



Harmonizing Formula Prescription Patterns in Patients With Chronic Kidney Disease: A Population-Based Cross-Sectional Study

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Objective: Harmonizing formulas are associated with beneficial renal outcomes in chronic kidney disease (CKD), but the therapeutic mechanisms are unclear. The study aims to explore the associations of intentions and independent factors with harmonizing formulas prescriptions for patients with CKD.

Methods: We conducted a population-based cross-sectional study to explore factors associated with harmonizing formulas prescription. Patients who had been prescribed harmonizing formulas after CKD diagnosis was defined as the using harmonizing formulas group. Disease diagnoses when having harmonizing formula prescriptions and patient characteristics related to these prescriptions were collected.

Results: In total, 24,971 patients were enrolled in this analysis, and 5,237 (21%) patients were prescribed harmonizing formulas after CKD diagnosis. The three most frequent systematic diseases and related health problems for which harmonizing formula prescriptions were issued in CKD were symptoms, signs, and ill-defined conditions (24.5%), diseases of the digestive system (20.67%), and diseases of the musculoskeletal system (12.9%). Higher likelihoods of harmonizing formula prescriptions were associated with young age (adjusted odds ratio: 0.98, 95% confidence interval: 0.97–0.98), female sex (1.79, 1.68–1.91), no diabetes (1.20, 1.06–1.36), no hypertension (1.38, 1.27–1.50), no cerebrovascular disease (1.34, 1.14–1.56), less disease severity (0.85, 0.83–0.88), using nonsteroidal anti-inflammatory drugs (NSAIDs) (1.65, 1.54–1.78), and using analgesic drugs other than NSAIDs (1.47, 1.35–1.59).

Conclusion: Harmonizing formulas are commonly used for treating symptoms of the digestive and musculoskeletal systems in CKD cases. Further research on harmonizing formula effectiveness with regard to particular characteristics of CKD patients is warranted.

Keywords: chronic kidney disease, Chinese herbal medicine, traditional Chinese medicine, Chinese herbal formula, prescription patterns

INTRODUCTION

Chronic kidney disease (CKD), defined as substantial renal damage persisting for three months, is prevalent and affects 8–16% of adults globally (Jha et al., 2013). CKD can be regarded as an irreversible condition. After a patient develops CKD, the renal function might progressively deteriorate over several years until reaching end-stage renal disease (ESRD) (Zhong et al., 2017). Although guidelines have recommended that CKD should be appropriately managed to slow its progression (Levey et al., 2002; Levin et al., 2013), maintaining stable renal function and relieving the symptoms and signs caused by accumulation of uremic toxins remain challenging. Chinese herbal medicines (CHMs), through syndrome differentiation and treatment selection, present a means to improve CKD care and may stabilize renal function.

Improving syndromes by treatment is the main philosophy of CHMs (Jiang et al., 2012). Syndromes could be differentiated and summarized by integrating four main comprehensive evaluations of symptoms through observation, listening, questioning, and pulse analyses (Chan, 1995). After differentiating syndromes from one patient, a physician would prescribe natural products following the principle of chief-deputy-assistant-envoy. The chief herb product within one prescription provides the main therapeutic effect for syndromes (Su et al., 2016).

Several experimental animal studies have concluded that certain herbs (e.g., *Rheum officinale* Balli., Rhubarb) in CHM have potential anti-inflammatory and antifibrotic effects and could be an agent in renal fibrosis therapy (Lu et al., 2015; Zhao et al., 2016). However, these findings are less applicable in clinical practice because illnesses in humans are often more complex than those in mice. For example, CKD in humans may have different etiologies and be accompanied by noncommunicable diseases. Therefore, observational human studies of CHM treatment effects provide an opportunity to understand current practices in CHM therapy and help explore new therapeutic formulas for use in CKD. Studies and our previous data have demonstrated the potential beneficial effects of CHM on CKD outcomes (Hsieh et al., 2014; Hsu et al., 2014; Lin et al., 2015; Hsieh et al., 2017), highlighting that further understanding of the target population in CKD for treatment with specific formulas is warranted.

