see commentary on page 1223

Association of prescribed Chinese herbal medicine use with risk of end-stage renal disease in patients with chronic kidney disease

Ming-Yen Lin[1,2,3], Yi-Wen Chiu[1,2], Jung-San Chang[2,4], Hung-Lung Lin[5], Charles Tzu-Chi Lee[6], Guei-Fen Chiu[7], Mei-Chuan Kuo[1,2], Ming-Tsang Wu[6], Hung-Chun Chen[1,2] and Shang-Jyh Hwang[1,2,8]

[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Faculty of Renal Care, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Instrument Technology Research Center, National Applied Research Laboratories, Hsinchu, Taiwan; [4]Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Department of Chinese Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [6]Department of Public Health, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan; [7]Department of Medical Informatics, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan and [8]Institute of Population Sciences, National Health Research Institutes, Miaoli, Taiwan

The evidence on whether Chinese herbal medicines affect outcome in patients with chronic kidney disease (CKD) is limited. Here we retrospectively explored the association of prescribed Chinese herbal medicine use and the risk of end-stage renal disease (ESRD) in patients with CKD. Patients with newly diagnosed CKD in the Taiwan National Health Insurance Research Database from 2000 to 2005 were categorized into new use or nonuse of prescribed Chinese herbal medicine groups. These patients were followed until death, dialysis initiation, or till the end of 2008. Among the 24,971 study patients, 11,351 were new users of prescribed Chinese herbal medicine after CKD diagnosis. Overall, after adjustment for confounding variables, the use group exhibited a significant 60% reduced ESRD risk (cause-specific hazard ratio 0.41, 95% confidence interval 0.37–0.46) compared with the nonuse group. The change was significantly large among patients using wind dampness–dispelling formulas (0.63, 0.51–0.77) or harmonizing formulas (0.59, 0.46–0.74), suggesting an independent association between specific Chinese herbal medicines and reduced ESRD risk. The findings were confirmed using propensity score matching, stratified analyses, and three weighting methods. However, dampness-dispelling and purgative formulas were associated with increased ESRD risk. Thus, specific Chinese herbal medicines are associated with reduced or enhanced ESRD risk in patients with CKD.

Kidney International (2015) **88,** 1365–1373; doi:10.1038/ki.2015.226; published online 5 August 2015

KEYWORDS: Chinese herbal medicine; chronic kidney disease; end-stage renal disease

Correspondence: *Shang-Jyh Hwang, Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, 100 TzYou 1st Road, San-Ming District, Kaohsiung 807, Taiwan. E-mail: sjhwang@kmu.edu.tw*

Received 9 October 2014; revised 6 May 2015; accepted 21 May 2015; published online 5 August 2015

Chinese herbal medicines are commonly used worldwide for preventive and therapeutic purposes. Numerous surveys have revealed that a large proportion of people worldwide use herbs to treat illnesses and improve health.[1–3] In the United States, an estimated 12% of the population, accounting for nearly 15 million adults in 1997, used prescribed medicine and herbal remedies concurrently.[1] In Asian countries, traditional Chinese medicine is common, particularly in Chinese societies.[2–4] Chen *et al.*[3] found that 28.4% of Taiwan National Health Insurance (NHI) beneficiaries were treated with Chinese medicine in 2001, and the most common mode of such treatment (85.8%) was Chinese herbal remedies.

Several studies have questioned the safety of herbal products, citing their potential nephrotoxicity.[5–9] The most well-known adverse reaction was nephropathy reported in Belgium, specifically rapid progressive interstitial nephritis caused by Chinese herbs containing aristolochic acid, and resulted in end-stage renal disease (ESRD) and urothelial malignancy.[10] Most epidemiological studies have supported the adverse effects of Chinese herb use by patients with chronic kidney disease (CKD),[11–13] particularly for herbal medicines potentially containing aristolochic acid. Lai *et al.*[14] reported that herbal drugs containing aristolochic acid were associated with increased ESRD risk and urothelial carcinoma.[15] Conversely, few studies have demonstrated that herbal medicine exerts beneficial effects on the kidney.[16,17]

Growing concerns have emerged regarding whether Chinese herbal medicine should be used by patients with CKD. The National Kidney Foundation has suggested that herbal supplements should not be used by patients with CKD because herbal products are underregulated, pose the possibility of contamination, and may interact with prescription drugs.[18] In Taiwan, prescribed Chinese herbal medicine use is regulated and covered by the NHI program through a

board-certified Chinese medicine physician and a qualified pharmacist. The prescription-related information for each patient can be traced through the NHIRD (National Health Insurance Research Database), and we used this to study the association between Chinese herbal medicine use and ESRD risk in patients with CKD. We conducted a retrospective and observational study to test our hypothesis that Chinese medicine use increases ESRD risk in patients with CKD.

RESULTS

Demographic characteristics

We identified 24,971 eligible patients for follow-up according to our inclusion criteria. In the use group, which comprised 45.3% of the study cohort, the median duration of prescribed Chinese herbal medicine use was 22 days (interquartile range 7–62 days) during the study period. Within this group, 416 patients began dialysis, 861 patients died, and 466 patients withdrew from the NHI. In the nonuse group, which comprised 55% of the study cohort, 1014 patients began dialysis, 3032 patients died, and 1471 patients withdrew from the NHI (Figure 1). Table 1 presents the demographic characteristics, comorbidities, confounding drugs, and the number of outpatient visits of the study patients. The distribution of covariates, excluding age, region, the Charlson comorbidity index score, and the number of outpatient visits, was balanced in both groups after propensity score matching.

