 0.51). The CHM cohort exhibited significantly lower risks for MI (aHR = 0.32, 95% CI = 0.21, 0.49), HF (aHR = 0.46, 95% CI = 0.30, 0.69), CVA (aHR = 0.40, 95% CI = 0.26, 0.62), and cardiac arrhythmia (aHR = 0.38, 95% CI = 0.26, 0.56) than did the non-CHM cohort. Moreover, the risk of all-cause mortality was 0.37-fold in CHM users compared with that in the CHM non-users (aHR = 0.37, 95% CI = 0.32, 0.43).

Table 3 lists the incidence rates (IRs) and the crude and adjusted HRs with 95% CIs of MACEs between HD patients, stratified by the duration of CHM treatment. The IR of MACEs in CHM users (30–180 days: 70.9 per 1000 person-years; >180 days: 48.8 per 1000 person-years) was lower than that in CHM non-users (150.0 per 1000 person-years). CHM treatment was associated with a significantly decreased risk of MACEs in HD patients with BP raising drugs. In addition, a higher number of days of receiving CHM was associated with lower risk of MACEs [30–180 days: aHR = 0.46, 95% CI = (0.36, 0.57); >180 days: aHR = 0.32, 95% CI = (0.22, 0.45)]. Fig. 2 presents the cumulative incidence of MACEs in HD patients receiving BP raising drugs with and without CHM treatment using the Kaplan–Meier method. The figure shows that the probability of MACEs of HD patients receiving both BP raising drugs and CHM was significantly lower than that of their counterparts with no CHM, and the probability of MACEs was the lowest among HD patients who received CHM for more than 180 days (log-rank p-value <0.001).

Table 4 presents Cox regression analyses of MACEs associated with covariates among HD patients receiving BP raising drugs. The risk for MACEs was higher in the elderly group (>=65 years old) (aHR = 1.46, 95% CI = 1.18, 1.82) than in the middle-aged group (40–64 years old), and higher for male gender than for female gender (aHR = 1.28, 95% CI = 1.03, 1.59). In terms of income, the risk was higher for those with a low monthly income than for those with a high monthly income (aHR = 1.36; 95% CI = 1.01, 1.83). More comorbidities (CCI score 7–9) had a higher association with risk of MACEs than fewer comorbidities (CCI score <3) (aHR = 1.53, 95% CI = 1.17, 2.01). Neither HD duration nor urbanization was associated with the development of MACEs in HD patients.

Table 5 presents the IRs and the crude and adjusted HRs with 95% CIs of MACEs of HD patients receiving BP raising drugs with and without CHM treatment, stratified by baseline characteristics and CCI score. Stratified by gender, the incidence rates of MACEs in female and male users with CHM were 62.0 per 1000 person-years and 67.5 per 1000 person-years, respectively. They were lower than those in the non-CHM cohort (126.7 per 1000 person-year and 190.9 per 1000 person-years for females and males, separately) (Table 5). Both females and males with CHM treatment had significantly lower risk by 0.47-fold (95% CI = 0.36, 0.63) and 0.34-fold (95% CI = 0.25, 0.48) respectively compared to those without CHM treatment. Similarly, CHM users had significantly lower risk for MACEs than CHM non-users when stratified by age group and CCI score group.

3.3. Ten most commonly used single- and multi-herb CHM drugs in HD patients

To investigate the prescription pattern for CHM users, the ten most common single herbs and herbal formulas were calculated, as listed in Table 6. The most common single herb was Da Huang *(Radix et Rhizoma Rhei)* and the most common herbal formula was Ji Sheng Shen Qi Wan (JSSQW). After adjustments for gender, age, HD duration, monthly income, residential area, and baseline CCI score, all of the top ten most common single herbs and herbal formulas were associated with reduced MACEs ($p < 0.001$).

Table 2
Risk of clinical outcomes in HD patients receiving BP raising drugs with and without CHM treatment.