Our previous study identified harmonizing formulas as having the most potential benefits for renal progression in CHMs. Usually, they are commonly used to treat disorders caused by contrasting illnesses including shaoyang (half interior and half exterior) syndromes, liver and spleen disharmonies, and intestine and stomach disharmonies (Chen and Chen, 2009). The effectiveness of harmonizing formulas has been widely recognized in reducing depressive syndromes (Yeung et al., 2015; Zeng et al., 2017) and improving survival in patients with stroke and cancer (Liao et al., 2015). However, applications for patients with CKD remain relatively less understood. Our study explored disease categories for which harmonizing formulas were prescribed and independent factors associated with harmonizing formula prescriptions in patients with CKD.

METHODS

Data Source and Subjects

The Taiwan government launched the National Health Insurance (NHI) program in 1995. It covers 99.6% of Taiwan's population and has service contracts with 93% of health care institutes. NHI reimburses medications (Western medicine and CHM), ambulatory, emergency, dental, and inpatient care after health care institutes complete medical services and uploads claims data. The claims data are further managed by the Taiwan National Health Research Institutes for inclusion in the National Health Insurance Research Database (NHIRD) and are available for academic research.

We conducted a population-based cross-sectional study by using the Longitudinal Health Insurance Database 2000 (LHID2000), a subset of the NHIRD. The LHID2000 contains the data of 1 million randomly sampled patients who were NHI beneficiaries in 2000. The randomly sampled patients exhibit similar distributions in age, sex, birth year, and average insured payroll-related amount with the general population. This research was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT(I)-20150063). All research procedures followed the guidelines of the Declaration of Helsinki.

CKD

The detailed methods of this study were in our previous study (Lin et al., 2015). In brief, we identified patients who received new diagnoses of CKD between 2000 and 2005 by using the frequency of appearance of specific *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes within 1 year (Collins et al., 2009). Although laboratory data were lacking in these databases, we can reasonably assume that most of these patients had stage 3–5 CKD [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²] on the basis of regional hospital data using the same algorithm. We excluded patients who were aged <18 or ≥85 years ($n = 2, 673$), had cancer ($n = 1,680$) or underwent dialysis before receiving a CKD diagnosis ($n = 28$), or had received any CHM prescription within 1 year before diagnosis ($n = 11,104$). Therefore, the cohort was suitable to assess for determining factors associated with CHM prescription.

Harmonizing Formulas

All CHM prescriptions from CKD diagnosis to the start of dialysis or the end of 2008 were collected. We distinguished these CHM prescriptions into harmonizing formulas and other formulas according to approaches suggested in textbooks, with minor modifications (Cao, 2000; Chen and Chen, 2009). To detect potential indicators for using harmonizing formulas, disease categories for prescribing harmonizing and other formulas were compared on the basis of a patient's first ICD-9-CM diagnosis code of the prescription and classified into various disease system and health problem groups. These systematic diseases and related health problems can be divided into infections and parasitic diseases (ICD-9-CM: 001–139); neoplasms (140–239); endocrine, nutritional, and metabolic diseases, and immunity disorders (240–279); diseases of the

blood and blood-forming organs (280–289); mental disorders (290–319); diseases of the nervous system and sensory organs (320–389); diseases of the circulatory system (390–459); diseases of the respiratory system (460–519); diseases of the digestive system (520–579); diseases of the genitourinary system (580–629); complications of pregnancy, childbirth, and the puerperium (630–679); diseases of the skin and subcutaneous tissue (680–709); diseases of the musculoskeletal system (710–739); congenital anomalies (740–759); certain conditions originating in the perinatal period (760–779); symptoms, signs, and ill-defined conditions (780–799); injury and poisoning (800–999); and supplementary classification and others (V01–V82, E800–E999).

Assessment of Associated Factors

We collected information on patient characteristics, namely age, sex (male or female), insurance amount (fixed premium or dependent, <New Taiwan dollar (NT\$)20,000, NT\$20,000–39,999, and ≥NT\$39,999 [~US\$1,333]), region (north, center, south, and east), urbanization of residence (urban or rural), main comorbidities (acute coronary syndrome, diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease), Charlson comorbidity index score, and primary Western medicines used (diabetic drugs, antihypertensive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesic drugs other than NSAIDs, and antilipid drugs) during the observation period.

Statistical Analysis

Continuous and categorical data were expressed as mean ± standard deviation or median (interquartile range) and percentage, respectively. Significant differences in patient characteristics between the harmonizing formula use and nonuse groups were evaluated using an independent *t* test for continuous variables and χ^2 test for categorical variables. We used the proportion of disease categories to determine the differences in disease treatment between using harmonizing formulas and other formulas. In addition, a multivariable logistic regression with backward elimination procedure ($\alpha = 0.2$) of all collected factors was performed to identify the independent factors of harmonizing formula prescription. Results of the logistic regression were represented as odds ratios (O.R.s) and 95% confidence intervals (C.I.s). All statistical operations were performed in SAS (version 9.4, SAS Institute, Cary, NC, United States). A *p* value < 0.05 was considered significant.