The 6-year cumulative incidence and cause-specific hazard ratio of ESRD

Figure 2 shows the cumulative incidence of ESRD after considering death as a competing event. During the study period, 23% of the nonuse group died before developing ESRD; this percentage was higher than the 6.2% in the use group ($P<0.001$). ESRD risk was significantly lower in patients who used prescribed Chinese herbal medicine (6-year cumulative incidence, 3.4%) than in nonusers (8.0%; $P<0.001$). In general, Chinese herbal medicine use was associated with significantly lower ESRD risk than that of nonuse in the multivariate analysis model (cause-specific hazard ratio (CSHR) 0.41, 95% confidence interval (CI) 0.37–0.46, $P<0.001$) and in a model that included only propensity score–matched patients (CSHR 0.47, 95% CI 0.41–0.54, $P<0.001$). ESRD risk in the use group was consistently lower than that in the nonuse group after stratification by follow-up period (Table 2) and use duration (Table 3).

Formulas associated with ESRD

Table 4 presents the associations of specific formulas with ESRD risk. Patients who used wind dampness–dispelling (CSHR 0.63, 95% CI 0.51–0.77, $P<0.001$) and harmonizing formulas (CSHR 0.59, 95% CI 0.46–0.74, $P<0.001$) exhibited lower ESRD risk, whereas those who used dampness-dispelling (CSHR 1.47, 95% CI 1.20–1.79, $P<0.001$) and

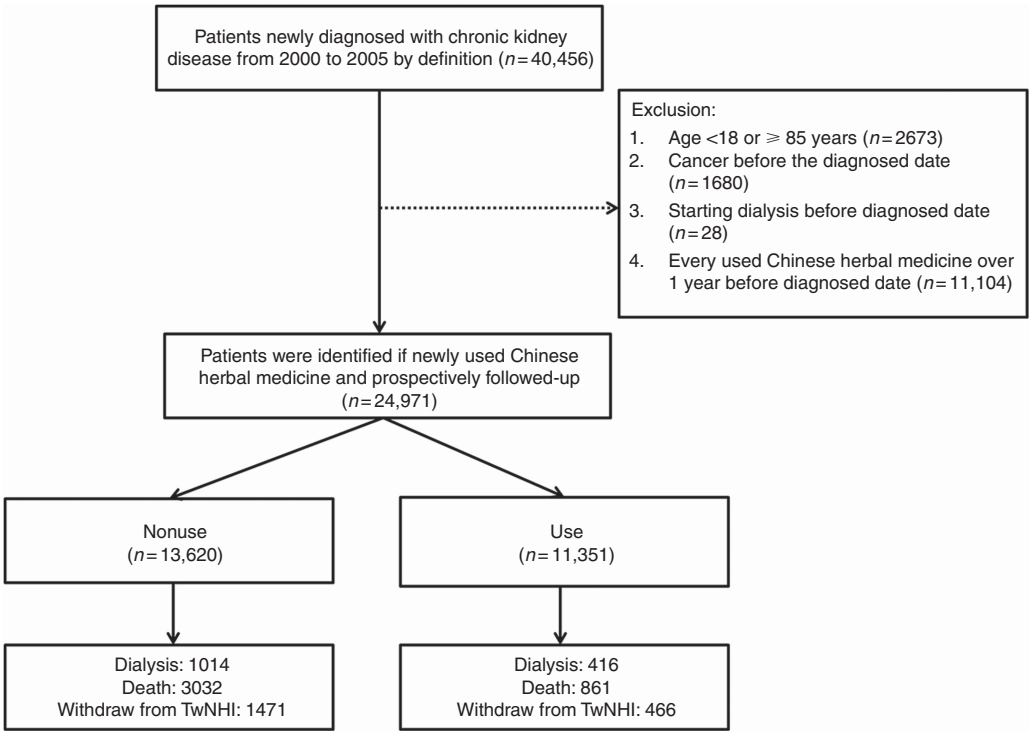

Figure 1 | Study flow diagram. Chronic kidney disease (CKD) was considered as present if corresponding ICD-9-CM codes were identified for one or more inpatient visit or two or more outpatient visits within 1 year. Patients who newly used prescribed Chinese herbal medicine after CKD diagnosis were assigned to the use group. Patients who did not meet this criterion were assigned to the nonuse group. Cancer was identified using ICD-9-CM codes from the Registry for Catastrophic Illness Patient Database, a subset of the National Health Insurance Research Database (Supplementary Table S4 online). ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; TwNHI, Taiwan National Health Insurance.

Table 1 | Characteristics of study cohort by the use of Chinese herbal medicine

Characteristic	Before matched				Propensity score matched		
		Prescribed Chinese herbal medicine			Prescribed Chinese herbal medicine		
	Overall	Nonuse	Use	*P*-value	Nonuse	Use	*P*-value
Patient no.	24, 971	13,620	11,351		8195	8195	
Age, years	56.8 ± 16.5	59.6 ± 16.5	53.5 ± 15.8	<0.001	54.2 ± 16.3	54.9 ± 15.7	0.007
Female (%)	40.5	35.9	46	<0.001	39.2	39.2	0.91
Insurance amount, NTD (%)				<0.001			0.88
Fixed premium or dependent	20.1	21.1	18.9		19.4	19.1	
<20,000	57.7	58.5	56.8		55.9	56.3	
20,000–39,999	14.3	12.9	16		15.5	15.6	
≧39,999	7.9	7.5	8.3		9.2	9	
Region (%)				<0.001			<0.001
North	46	48	43.7		48.1	44.8	
Center	21.7	19.8	23.9		19.5	24.2	
South	28.8	28.5	29.1		28.9	28.1	
East	3.5	3.7	3.3		3.5	2.9	
Urbanization (%)				<0.001			0.28
Urban	73.7	72.6	75.1		75.1	74.4	
Comorbidities (%)							
Acute coronary syndrome	11.5	13.5	9.1	<0.001	9.3	9.6	0.42
Diabetes	27.7	31.6	23	<0.001	24.1	24.9	0.23
Hypertension	37.7	43.1	31.4	<0.001	33.4	34.3	0.23
Hyperlipidemia	13	13.3	12.7	0.67	13.2	13	0.78
COPD	8.4	10.4	6	<0.001	6.1	6.4	0.48
Cerebrovascular disease	10	13.7	5.6	<0.001	6.1	6.8	0.1
Charlson score							
Mean (s.d.)	1.35 ± 1.78	1.70 ± 2.01	0.93 ± 1.36	<0.001	0.98 ± 1.35	1.03 ± 1.45	0.02
Median (IQR)	1 (0–2)	1 (0–3)	0 (0–1)	<0.001	0 (0–1)	0 (0–2)	0.08
Confounding drugs, %							
Diabetic drugs	28.7	29	28.2	0.18	27.9	28.3	0.66
Antihypertensive drugs	55.4	55.5	55.4	0.89	54.3	54.8	0.55
NSAIDs	31.8	25.7	39.1	<0.001	31.5	31.9	0.6
Analgesic drugs other than NSAIDs	43.5	40.7	46.7	<0.001	42.3	42.4	0.81
Anti-lipid drugs	20.9	19.4	22.8	<0.001	21.9	21.7	0.73
Number of outpatient visits	145 ± 127	113 ± 109	182 ± 134	<0.001	144 ± 121	150 ± 108	0.001
Number of prescribed Chinese herbal medicine visits							
Median (IQR)	0 (0–16)	0 (0–0)	19 (7–56)	<0.001	0 (0–0)	16 (6–46)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; NTD, New Taiwan dollar.
The differences of characteristics among groups were compared using χ^2 tests for categorical variables and independent *t*-tests for continuous variables. A *P*-value of <0.05 was considered statistically significant.
NT$30 equals approximately US$1.