Clinical outcome	User N = 730		Non-users N = 730		User vs non-users	
					Crude	Adjusted
	Events	IR[a]	Events	IR[a]	HR (95% CI)	HR (95% CI)
Vascular access revision/reconstruction	101	38.8	133	107.3	0.37 (0.28,0.48)***	0.34 (0.26, 0.45)***
MACEs	167	64.1	186	150.0	0.43 (0.35, 0.54)***	0.41 (0.33, 0.51)***
Myocardial infarction	41	15.7	57	46.0	0.34 (0.23, 0.51)***	0.32 (0.21, 0.49)***
Herat failure	47	18.0	48	38.7	0.48 (0.32, 0.72)***	0.46 (0.30, 0.69)***
Cerebrovascular accident	42	16.1	46	37.1	0.43 (0.28, 0.65)***	0.40 (0.26, 0.62)***
Cardiac arrhythmia	46	17.7	59	47.6	0.39 (0.27, 0.58)***	0.38 (0.26, 0.56)***
All-cause mortality	295	0.27	458	0.70	0.40 (0.35, 0.46)***	0.37 (0.32, 0.43)***

Abbreviation: BP, blood pressure; CHM, Chinese Herbal Medicine; CI, Confidence Interval; HR, Hazard Ratio; HD, hemodialysis; IR, Incidence Rate.

[a] Incidence rate per 1000 person-years; Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for gender, age, HD duration, monthly income, residential area, baseline CCI score in Cox proportional hazard regression. *** < 0.001.

Table 3
IRs and crude and adjusted HRs with 95% CIs of MACEs between HD patients stratified by the duration of CHM treatment.

Variable	Event	Person-Years	IR	Crude		Adjusted[a]	
	n = 353		1000 person-years	HR (95% CI)	*p*- value	HR (95% CI)	*p*- value
CHM non-users	186	1240	150.0	1 (Reference)		1 (Reference)	
CHM users							
30–180 days	128	1805	70.9	0.48 (0.38, 0.60)	<0.001	0.46 (0.36, 0.57)	<0.001
>180 days	39	800	48.8	0.33 (0.23, 0.47)	<0.001	0.32 (0.22, 0.45)	<0.001

Abbreviation: CHM, Chinese Herbal Medicine; CI, Confidence Interval; HR, Hazard Ratio; HD, hemodialysis; IR, Incidence Rate; MACEs, major adverse cardiovascular events.
[a] Adjusted for gender, age, HD duration, monthly income, residential area, baseline CCI score.

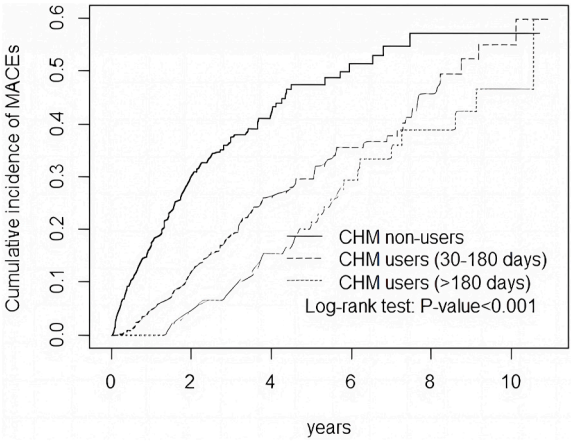

Fig. 2. Cumulative incidence of MACEs in HD patients with and without adjuvant CHM treatment, determined by Kaplan–Meier method.

4. Discussion

This study is the first large-scale population-based retrospective cohort study, based on claims data from the NHIRD in Taiwan, to provide evidence of the association between CHM use and MACEs risk in HD patients receiving BP raising drugs. The main findings were as follows: (1) CHM use may prevent MACEs in HD patients receiving BP raising drugs, for it is associated with a 0.41-fold lower risk of MACEs. This effect is related to the duration of CHM treatment, as evidenced by the risk of MACEs in the cohort who used CHM for more than 180 days falling to 0.32 times that of the CHM non-user cohort. (2) Compared with controls, in male HD patients or those aged more than 65 years, a greater CCI score was associated with a higher risk of developing MACEs. However, CHM use could reduce the risk of MACEs in HD patients receiving BP raising drugs, regardless of age, gender or CCI score, except for those with CCI scores greater than 9. (3) Compared with CHM non-users, CHM users have a 0.34-fold risk for vascular access revision or reconstruction among HD patients receiving BP raising drugs. (4) The most common CHM formula prescribed was JSSQW, and the most common single herb prescribed was Da Huang.