RESULTS

Patient Characteristics by Use of Harmonizing Formulas

We included 24,971 patients who received new diagnoses of CKD, and 21% of these patients were prescribed harmonizing formulas. Compared with patients in the harmonizing formulas nonuse group, patients in the group using harmonizing formulas were significantly more likely to be young, female, and living in

TABLE 1 | Characteristics of study cohort by harmonizing formula use.

Characteristic	Harmonizing formulas		<i>p</i> value
	Nonuse	Use	
Patient no	19,734	5,237	
Age, y	58.3 ± 16.4	51.3 ± 15.6	<0.001
Female (%)	37.9	50.2	<0.001
Insurance amount, NT\$ (%)			<0.001
Fixed premium or dependent	20.5	18.8	
<20,000	58.1	56.4	
20,000–39,999	13.7	16.4	
≥39,999	7.7	8.5	
Region (%)			<0.001
North	46.6	43.9	
Center	21.1	23.6	
South	28.5	29.7	
East	3.7	2.8	
Urbanization (%)			<0.001
Urban	72.9	76.6	
Comorbidities (%)			
Acute coronary syndrome	12.5	7.7	<0.001
Diabetes	29.9	19.4	<0.001
Hypertension	40.7	26.6	<0.001
Hyperlipidemia	13.5	11.1	<0.001
COPD	9.2	5.4	<0.001
Cerebrovascular disease	11.5	4.3	<0.001
Charlson score			
Mean ± SD	1.49 ± 1.87	0.82 ± 1.28	<0.001
Median (IQR)	1 (0–2)	0 (0–1)	<0.001
Confounding drugs, %			
Diabetic drugs	29.7	24.6	<0.001
Antihypertensive drugs	55.6	51.1	<0.001
NSAIDs	29.4	40.6	<0.001
Analgesic drugs other than NSAIDs	42.9	45.8	<0.001
Anti-lipid drugs	20.9	21.1	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; NT\$, New Taiwan Dollar.

The differences in 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.

central Taiwan and urban areas. They were significantly more likely to have high insurance amounts, fewer comorbidities (acute coronary syndrome, diabetes, hypertension, hyperlipidemia, COPD, or cerebrovascular disease), less disease severity, and less use of diabetic and antihypertensive drugs, but more use of NSAIDs, analgesic drugs other than NSAIDs, and anti-lipid drugs (Table 1).

Disease Categories for Prescribing Harmonizing Formulas

The disease categories for prescribing harmonizing formulas and the other types of Chinese herbal formulas in patients with CKD were compared and are listed in Table 2. The three most frequent disease categories for prescribing harmonizing formula in CKD were symptoms, signs, and ill-defined conditions (24.5%); diseases of the digestive system (20.67%); and diseases of the musculoskeletal system (12.9%). Similar frequencies of disease categories were observed for other formula prescriptions in patients with CKD. Notably, an increased proportion of

TABLE 2 | Systematic diseases and related health problems for harmonizing formula prescription claims.

Disease category (ICD-9-CM)	Harmonizing formulas (a)	Other formulas (b)	Difference [(a) – (b)]	Ratio [(a)/(b)]
Infection and parasitic diseases (001–139)	0.87	0.52	0.35	1.67
Neoplasms (140–239)	0.78	0.68	0.10	1.15
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	3.52	5.02	–1.5	0.7
Diseases of the blood and blood-forming organs (280–289)	0.32	0.37	–0.05	0.86
Mental disorders (290–319)	1.76	0.9	0.86	1.96
Diseases of the nervous system and sense organs (320–389)	3.37	3.71	–0.34	0.91
Diseases of the circulatory system (390–459)	2.49	4.29	–1.80	0.58
Diseases of the respiratory system (460–519)	6.54	12.09	–5.55	0.54
Diseases of the digestive system (520–579)	20.67	14.28	6.39	1.45
Diseases of the genitourinary system (580–629)	12.38	11.93	0.45	1.04
Complications of pregnancy, childbirth, and the puerperium (630–679)	0.17	0.18	–0.01	0.94
Diseases of the skin and subcutaneous tissue (680–709)	2.10	2.90	–0.80	0.72
Diseases of the musculoskeletal system (710–739)	12.9	12.51	0.39	1.03
Congenital anomalies (740–759)	0.37	0.28	0.09	1.32
Certain conditions originating in the perinatal period (760–779)	0.01	0.00	0.01	-
Symptoms, signs, and ill-defined conditions (780–799)	24.50	24.54	–0.04	1.00
Injury and poisoning (800–999)	5.48	3.51	1.97	1.56
Supplementary classification and others (V01–V82, E800–E999)	1.78	2.27	–0.49	0.78