purgative formulas (CSHR 1.58, 95% CI 1.22–2.05, $P = 0.001$) exhibited higher ESRD risk. These results were verified using multivariate and propensity score–matched models (Supplementary Figure S1 online). In addition, blood-regulating, qi-regulating, and summer heat–clearing formulas exhibited significantly protective effects in one of these models. Supplementary Table S1 online lists the herbs in the prescribed formulas.

Sensitivity analyses

The sensitivity analysis results strongly support the main finding of this study, namely that the use group exhibited significantly lower ESRD risk than did the nonuse group, even in stratified analyses (Figure 3) conducted using different definitions of Chinese herbal medicine use (Supplementary Table S2 online) and different weighted propensity score approaches (Supplementary Table S3 online).

DISCUSSION

According to a review of relevant literature, this is the first population-based retrospective cohort study providing solid evidence of the association between Chinese herbal medicine use and ESRD risk in patients with CKD. This study revealed that numerous patients were prescribed

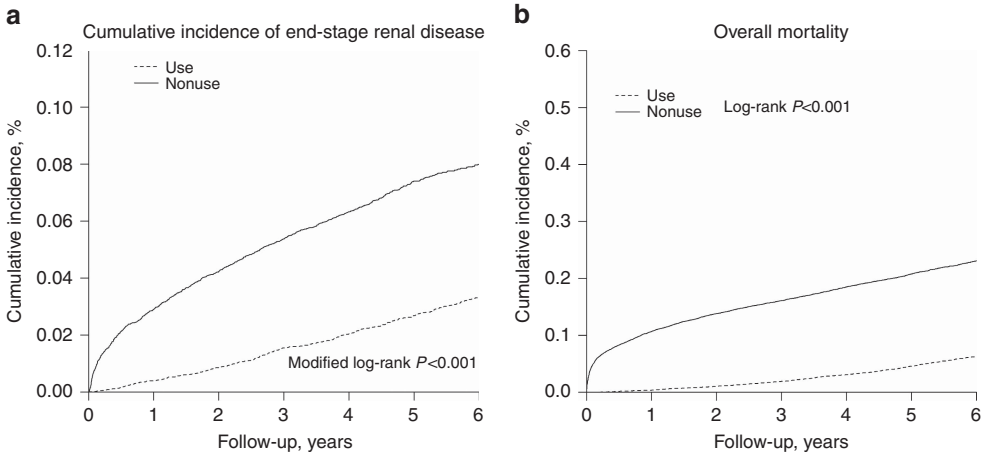

Figure 2 | Risk of end-stage renal disease and mortality. Cumulative incidences of **(a)** end-stage renal disease and **(b)** overall mortality. Data were calculated after considering death as a competing event. The cumulative incidence of end-stage renal disease was estimated in consideration of the competing risk of mortality, and the differences between prescribed Chinese herbal medicine use and nonuse groups were analyzed using modified Kaplan–Meier and Grey methods, whereas only the Kaplan–Meier method was used to analyze mortality.

Table 2 | End-stage renal disease occurrence in relation to the use of prescribed Chinese herbal medicine, by follow-up duration

Time	Nonuse			Use			Before matched		Propensity score matched	
	Case	PY	I[a]	Case	PY	I[a]	aCSHR (95% CI)[b]	*P*-value	CSHR (95% CI)	*P*-value
All observed period	1014	59,572	17	416	69,457	6	0.41 (0.37–0.46)	<0.001	0.47 (0.41–0.54)	<0.001
Follow-up duration										
<1 y	389	11,963	32.5	45	11,294	4	0.15 (0.11–0.21)	<0.001	0.19 0.13–0.26)	<0.001
1–2 y	172	10,833	15.9	54	11,133	4.9	0.33 (0.24–0.45)	<0.001	0.40 (0.28–0.57)	<0.001
2–3 y	144	10,121	14.2	76	10,940	6.9	0.53 (0.39–0.71)	<0.001	0.58 (0.42–0.82)	0.002
3–4 y	108	8746	12.3	53	10,230	5.2	0.43 (0.31–0.61)	<0.001	0.45 (0.30–0.66)	<0.001
>4 y	201	17,909	11.2	188	25,859	7.3	0.76 (0.62–0.94)	0.01	0.86 (0.68–1.09)	0.21

Abbreviations: aCSHR, adjusted cause-specific hazard ratio; CI, confidence interval; CSHR, cause-specific hazard ratio; I, incidence; PY, person-years; y, year.
[a]Incidence rate (per 1000 person-years).
[b]Models adjusted for age, sex, insurance amount, region, urbanization of residence, comorbidities, the Charlson comorbidity index score, diabetic drugs, antihypertensive drugs, nonsteroidal anti-inflammatory drugs, analgesic drugs other than nonsteroidal anti-inflammatory drugs, anti-lipid drugs, and the number of outpatient visits.