The risk factors for MACEs in HD patients include male gender, age of more than 65 years, history of diabetes, MI, stroke, congestive HF, and peripheral vascular disease.[4,24] HD patients with IDH have higher risk of CV morbidity and mortality compared with those without IDH.[15] Of the many risk factors for MACEs, some can be controlled, but not others.[4,25] Age and gender are two uncontrollable risk factors for MACEs. In general, the incidence of MACEs is higher in older than in younger people.[4] Simply getting older could increase the risk of MACEs because of functional changes, such as diastolic, systolic, or electrical dysfunction in aging hearts.[25] Overall, premenopausal women have lower incidence of MACEs due to the cardioprotective role of estrogen.[25] The findings in our study showed that HD patients receiving BP raising drugs who were aged more than 65 years and those with male gender separately had

Table 4
Cox regression analyses of MACEs associated with covariates among HD patients receiving BP raising drugs.

	Event	PY	Rate[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
CHM					
No	186	1240	150.0	1.00	1.00
Yes	167	2605	64.1	0.43 (0.35, 0.54) ***	0.41 (0.33, 0.51) ***
Age, y					
40–64	156	1993	78.3	1.00	1.00
≥65	197	1852	106.3	1.33 (1.08, 1.65) **	1.46 (1.18, 1.82) ***
Gender					
Female	200	2402	83.3	1.00	1.00
Male	153	1443	106.0	1.25 (1.01, 1.55) *	1.28 (1.03, 1.59)*
HD duration, y					
<1	275	2964	92.8	1.06 (0.81, 1.37)	1.10 (0.84, 1.43)
1–5	73	815	89.6	1.00	1.00
>5	5	67	74.9	0.82 (0.33, 2.02)	1.00 (0.40, 2.48)
Monthly income					
Low	121	1064	113.8	1.38 (1.03, 1.85) *	1.36 (1.01, 1.83)*
Median	162	1919	84.4	1.03 (0.78, 1.36)	1.03 (0.78, 1.37)
High	70	863	81.2	1.00	1.00
Residential area					
Rural	21	285	73.6	1.00	1.00
Suburban	139	1594	87.2	1.17 (0.74, 1.86)	1.10 (0.70, 1.75)
Urban	193	1966	98.2	1.32 (0.84, 2.07)	1.22 (0.78, 1.93)
Baseline CCI score					
<3	139	1750	79.4	1.00	1.00
4–6	111	1235	89.9	1.12 (0.87, 1.44)	1.15 (0.90, 1.48)
7–9	91	745	122.1	1.49 (1.14, 1.95) **	1.53 (1.17, 2.01)**
>9	12	115	104.5	1.28 (0.71, 2.31)	1.36 (0.75, 2.48)

CI, confidence interval; HR, hazard ratio; PY, person-years.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Incidence rate per 1000 person-years.
[b] Multivariable analysis including age, gender, HD duration, monthly income, residential area, and baseline CCI score.

1.46-fold and 1.28-fold higher risk of developing MACEs as compared with those aged less than 65 years. It was surprising that we found CHM treatment to be associated with a significantly lower risk of MACEs regardless of age and gender among HD patients who needed to use BP raising drugs. In addition, under CHM treatment, the risk of MACEs was reduced more in men than in women.

The CCI score is commonly used for assessing and quantifying comorbidity in chronic diseases, including ESRD. The CCI score is also a strong predictor of mortality in HD patients.[26] In general, a higher CCI score is associated with higher risk of MACEs and mortality. The findings of our study revealed that patients with CCI scores of 7–9 had significantly higher risk for developing MACEs than did those with CCI scores of less than 3. This phenomenon has also been observed in patients with CCI scores greater than 9, but without significance. A possible reason is that relatively few people had CCI scores greater than 9, as compared with other groups in the study cohort. Our study results revealed that

Table 5
IRs and crude and adjusted HRs with 95% CIs of MACEs between HD patients receiving BP raising drugs with and without adjuvant CHM treatment, stratified by baseline characteristics, and CCI score.

Variables	CHM users (n = 730			CHM non-users (n = 730)			Crude HR (95% CI)	Adjusted HR (95% CI)
	Events	Person-years	IR[a]	Events	Person-years	IR[a]		
Gender								
Female	100	1613	62.0	100	789	126.7	0.50 (0.38, 0.66)***	0.47 (0.36, 0.63)***
Male	67	993	67.5	86	450	190.9	0.35 (0.26, 0.49)***	0.34 (0.25, 0.48)***
Age								
40-64	66	1290	51.2	90	703	128.0	0.42 (0.30, 0.58)***	0.40 (0.29, 0.56)***
≥65	101	1315	76.8	96	537	178.8	0.40 (0.30, 0.54)***	0.38 (0.28, 0.51)***
CCI score								
<3	56	1165	48.1	83	585	141.9	0.35 (0.25, 0.49)***	0.34 (0.24, 0.49)***
4-6	47	840	56.0	64	396	161.8	0.34 (0.23, 0.50)***	0.34 (0.23, 0.50)***
7-9	56	515	108.7	35	230	152.1	0.68 (0.44, 1.04)	0.63 (0.41, 0.99)*
>9	8	85	93.6	4	29	136.3	0.73 (0.21, 2.45)	0.62 (0.16, 2.35)

Abbreviation: BP, blood pressure; CHM, Chinese Herbal Medicine; CI, Confidence Interval; HR, Hazard Ratio; HD, hemodialysis; MACEs, major adverse cardiovascular events.