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; aOR, adjusted odds ratio; CI, confidence interval. Number of Chinese medicine visits is 24,226 for harmonizing formulas and 622,790 for other formulas. Proportion of disease categories by harmonizing and other formulas are displayed.

patients with diseases of the digestive system (6.39% difference) and a reduced proportion of those with diseases of the respiratory system (–5.5% difference) received harmonizing formula prescriptions compared with other formula prescriptions in this analysis.

Prescription Frequency of Constituent Herbs in Harmonizing Formulas

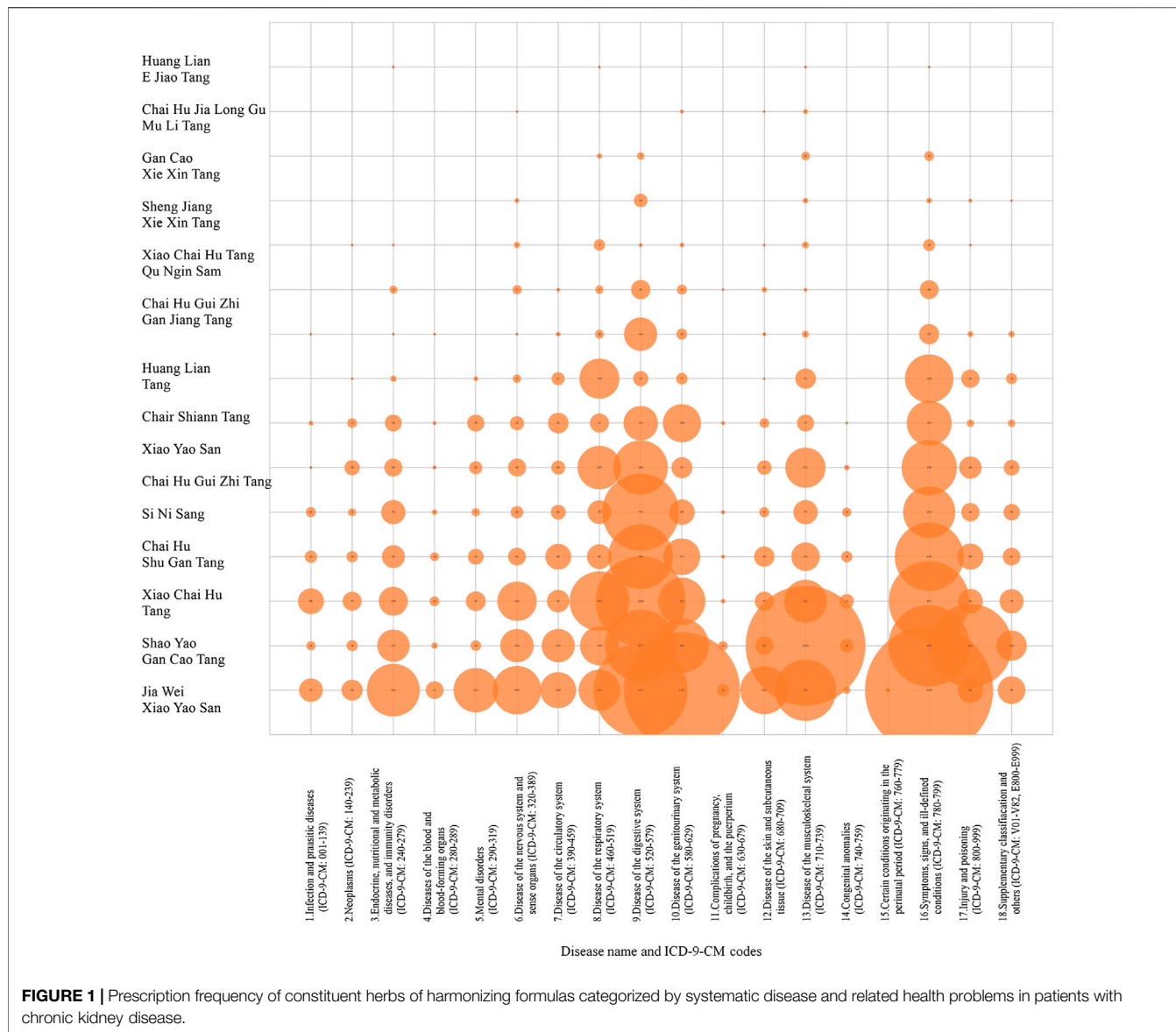
As **Figure 1** presents, the three most frequently prescribed herbs for harmonizing formulas during the observed period were Jia Wei Xiao Yao San (Composition: *Angelica sinensis* (Oliv.) Diels; *Atractylodes macrocephala* Koidz.; *Paeonia lactiflora* Pall.; *Bupleurum chinense* DC.; *Wolfiporia extensa* (Peck) Ginns (syn. *Poria cocos* (Schwein.) F. A. Wolf); *Glycyrrhiza uralensis* Fisch ex DC.; *Paeonia x suffruticosa* Andrews; *Gardenia jasminoides* J. Ellis; *Zingiber officinale* Roscoe; *Mentha canadensis* L. (syn. *Mentha haplocalyx* Briq.)), Shao Yao Gan Cao Tang (Composition: *Paeonia lactiflora* Pall.; *Glycyrrhiza uralensis* Fisch ex DC.), and Xiao Chai Hu Tang (Composition: *Bupleurum chinense* DC.; *Scutellaria baicalensis* Georgi, *Panax ginseng* C. A. Mey.; *Glycyrrhiza uralensis* Fisch ex DC.; *Pinellia ternata* (Thunb.) Makino; *Zingiber officinale* Roscoe; *Ziziphus jujuba* Mill.) (Additives and Feed, 2015; Selyutina and Polyakov, 2009). Frequent disease categories for Jia Wei Xiao Yao San prescriptions were symptoms, signs, and ill-defined conditions ($n = 2,143$ times); genitourinary disease ($n = 1,767$ times); and diseases of the digestive system ($n = 1,157$ times). The most frequent disease category for Shao Yao Gan Cao Tang prescriptions was diseases of the musculoskeletal system ($n = 1,876$ times). Furthermore, the most frequent disease category for Xiao Chai Hu Tang prescription was diseases of the digestive system ($n = 1,056$ times).