Table 3 | End-stage renal disease occurrence in relation to duration of the use of prescribed Chinese herbal medicine

Use prescribed Chinese herbal medicine, day	Duration of use, median (interquartile range)	Case	PY	I[a]	Before matched		Propensity score matched	
					aCSHR (95% CI)[b]	*P*-value	CSHR (95% CI)	*P*-value
0	0 (0–0)	1014	59,572	17	1.00 (Reference)		1.00 (Reference)	
1–6	5 (4–6)	123	16,009	7.7	0.51 (0.42–0.61)	<0.001	0.60 (0.48–0.73)	<0.001
7–21	12 (10–17)	112	17,371	6.4	0.47 (0.38–0.57)	<0.001	0.51 (0.41–0.65)	<0.001
22–61	36 (28–46)	97	17,503	5.5	0.40 (0.33–0.50)	<0.001	0.46 (0.36–0.58)	<0.001
≥62	129 (87–228)	84	18,573	4.5	0.28 (0.22–0.36)	<0.001	0.32 (0.24–0.42)	<0.001

Abbreviations: aCSHR, adjusted cause-specific hazard ratio; CI, confidence interval; CSHR, cause-specific hazard ratio; I, incidence; PY, person-years.
[a]Incidence rate (per 1000 person-years).
[b]Models adjusted for age, sex, insurance amount, region, urbanization of residence, comorbidities, the Charlson comorbidity index score, diabetic drugs, antihypertensive drugs, nonsteroidal anti-inflammatory drugs, analgesic drugs other than nonsteroidal anti-inflammatory drugs, anti-lipid drugs, and the number of outpatient visits.

Chinese herbal medicines after CKD diagnosis and that, in contrast to the existing belief, the use of these medicines was associated with significantly reduced ESRD risk. After systemically surveying every prescribed Chinese herbal medicine formula, we observed that the protection effect against ESRD was the strongest among blood-regulating, wind dampness–dispelling, qi-regulating, harmonizing, and summer heat–clearing formulas. However, dampness-dispelling

Table 4 | Cause-specific hazard ratios (CSHRs) of end-stage renal disease by the use of various classes of prescribed Chinese herbal medicine

Classes	Before matched		Propensity score matched	
	aCSHR (95% CI)[a]	*P*-value	CSHR (95% CI)	*P*-value
Tonic formulas	1.00 (0.82–1.22)	1	1.06 (0.84–1.34)	0.6
Blood-regulating formulas	0.73 (0.6–0.89)	0.002	0.83 (0.66–1.04)	0.1
Heat-clearing formulas	0.84 (0.68–1.03)	0.08	0.92 (0.73–1.16)	0.48
Exterior-releasing formulas	0.84 (0.68–1.03)	0.09	0.80 (0.62–1.01)	0.06
Dampness-dispelling formulas	1.47 (1.20–1.79)	<0.001	1.29 (1.03–1.63)	0.03
Wind dampness–dispelling formulas	0.63 (0.51–0.77)	<0.001	0.67 (0.53–0.85)	<0.001
Phlegm-dispelling formulas	0.86 (0.68–1.09)	0.21	0.76 (0.57–1.00)	0.05
Sedative formulas	0.89 (0.7–1.14)	0.36	1 (0.75–1.32)	0.98
Qi-regulating formulas	0.70 (0.55–0.89)	0.003	0.86 (0.65–1.13)	0.28
Harmonizing formulas	0.59 (0.46–0.74)	<0.001	0.52 (0.40–0.69)	<0.001
Downward draining formulas	0.94 (0.75–1.18)	0.58	0.87 (0.67–1.14)	0.32
Dryness-relieving formulas	0.86 (0.68–1.08)	0.2	0.82 (0.62–1.07)	0.14
Cold-dispelling formulas	1.23 (0.93–1.61)	0.14	1.25 (0.91–1.71)	0.17
Exterior- and interior-releasing formulas	0.84 (0.61–1.17)	0.3	0.85 (0.57–1.27)	0.44
Astringent formulas	1.11 (0.86–1.45)	0.42	1.03 (0.76–1.41)	0.83
Purgative formulas	1.58 (1.22–2.05)	0.001	1.56 (1.15–2.13)	0.005
Cough-suppressing and panting-calming formulas	0.98 (0.73–1.31)	0.86	0.93 (0.65–1.32)	0.68
Liver-pacifying and wind-extinguishing medicinals	1.10 (0.82–1.49)	0.53	1.25 (0.88–1.76)	0.21
Summer heat–clearing formulas	0.78 (0.57–1.08)	0.13	0.66 (0.45–0.99)	0.04
Orifice-opening formulas	0.69 (0.41–1.14)	0.15	0.76 (0.42–1.35)	0.35
Shen-calming formulas	0.72 (0.42–1.25)	0.25	0.74 (0.36–1.51)	0.41
Formulas that treat abscesses and sores	0.83 (0.54–1.27)	0.4	0.93 (0.57–1.5)	0.76
Antiparasitic formulas	0.99 (0.53–1.83)	0.96	0.75 (0.33–1.73)	0.5
Interior-warming formulas	1.19 (0.9–1.58)	0.23	1.34 (0.97–1.87)	0.08
Emetic formulas	<0.01 (0.00–>100)	0.93	<0.01 (0.00–>100)	0.95
Undetermined formulas	1.18 (0.87–1.6)	0.3	1.09 (0.75–1.60)	0.64

Abbreviations: aCSHR, adjusted cause-specific hazard ratio; CI, confidence interval.
[a]Models adjusted for age, sex, insurance amount, region, urbanization of residence, comorbidities, the Charlson comorbidity index score, diabetic drugs, antihypertensive drugs, nonsteroidal anti-inflammatory drugs, analgesic drugs other than nonsteroidal anti-inflammatory drugs, anti-lipid drugs, the number of outpatient visits, and various classes of prescribed Chinese herbal medicine.