[a] IR per 1000 person-years; Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for gender, age, HD duration, monthly income, residential area, baseline CCI score in Cox proportional hazard regression. * < 0.05, ** < 0.01, and *** < 0.001.

CHM treatment reduced MACEs by 66% and 37 % in those with CCI scores below 6 and in the range of 7–9, respectively. This benefit was not observed when the CCI score was greater than 9. A possible reason is that people with CCI scores greater than 9 have higher comorbidity severity.

According to clinical practice and previous literature, a higher frequency of episodes of IDH is associated with increased rates of vascular access thrombosis.[27,28] The cohort selected in our study were HD patients who required vasopressors during the study period. This suggests that the selected cohorts in our study were more severely or frequently affected by hypotension during HD, as pharmacological interventions are not usually a first line strategy for IDH. Consistent with a previous report,[16] midodrine was found to be the most commonly used vasoconstrictor in our study. However, previous studies reported that midodrine use was associated with higher incidence of mortality, all-cause hospitalization, and CV hospitalization.[16,29] Therefore, the safety of long-term use of midodrine still requires further research. Nonetheless, our study surprisingly found that CHM users had a 0.34-fold lower risk of vascular access revision or reconstruction. Furthermore, the all-cause mortality among CHM users was reduced by 63% relative to that of CHM non-users.

From the standpoint of TCM, individuals experiencing IDH commonly manifest a syndrome of Yang deficiency. This syndrome is marked by warm dysfunction and a metabolic imbalance in body fluids, leading to symptoms such as backache, cold extremities, tinnitus, fatigue, and, in some cases, edema.[30] Specifically, a deficiency in Yang-*qi* within the Heart and Kidney is often cited by clinical TCM practitioners as the reason for selecting those herbs in the treatment of IDH. For instance, recent research has highlighted the preference for Shenfu decoction, Sheng Mai San (SMS), ginseng, and Huang Qi *(Rx. Astragali)* in TCM practices for addressing IDH, as these herbs are known to invigorate Heart- and Kidney-*qi*.[31,32] The findings showed that JSSQW, also called Gosha-jinki-gan in Kampo medicine, is the most prescribed formula. It is usually prescribed for the treatment of genitourinary symptoms[33] and applied as Kidney-*qi* invigorating therapy to improve physiological symptoms in patients with chronic kidney disease (CKD).[34] It also has protective effects on the hypothalamic-pituitary-adrenal axis in a rat model.[30] The potential mechanisms underlying the cardioprotective effects of JSSQW may involve the inhibition of platelet aggregation and the promotion of nitric oxide-mediated vasodilation.[35,36] These actions contribute to favorable outcomes in the treatment of CVD. Zhen Wu Tang (ZWT) has been widely used as a remedy for CKD through a warming Kidney Yang effect to promote diuresis. The vasopressor and inotropic effect of ZWT is known to adjust the BP set point, increase the secretion of plasma aldosterone,[32] and delay ventricular hypertrophy by suppressing the expression of B-type natriuretic peptide and pro-inflammatory cytokines.[37] Moreover, certain commonly prescribed inotropic CHMs designed to nourish the *qi* and blood of the Heart, such as Zhi Gan Cao Tang, Tian Wang Bu Xin Dan, Gui Pi Tang, and SMS, have demonstrated efficacy in improving cardiac function.[38] This, in turn, plays a role in reducing the risk of IDH, thus contributing to the reduction of IDH risk. Additionally, the use of Ma Zi Ren Wan, known for its laxative properties, is frequent in IDH patients. This choice may be attributed to the higher susceptibility of patients with heart disease to constipation, which can be induced by factors such as phosphate binders like sevelamer, fluid restriction, inactivity, and slowed bowel motility.[39,40] Da Huang, the most commonly prescribed single herb in our study, is typically used for constipation.[32] Da Huang can reduce serum creatinine, blood urea nitrogen and uric acid; increase the creatinine clearance rate; and improve the symptoms and signs in ESRD patients.[41] Although these commonly used CHM can be used to improve the clinical symptoms of HD patients in TCM clinical practice, further research will be needed to confirm whether these medicinal plants really have a protective effect against MACEs as well as the potential mechanisms.