Factors Associated With Harmonizing Formulas Prescription

Table 3 presents the associations of baseline patient characteristics with harmonizing formula prescriptions. Patients who were young (adjusted OR: 0.98, 95% CI: 0.97–0.98); female (1.79, 1.68–1.91); had high insurance amounts (range of adjusted OR: 1.14–1.31); lived in central Taiwan (1.26, 1.16–1.37), southern Taiwan (1.20, 1.11–1.30), or urban areas (1.17, 1.07–1.26); did not have diabetes (1.20, 1.06–1.36), hypertension (1.38, 1.27–1.50), or cerebrovascular disease (1.34, 1.14–1.56); had lower disease severity (0.85, 0.83–0.88); used NSAIDs (1.65, 1.54–1.78); and used analgesic drugs other than NSAIDs (1.47, 1.35–1.59) were more likely to have harmonizing formula prescriptions.

DISCUSSION

The current study demonstrated that one-fifth of patients with CKD have been prescribed harmonizing formulas, which were associated with risk reduction of ESRD in our previous study (Lin et al., 2015). Symptoms, signs, and ill-defined conditions, diseases of the digestive system, and musculoskeletal system diseases were the three most frequent disease classifications for prescribing harmonizing formulas. Patients with CKD who were young, female, had high premiums, lived in central or southern Taiwan or urban areas, did not have comorbidities (acute coronary syndrome, diabetes, hypertension, or cerebrovascular disease), had lower disease severity, used NSAIDs, and analgesic drugs other than NSAIDs were more likely to have harmonizing formulas prescriptions.