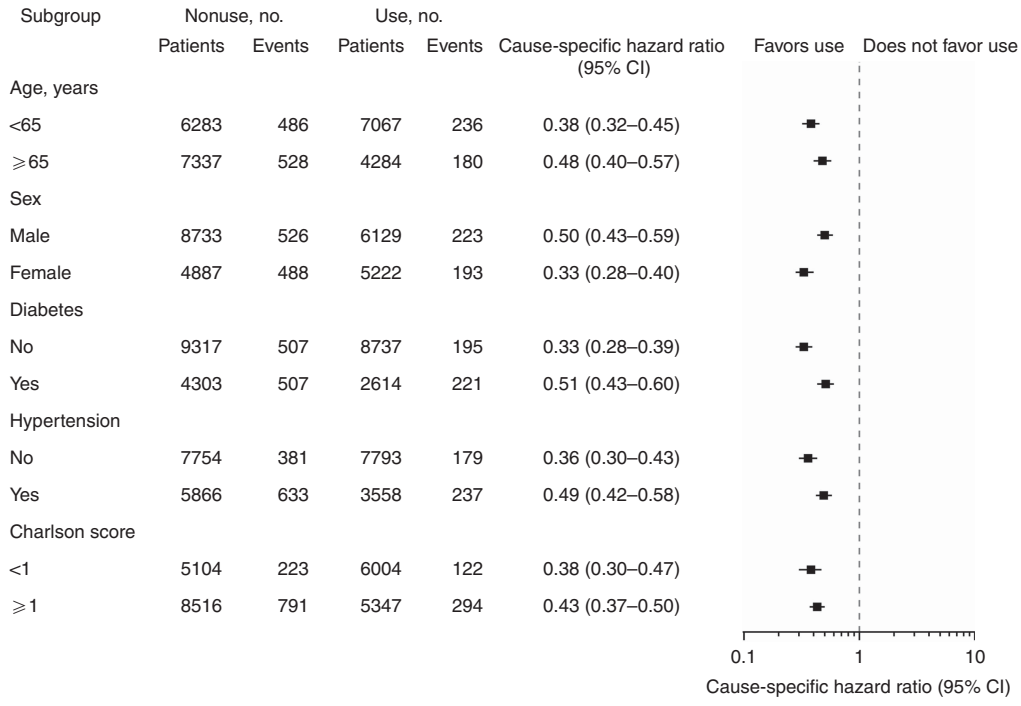

Figure 3 | Multivariate stratified analyses for the association between the use of prescribed Chinese herbal medicine and end-stage renal disease. CI, confidence interval.

and purgative formulas were associated with increased ESRD risk.

Although medical guidelines do not currently recommend that alternative medicine be used in treating patients with chronic diseases, Chinese herbs and herbal products are commonly used worldwide. Our study found that nearly half (45.3%) of the patients with CKD in Taiwan had been prescribed and used Chinese herbal medicine after diagnosis, although the indications could not be determined. Other studies have reported that ~11% of women with early-stage breast cancer,[19] 21% of patients with liver diseases,[20] 22% of patients with human immunodeficiency virus infections,[21] 24% of patients with asthma,[22] 26% of patients with rheumatological disorders,[23] and 52.6% of patients with prostate cancer[24] had used Chinese herbal medicine to relieve symptoms or otherwise improve their quality of life. As with these diseases, the limitations of Western medicine in curing CKD drive numerous patients to seek alternative treatments. However, the lack of study into the side effects and complications of Chinese herbal medicine might endanger this population. Before this study, little evidence existed supporting the efficacy of Chinese herbal medicine in retarding CKD progression, and no systematic investigation had evaluated the renal side effect of Chinese herbal formulas. Our findings, despite not guaranteeing the safety of Chinese herbal medicine use by patients with CKD, challenge the recommendation against prescribing all such medicines to these patients.

Evidence of the association between Chinese herb use and the progress of kidney disease is still limited. Most studies of Chinese herbs and CKD have examined aristolochic acid–caused nephrology, with few investigating other Chinese herbal medicines for patients with CKD.[10,25] Unlike previous studies that focused on the association between herb use and the appearance of kidney disease,[11,13,25] our study demonstrated that prescribed Chinese herbal medicine use reduced ESRD risk by 60%. The dose–response relationship of this association further strengthens the evidence that Chinese herbal medicine use exerts a protective effect against CKD progression (Table 3). Similar to Hsieh *et al.*,[26] our study found that a proportion of patients with CKD (30.8%) used Chinese herbal medicines potentially containing aristolochic acid. However, we compared this subgroup with those who took only herbs not containing aristolochic acid and found that ESRD risk did not vary ($P = 0.27$). Aristolochic acid may be misused or mixed in certain Chinese herbal medicines or slimming pills and cause progressive interstitial fibrosis. The likelihood of aristolochic acid being misused or mixed probably decreased after it was banned in Taiwan; however, the establishment of additional regulations on aristolochic acid and other toxic herbs is required to minimize the likelihood of side effects of Chinese herbal medicine use.

Using a large data set and long observation period, our study demonstrated that two Chinese herbal formulas, namely wind dampness–dispelling (containing 46 herbal products) and harmonizing formulas (containing 16 herbal products), may contain therapeutic components that prevent CKD progression. We cannot be certain that these two formulas prescribed to the patients were indicated for their CKD; however, our results may guide future studies in exploring the possibility of using Chinese herbal medicines to retard CKD progression. The effects and side effects of these medicines are difficult to evaluate because the therapeutic philosophy of Chinese medicine differs greatly from that of Western medicine. Chinese medicine prescriptions may contain various herbal doses of the same formulas according to the symptoms and signs of the patient rather than of the disease. Previous animal studies have reported that some components of Chinese herbs might exert renoprotective effects.[27–34] However, these animal study results were only weakly confirmed by a human study.[35] The method used in the current study enabled us to identify potentially beneficial formulas and those with potential renal toxicity. Chinese herbal formulas like dampness-dispelling and purgative formulas were associated with an increased ESRD risk. The constituent herbs of both formulas were reviewed and a literature review revealed no evidence of renal toxicity in these herbs, except in a small portion of herbal products in dampness-dispelling formulas that potentially contain aristolochic acid. Dampness-dispelling formulas are used for removing surplus body fluid. Our prior study showed that fluid overload is a risk factor strongly predicting CKD progression to ESRD,[36] and the rapid removal of body fluid in patients with CKD may cause further renal ischemic injury. Again, further study is required to elucidate the mechanisms of these formulas on renal progression.