The strengths of this study include the comprehensiveness of the nationwide database, which eliminated the possibility of recall bias in questionnaire assessments and ensured that CHM was used before MACEs occurred. Furthermore, this study used a multivariate adjusted hazard ratio with a period of 12 years follow-up to confidently estimate the effects of CHM treatment on associations between IDH and the risk of MACEs over a long latency period.

The main limitation of this study was the absence of data on BP levels, dry weight measurements, body mass index, medical compliance, lifestyle, and additional clinical characteristics, such as smoking and alcohol consumption. This limitation arose due to the retrospective design of the data analysis utilizing the NHIRD. The inability to account for presumed risk factors may have introduced bias into the estimates of MACEs within our chosen cohort. Second, because other CHM preparations, natural herbal health foods, folk medicinal plants, and crude herbs purchased directly from TCM herbal pharmacies are not covered by NHI reimbursement, they were not analyzed in this study. However, the high NHI coverage and low prices of government-approved CHM products have led to a decrease in the use of the herbal medicines listed above. Such missing data may have led to an underestimation of the cumulative frequency and may weaken the effect of the specified CHM, but the effect, if any, should be negligible. Finally, this study could only identify an association between CHM and MACEs, not causation. Although statistical methods were used to control for clinically relevant covariates, other factors not assessed in this study may have contributed to the observed associations.

Table 6
Crude and adjusted HRs with 95% CIs of MACEs associated with ten most common used single- and multi-herb CHM drugs in HD patients receiving BP raising drugs.