Nearly half of incident CKD patients used conventional CHM. Harmonizing formulas accounted for 46.1% of prescriptions. Although the efficacy of harmonizing formulas in reducing depression and improving survival in patients with liver cancers and systemic lupus erythematosus have been reported in studies (Liao et al., 2015; Ma et al., 2016), few studies have paid attention to prescription patterns and outcomes in treating patients with CKD (Yang et al., 2014; Chen et al., 2018). Combined with the results of Yang et al. (2014), Chen et al. (2018), and our previous findings, the current study indicated that one harmonizing formula, Jia Wei Xiao Yao San, is the main prescription for patients with late CKD. This formula potentially improves patient renal function after short- or long-term observation (Yang et al., 2014; Chen et al., 2015; Lin et al., 2015). Jia Wei Xiao Yao San is traditionally used to relieve stagnation in liver qi, reduce depression symptoms, and improve spleen qi deficiency. Although the mechanisms of

delaying ESRD are complex and worthy of further study, Jia Wei Xiao Yao San may affect renal clinical outcome by improving depressive symptoms, which are a novel predictor of accelerated eGFR decrease, dialysis therapy initiation, death, or hospitalization (Chen et al., 2015; Shirazian et al., 2017). We are unsure of the effect harmonizing formulas have in relieving uremic symptoms or slowing renal progression.

Saikosaponins are the main bioactive compounds in the dry root of *Bupleurum chinense* DC., which is the chief herb of harmonizing formulas. The recent comprehensive review shows that it is promising to improve renal cell injuries by mediating either activity of anti-oxidant-dant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and heat shock protein 72, SirT3, or mitogen-activated protein kinase and nuclear factor-κB (Li et al., 2018b). Other animal studies further proved the roles of saikosaponins on diabetes nephropathy, glomerulonephritis, and renal fibrosis (Li et al.,

TABLE 3 | Factors associated with harmonizing formula prescription in patients with chronic kidney disease.

	Adjusted odds ratio (95%CI)	p Value
Age, y	0.98 (0.97–0.98)	<0.001
Female (male as References)	1.79 (1.68–1.91)	<0.001
Insurance amount, NT\$		
Fixed premium or dependent	1.00 [reference]	
<20,000	1.14 (1.04–1.24)	0.004
20,000–39,999	1.25 (1.12–1.40)	<0.001
≥39,999	1.31 (1.15–1.50)	<0.001
Region		
North	1.00 [reference]	
Center	1.26 (1.16–1.37)	<0.001
South	1.20 (1.11–1.30)	<0.001
East	0.88 (0.73–1.07)	0.20
Urbanization		
Rural	1.00 [reference]	
Urban	1.17 (1.07–1.26)	<0.001
Comorbidities (yes as References)		
No diabetes	1.20 (1.06–1.36)	0.004
No hypertension	1.38 (1.27–1.50)	<0.001
No COPD	0.87 (0.75–1.01)	0.06
No cerebrovascular disease	1.34 (1.14–1.56)	<0.001
Charlson score, point	0.85 (0.83–0.88)	<0.001
Confounding drugs (none as References)		
Diabetic drugs	1.08 (0.97–1.20)	0.17
Antihypertensive drugs	1.08 (0.99–1.17)	0.07
NSAIDs	1.65 (1.54–1.78)	<0.001
Analgesic drugs other than NSAIDs	1.47 (1.35–1.59)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; NT\$, New Taiwan dollar.

Multiple logistic regression analysis starts with a model that contains all variables in **Table 1** and backward eliminates insignificant variables by a significance level of 0.2. NT\$30 equals approximately US\$1.

2005; Lin et al., 2012; Ren et al., 2020). In addition, other chief herb likes *Paeonia lactiflora* Pall. within Shao Yao Gan Cao Tang provides possibilities on kidney benefits through improving hemorheological abnormalities and protecting vascular endothelial function (Li et al., 2020; Tan et al., 2020). Although these active compounds of saikosaponins bring insights for kidney injuries, a previous animal study proposes their safety concerns about liver injury when treating mice with saikosaponins higher than 13 g/kg (Yao et al., 2013; Li X. et al., 2018). Anyway, more studies ensuring the efficacy and safety of harmonizing formulas for humans are needed.