Our study has four strengths. First, identifying prescribed Chinese herbal medicine by using a database enabled us to avoid recall bias that may have been present if we had used a questionnaire, and ensured that the exposure to prescribed Chinese herbal medicine occurred before ESRD development. Second, the new-use design reduced the potential residual effect of using prescribed Chinese herbal medicine before CKD diagnosis. Third, we used a competing-risk approach to estimate the incidence rate of ESRD accurately. Fourth, the propensity score–matching and stratified analyses minimized confounding effects. However, we must acknowledge several limitations. First, because we identified patients with CKD using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes rather than laboratory data, most patients included in the study had stage 3–5 CKD. Therefore, our results may not be generalizable to patients with early-stage CKD. Second, although we used propensity score matching, we could not avoid the potential confounding effects of the different patient characteristics of the groups, such as Chinese medicine–seeking behavior, that cannot be collected from our data set. However, when we analyzed only the use group, the results were similar. Third, as mentioned, being certain that the formulas used in this study were indicated for CKD progression is difficult. Furthermore, we could use only the prescribed duration to reflect the

duration of use because drug compliance was unobtainable. Fourth, because of scrambled identification, the death numbers might have been slightly underestimated. Finally, we could collect information only on Chinese herbal medicines for which the NHI provides reimbursement. The NHI provides reimbursement only for Chinese herbal medicines in pill or powder form that are produced by pharmaceutical companies with certified manufacturing practices and does not cover sources that contain crude herbal products.

In conclusion, our results demonstrate that patients with CKD who used prescribed Chinese herbal medicine exhibited a reduced risk of ESRD. According to this finding, we might reconsider whether prohibiting the use of all herbal medicines by patients with CKD is appropriate and encourage further exploration regarding how Chinese herbal medicine may retard CKD progression.

MATERIALS AND METHODS

Study population

In 1995, Taiwan launched the NHI program that reimburses patients using prescribed Chinese herbal medicines that are extracted and condensed from crude herbs. The NHI does not cover crude Chinese herbal products. Patients can access Chinese medicine services with low copayments for prescriptions of NT$50 (approximately US $1.50) per prescription.

We used the LHID2000 (Longitudinal Health Insurance Database 2000), a subset of the NHIRD, that is managed by the National Health Research Institutes and freely available for academic research. The LHID2000 contains the data of 1 million randomly sampled patients who were NHI beneficiaries in 2000. The sampled patients exhibit no significant differences in age, sex, birth year, or average insured payroll-related amount from the general population. We used LHID2000 data from 1997 to 2008, including scrambled identification, sex, birth dates, medications, and ICD-9-CM codes. This study was approved by the ethical review board of Kaohsiung Medical University (KMUH-IRB-EXEMPT-20130028). All research procedures followed the directives of the Declaration of Helsinki Principles.

Chronic kidney disease

The CKD cohort comprised patients who were newly diagnosed with CKD between 2000 and 2005, identified by following the approach of a previous study that classified patients with ICD-9-CM codes for one or more inpatient visit or two or more outpatient visits within 1 year as having CKD.[37] To ensure the accuracy of the CKD diagnostic codes, we validated them by using the standard definition of CKD (estimated glomerular filtration rate $<60\,ml\,min^{-1}$ per $1.73\,m^2$, microalbuminuria, or overt proteinuria) and a data set from one regional hospital. We studied 800 patients with CKD diagnosis codes from January 2010 to December 2010 and verified the codes of 790 of these patients by examining serum creatinine and urine protein data. The positive predictive value of using the ICD-9-CM codes for CKD was 90.4 (714 of 790), and the CKD of most patients was categorized as stage 3–5 (99.6%, 711 of 714). The date of the first CKD diagnosis was obtained from claims data on ambulatory, emergency, and inpatient care received between 2000 and 2005.

Chinese herbal medicine use

Chinese medicine prescriptions for patients with CKD were retained after excluding for acupuncture, moxibustion, massage, relocation, and pain patches. The exclusion criteria were (1) an age <18 years or >85 years, (2) cancer diagnosis, (3) CKD diagnosed after dialysis initiation, and (4) Chinese herbs prescribed within 1 year before CKD diagnosis. Patients were assigned to the use group only if they were prescribed Chinese herbs before dialysis initiation, whereas those with no such prescription or who were prescribed Chinese herbs after dialysis initiation were assigned to the nonuse group. To detect the potential effect of specific Chinese herbal formulas on renal disease, we categorized all prescribed herbs as one of the 25 formulas or into an undetermined group according to their therapeutic functions. This method followed approaches suggested in textbooks, with minor modifications.[38,39]

Main outcome measurements

Incident dialysis patients were identified by examining ICD-9-CM codes in the Registry of Catastrophic Illness (Supplementary Table S4 online). By tracing the specific payment codes of these patients (Supplementary Table S5 online), we obtained the event date of their first dialysis treatment. In addition to death reported in medical records, patients discharged in critical conditions for whom no outpatient follow-up records existed were also considered deceased. We followed patients until dialysis initiation, death, withdrawal from the NHI, or the end of the observation period. Dialysis initiation was considered the event of interest, whereas death before dialysis initiation was the competing event. The other outcomes were considered censored events.