Herbal formula	Frequency	Number of person-days	Average daily dose (g)	Average duration for prescription (Days)	Crude HR (95% CI)	Adjusted HR (95% CI)
Single herb						
Da Huang (*Rx. et Rz. Rhei*)	2373	20 704	0.9	8.7	0.36 (0.26, 0.49)***	0.35 (0.26, 0.48)***
Huang Qi (*Rx. Astragali*)	1451	15 331	1.8	10.6	0.32 (0.23, 0.45)***	0.31 (0.22, 0.43)***
Du Zhong (*Cx. Eucommiae*)	1077	11 796	1.2	11.0	0.38 (0.26, 0.55)***	0.37 (0.25, 0.53)***
Dan Shen (*Rx. Salviae Miltiorrhizae*)	1270	11 181	1.5	8.8	0.42 (0.31, 0.57)***	0.42 (0.30, 0.57)***
Bai Zhu (*Rz. Atractylodis Macrocephalae*)	971	9051	2.1	9.3	0.38 (0.27, 0.55)***	0.38 (0.26, 0.54)***
Mai Men Dong (*Tub. Ophiopogonis*)	1154	8841	1.5	7.7	0.34 (0.23, 0.48)***	0.33 (0.23, 0.48)***
Jie Geng (*Rx. Platycodi*)	1147	8655	1.5	7.5	0.37 (0.26, 0.52)***	0.38 (0.27, 0.53)***
Dang Gui (*Rx. Angelicae Sinensis*)	888	8208	1.8	9.2	0.36 (0.25, 0.52)***	0.35 (0.24, 0.51)***
Sheng Di Huang (*Rx. Rehmanniae*)	766	7881	1.4	10.3	0.29 (0.18, 0.44)***	0.28 (0.18, 0.43)***
Hou Po (*Cx. Magnoliae*)	942	7847	2.0	8.3	0.35 (0.25, 0.50)***	0.35 (0.24, 0.49)***
Formula (components)						
Ji Sheng Shen Qi Wan (*Rx. Rehmanniae Preparata, Fr. Corni, Rx. Dioscoreae, Poria, Cx. Moutan, Rz. Alismatis, Cx. Cinnamomi Loureroi, Rx. Aconiti Lateralis Preparata, Rx. Cyathulae, Sm. Plantaginis*)	1681	15 657	6.4	9.3	0.41 (0.30, 0.56)***	0.40 (0.29, 0.55)***
Ma Zi Ren Wan (*Sm. Cannabis, Sm. Armeniacae, Rx. Paeoniae Alba, Fr. Aurantii Immaturus, Cx. Magnoliae Officinalis, Rx. et Rz. Rhei*)	1815	15 213	3.0	8.4	0.34 (0.23, 0.50)***	0.33 (0.23, 0.49)***
Zhi Gan Cao Tang (*Radix Glycyrrhizae Preparata, Radix Ginseng, Ramulus Cinnamomi, Radix Rehmanniae, Tuber Ophiopogonis, Colla Corii Asini, Semen Cannabis, Rhizoma Zingiberis Recens, Fructus Zizyphi Jujubae*)	1233	11 121	4.2	9.0	0.33 (0.23, 0.48)***	0.32 (0.22, 0.46)***
Tian Wang Bu Xin Dan (*Rx. Rehmanniae, Rx. Ginseng, Rx. Asparagi, Rx. Ophiopogonis, Rx. Scrophulariae, Rx. Salviae Miltiorrhizae, Poria, Rx. Polygalae, Rx. Angelicae Sinensis, Fr. Schisandrae, Sm. Platycladi, Sm. Zizyphi Spinosae, Rx. Platycodi, Cinnabaris*)	1074	8848	4.0	8.2	0.39 (0.27, 0.57)***	0.38 (0.27, 0.55)***
Zhen Wu Tang (*Radix Aconiti Lateralis Preparata, RhizomaAtractylodis Macrocephalae, Scierotium Poriae Cocos, uncooked Rhizoma Zingiberis, Radix Albus Paeoniae Lactiflorae*)	963	8564	5.4	8.9	0.43 (0.31, 0.61)***	0.41 (0.29, 0.59)***
Shao Yao Gan Cao Tang (*Rx. Paeoniae Alba, Rx. Glycyrrhizae Preparata*)	1128	8316	4.3	7.4	0.35 (0.25, 0.50)***	0.35 (0.24, 0.50)***
Shu Jing Huo Xue Tang (*Rx. Paeoniae Alba, Rx. Angelicae Sinensis, Rz. Chuanxiong, Rx. Rehmanniae, Sm. Persicae, Rz. Atractylodis, Poria, Rx. Achyranthis Bidentatae, Rx. Clematidis, Rx. Stephaniae Tetrandrae, Rz. seu Rx. Notopterygii, Rx. Saposhnikoviae, Rx. Gentianae, Rx. Angelicae Dahuricae, Per. Citri Reticulatae, Rx. Glycyrrhizae, Rz. Zingiberis Recens*)	1024	8090	5.0	7.9	0.33 (0.23, 0.47)***	0.33 (0.23, 0.48)***
Liu Wei Di Huang Wan (*Rx. Rehmanniae Preparata, Fr. Corni, Rx. Dioscoreae, Poria, Cx. Moutan, Rz. Alismatis*)	924	7457	6.6	8.1	0.41 (0.29, 0.57)***	0.39 (0.28, 0.55)***
Gui Pi Tang (*Rx. Ginseng, Rx. Astragali, Rz. Atractylodis Macrocephalae, Poria, Sm. Zizyphi Spinosae, Arillus Longan, Rx. Aucklandiae, Fried Rx. Glycyrrhizae, Rx. Angelicae Sinensis, Fried Rx. Polygalae, Rx. Zingiberis Recens, Fr. Jujube*)	707	7027	6.0	9.9	0.40 (0.27, 0.58)***	0.40 (0.27, 0.59)***
Sheng Mai San (*Radix Ginseng, Tuber Ophiopogonis Japonici, Fructus Schisandrae Chinensis*)	907	6809	4.5	7.5	0.33 (0.22, 0.48)***	0.31 (0.21, 0.46)***

Abbreviation: BP, blood pressure; CHM, Chinese Herbal Medicine; CI, Confidence Interval; HR, Hazard Ratio; HD, hemodialysis; MACEs, major adverse cardiovascular events. Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for gender, age, HD duration, monthly income, residential area, baseline CCI score in Cox proportional hazard regression. * < 0.05, ** < 0.01, and *** < 0.001.

5. Conclusions

This large, real-world study of HD cohorts who did and did not use CHM provides further evidence of the relationship between IDH and the incidence of MACEs. HD patients with IDH are at an increased risk of MACEs. The findings of this study showed that CHM treatment was associated with lower risk of developing MACEs and vascular access dysfunction among HD patients receiving BP raising drugs. Further studies should be performed to investigate the potential compounds of commonly used CHM for IDH treatment.

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Declaration of competing interest

The authors declare that they have no conflict of interest. In the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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