Covariate assessment

Information on patient characteristics, namely age, sex, insurance amount, region, urbanization of residence, comorbidities (acute coronary syndrome, diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and cerebrovascular disease), Charlson comorbidity index score, confounding drugs, and the number of outpatient visits during the observation period, were considered covariates in modeling. The insurance amount was classified into four categories (fixed premium or dependent, $<$ NT$20,000, NT $20,000–NT$39,999, and $\geqq$NT$39,999), regions was divided into four categories (North, Central, South, and East), and residence was divided into two categories (urban and rural), as described by previous studies.[40] Comorbidities were considered present if ICD-9-CM codes (Supplementary Table S5 online) appeared two or more times in outpatient claims or one or more times in inpatient claims within 1 year before CKD diagnosis. The Charlson comorbidity index scores were calculated according to diseases listed in a previous study.[41] In multivariate analyses, the confounding drugs were diabetic, antihypertensive, and anti-lipid drugs, nonsteroidal anti-inflammatory drugs, and analgesic drugs other than nonsteroidal anti-inflammatory drugs (Supplementary Table S6 online). Patients who used a prescribed drug for over 5% of the follow-up period were considered to have been treated with the drugs.

Statistical analysis

The distributions of patient characteristics between the use and nonuse groups are expressed as the mean $\pm$ s.d., median (interquartile range), or percentage. The differences between groups were tested using an independent t-test or χ^2 test.

We used the competing-risk approach to estimate the 6-year cumulative incidence of ESRD and cumulative mortality rate and tested the difference between the groups by using a modified log-rank test[42] and a log-rank test. Propensity score approaches were used to reduce confounding by indication of Chinese herb use. The propensity score of using Chinese herbal medicine was calculated by considering all covariates as independent variables through multiple binary logistic regression analysis and matching the groups by propensity score by using greedy matching techniques with a $5 \rightarrow 1$ digit match.[43] For ESRD risk comparison between the groups, multivariate analyses with adjustment for all covariates and univariate analyses including only propensity score–matched patients were conducted using modified Cox regression hazard models to obtain CSHRs. We inspected the overall effect of prescribed Chinese herbal medicine use on ESRD risk and explored the influence of specific Chinese herbal formulas on ESRD risk. Because of violations of the proportional hazards assumption, we estimated the CSHRs of ESRD by comparing the use and nonuse groups and stratifying the results by follow-up duration. Patients who encountered events in a duration were removed from the data set, and the remaining patients were considered the at-risk population in the following duration. Patients who did not encounter events were censored at the end of each duration. Data were represented as CSHRs and 95% CIs.

In addition, we conducted sensitivity analyses to validate our main finding. First, we redefined the use group by the cumulative period of prescribed Chinese herbal medicine use: >30 days, >60 days, and >90 days. Second, multivariate stratified analyses were conducted for different subgroups. Finally, we recalculated the models by weighting all patients by using inverse probability of treatment, stabilized inverse probability of treatment, and standardized mortality ratio weightings.

Statistical analysis was performed and figures were created using SAS 9.2 (SAS Institute, Cary, NC), R software (Taipei, Taiwan), and GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). $P<0.05$ in two-tailed tests indicated statistical significance.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank the Statistical Analysis Laboratory of the Department of Internal Medicine of Kaohsiung Medical University Hospital for providing access to the NHIRD (registration number 99324) and the National Science Council of Taiwan (NSC 102-3114-Y-492-076-023) for supporting this study. Some results of this study were presented in abstract form at Kidney Week 2011, organized by the American Society of Nephrology. The interpretation and reporting of data in the study is the responsibility of the authors and in no way should be seen as an official policy or an interpretation of the Taiwan government.

SUPPLEMENTARY MATERIAL

Table S1. All formulas associated with end-stage renal disease and their constituent herbs.
Table S2. Cause-specific hazard ratios (CSHRs) of end-stage renal disease by definition of Chinese herbal medicine use.
Table S3. Cause-specific hazard ratios (CSHRs) of end-stage renal disease by weighting approach.
Table S4. Diseases and corresponding ICD-9-CM codes.
Table S5. Payment codes for clinical treatment covered by Taiwan National Health Insurance.
Table S6. Anatomical Therapeutic Chemical codes of drugs used concomitantly by patients during the study period.

Figure S1. Propensity score distribution by use group (a) all study patients, (b) only including matched patients.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Eisenberg DM, Davis RB, Ettner SL *et al.* Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; **280**: 1569–1575.
2. Hong CD. Complementary and alternative medicine in Korea: current status and future prospects. *J Altern Complement Med* 2001; **7**: S33–S40.
3. Chen FP, Chen TJ, Kung YY *et al.* Use frequency of traditional Chinese medicine in Taiwan. *BMC Health Serv Res* 2007; **7**: 26.
4. Yamashita H, Tsukayama H, Sugishita C. Popularity of complementary and alternative medicine in Japan: a telephone survey. *Complement Ther Med* 2002; **10**: 84–93.
5. Bent S, Ko R. Commonly used herbal medicines in the United States: a review. *Am J Med* 2004; **116**: 478–485.
6. Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J Gen Intern Med* 2008; **23**: 854–859.
7. Ko RJ. A U.S. perspective on the adverse reactions from traditional Chinese medicines. *J Chin Med Assoc* 2004; **67**: 109–116.
8. Isnard Bagnis C, Deray G, Baumelou A *et al.* Herbs and the kidney. *Am J Kidney Dis* 2004; **44**: 1–11.
9. Colson CR, De Broe ME. Kidney injury from alternative medicines. *Adv Chronic Kidney Dis* 2005; **12**: 261–275.
10. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008; **74**: 158–169.
11. Tsai SY, Tseng HF, Tan HF *et al.* End-stage renal disease in Taiwan: a case-control study. *J Epidemiol* 2009; **19**: 169–176.
12. Guh JY, Chen HC, Tsai JF *et al.* Herbal therapy is associated with the risk of CKD in adults not using analgesics in Taiwan. *Am J Kidney Dis* 2007; **49**: 626–633.
13. Ingsathit A, Thakkinstian A, Chaiprasert A *et al.* Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. *Nephrol Dial Transplant* 2010; **25**: 1567–1575.
14. Lai MN, Lai JN, Chen PC *et al.* Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: a population-based case-control study. *Am J Kidney Dis* 2010; **55**: 507–518.
15. Lai MN, Wang SM, Chen PC *et al.* Population-based case-control study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk. *J Natl Cancer Inst* 2010; **102**: 179–186.
16. Wojcikowski K, Johnson DW, Gobe G. Herbs or natural substances as complementary therapies for chronic kidney disease: ideas for future studies. *J Lab Clin Med* 2006; **147**: 160–166.
17. Wojcikowski K, Johnson DW, Gobe G. Medicinal herbal extracts–renal friend or foe? Part two: herbal extracts with potential renal benefits. *Nephrology (Carlton)* 2004; **9**: 400–405.
18. National Kidney Foundation. *Use of Herbal Supplements in Chronic Kidney Disease*. A to Z Health Guide, 2002 (date last accessed 15 July 2014; http://www.kidney.org/atoz/content/herbalsupp.cfm).
19. Burstein HJ, Gelber S, Guadagnoli E *et al.* Use of alternative medicine by women with early-stage breast cancer. *N Engl J Med* 1999; **340**: 1733–1739.
20. Strader DB, Bacon BR, Lindsay KL *et al.* Use of complementary and alternative medicine in patients with liver disease. *Am J Gastroenterol* 2002; **97**: 2391–2397.
21. Kassler WJ, Blanc P, Greenblatt R. The use of medicinal herbs by human immunodeficiency virus-infected patients. *Arch Intern Med* 1991; **151**: 2281–2288.
22. Blanc PD, Trupin L, Earnest G *et al.* Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis: data from a population-based survey. *Chest* 2001; **120**: 1461–1467.
23. Rao JK, Mihaliak K, Kroenke K *et al.* Use of complementary therapies for arthritis among patients of rheumatologists. *Ann Intern Med* 1999; **131**: 409–416.
24. Lin YH, Chen KK, Chiu JH. Use of Chinese medicine among prostate cancer patients in Taiwan: a retrospective longitudinal cohort study. *Int J Urol* 2011; **18**: 383–386.
25. Lai MN, Lai JN, Chen PC *et al.* Increased risks of chronic kidney disease associated with prescribed Chinese herbal products suspected to contain aristolochic acid. *Nephrology (Carlton)* 2009; **14**: 227–234.
26. Hsieh SC, Lin IH, Tseng WL *et al.* Prescription profile of potentially aristolochic acid containing Chinese herbal products: an analysis of

National Health Insurance data in Taiwan between 1997 and 2003. *Chin Med* 2008; **3**: 13.
27. Lee GT, Ha H, Jung M *et al.* Delayed treatment with lithospermate B attenuates experimental diabetic renal injury. *J Am Soc Nephrol* 2003; **14**: 709–720.
28. Ahn YM, Kim SK, Lee SH *et al.* Renoprotective effect of Tanshinone IIA, an active component of Salvia miltiorrhiza, on rats with chronic kidney disease. *Phytother Res* 2010; **24**: 1886–1892.
29. You Z, Xin Y, Liu Y *et al.* Protective effect of Salvia Miltiorrhizae injection on N(G)-nitro-d-arginine induced nitric oxide deficient and oxidative damage in rat kidney. *Exp Toxicol Pathol* 2010; **64**: 453–458.
30. Lee SH, Kim YS, Lee SJ *et al.* The protective effect of Salvia miltiorrhiza in an animal model of early experimentally induced diabetic nephropathy. *J Ethnopharmacol* 2011; **137**: 1409–1414.
31. Liu X, Wang Y, Ma C *et al.* Proteomic assessment of tanshinone IIA sodium sulfonate on doxorubicin induced nephropathy. *Am J Chin Med* 2011; **39**: 395–409.
32. Kim SK, Jung KH, Lee BC. Protective effect of Tanshinone IIA on the early stage of experimental diabetic nephropathy. *Biol Pharm Bull* 2009; **32**: 220–224.
33. Kang DG, Oh H, Sohn EJ *et al.* Lithospermic acid B isolated from Salvia miltiorrhiza ameliorates ischemia/reperfusion-induced renal injury in rats. *Life Sci* 2004; **75**: 1801–1816.
34. Liu SJ, Zhou SW. Panax notoginseng saponins attenuated cisplatin-induced nephrotoxicity. *Acta Pharmacol Sin* 2000; **21**: 257–260.
35. Goto H, Shimada Y, Tanikawa K *et al.* Clinical evaluation of the effect of daio (rhei rhizoma) on the progression of diabetic nephropathy with overt proteinuria. *Am J Chin Med* 2003; **31**: 267–275.
36. Tsai Y-C, Tsai J-C, Chen S-C *et al.* Association of fluid overload with kidney disease progression in advanced CKD: a prospective cohort study. *Am J Kidney Dis* 2014; **63**: 68–75.
37. Collins AJ, Chen SC, Gilbertson DT *et al.* CKD surveillance using administrative data: impact on the health care system. *Am J Kidney Dis* 2009; **53**: S27–S36.
38. Chen JK, Chen TT. *Chinese Herbal Formulas and Applications: Pharmacological Effects & Clinical Research*. Art of Medicine Press: City of Industry, CA, 2009.
39. Cao M. [Wang Ang and his Variorum of medical recipes (Yi fang ji jie)]. *Zhonghua Yi Shi Za Zhi* 2000; **30**: 179–181.
40. Chien IC, Hsu JH, Lin CH *et al.* Prevalence of diabetes in patients with schizophrenia in Taiwan: a population-based National Health Insurance study. *Schizophr Res* 2009; **111**: 17–22.
41. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613–619.
42. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16**: 1141–1154.
43. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at the Proceedings of the 26th Annual SAS Users Group International Conference. 2001.