We attempted to use the ICD-9-CM as a reference for identifying the indications of harmonizing formula prescription in CKD patients. CHM has its own historical and systematic philosophy of symptom differentiation (Bian Zheng) to assess, explicate, diagnose, and treat patient symptoms. In Western medicine, numerous symptoms are either unrecognized or suboptimally managed by clinical care workers in CKD patients not requiring dialysis (van der Veer et al., 2017). Brown et al. assessed 283 patients with stage 1–5 CKD and reported that tiredness (81%; 95% CI: 76.0–85.6), sleep disturbance (70%; 64.3–75.3), and pain in bones or joints (69%; 63.4–74.6) were the most common symptoms regardless of CKD stage (Brown et al., 2017). Loss of appetite, nausea, vomiting, fatigue, and edema are common symptoms in late-stage CKD, which are similar to “spleen

deficiency syndrome” in CHM and tend to involve the digestive system. In addition, local pain, weakness in the loin and knee, and calf cramps are frequently encountered CKD symptoms, which are similar to “liver–kidney insufficiency syndromes” in CHM and tend to involve the musculoskeletal system. Jia-Wei-Xiao-Yao-San has been demonstrated that it can adjust the abnormal gastric motility and gastric myoelectrical activity of patients with functional dyspepsia (Qu et al., 2010). Shao Yao Gan Cao Tang, a frequently prescribed harmonizing formula in CKD, is efficacy in relieving muscle pain or skeletal muscle tremors in patients undergoing hemodialysis or with cirrhosis or lumbar spinal stenosis (Hinoshita et al., 2003; Ota et al., 2020). Our findings suggest symptoms involving the digestive system composite the main syndromes for typical harmonizing formulas prescription (**Table 2**). These main syndromes have been listed in our **Supplementary Table S1** with their corresponding formulas. Radix Bupleuri (*Bupleurum chinense* DC.) is the main chief herb within the listed composition of many harmonizing formulas identified in our study (**Supplementary Table S2**) (Xie et al., 2013; Ji et al., 2014; Tian et al., 2014; Zhang et al., 2017; Pastorino et al., 2018; Stanisiere et al., 2018; Mao et al., 2019; Wang et al., 2019; Yang et al., 2020). Other candidates of chief herbs within each harmonizing formula, and their pharmacological actions and toxicity assessment are also listed in **Supplementary Tables S2–S4**. In brief, the harmonizing formulas probably diminish the symptoms of CKD patients through improving both digestive and musculoskeletal systems.

Female sex, low prevalence of comorbidity, and high use of analgesic drugs were associated with higher prescription frequency for harmonizing formulas in CKD. Although the causal relationships are difficult to establish in this study, a possible explanation is that prevalence of pain for females is high, and they are more likely to be aware of pain and receive relevant treatments (Fillingim, 2000; Johannes et al., 2010). NSAIDs are commonly used for pain control in clinical practice, but caution should be exercised when they are applied in CKD because they can induce more severe renal injuries (Luciano et al., 2015). How harmonizing formulas interact with NSAIDs for pain control in patients with CKD remains unclear. Thus, more research is required on this combination therapy to study its efficacy in pain control in CKD and preventing further renal injury.

Our study has some advantages. First, assessments of Chinese herbal formulas in the study were drawn from a nationwide health insurance database with highly comprehensive records of CHM prescriptions. Second, CHM in this study was prescribed by quality assurance physicians who were educated in the same system and accredited by Taiwan’s government; this strengthens the reliability of symptomatic differentiation and accuracy of disease diagnostic coding. Third, Taiwan’s NHI is one of the few national insurance programs that reimburse both Western medicine and CHM, providing an opportunity to explore the foundational philosophies of these two different modes for treating certain diseases. However, some limitations must be declared. First, the lack of laboratory and patient-reported data in the claims database prevents us from exploring the possible mechanisms of harmonizing formulas on health outcomes such as emotion, pain, and renal function. In addition, our study lacks

original indications for these harmonizing formulas prescription from CHMs. Using the ICD-9-CM diagnosis system to identify disease classification of CHM prescriptions may not appropriately reflect the indications of CHM formulas. Third, CKD usually accompanies by different chronic conditions. The indications of harmonizing formulas prescription identified in our study may not be direct from CKD, and one should interpret the result with caution. Finally, our results were from the Asian population covered by the NHI program in Taiwan and derived from older sample data, limiting their generalizability.

CONCLUSION

In conclusion, this study determined that harmonizing formulas are commonly used in treating CKD for symptoms, signs, and ill-defined conditions; genitourinary diseases; and digestive system diseases. Patients who were young, female, had fewer comorbidities, and used analgesic drugs were more likely to be prescribed harmonizing formulas, which suggests that more research on the efficacy of Western medicine and CHM in patients with CKD and these characteristics is required.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because these Data used in our study should be acquired through formal application to the Health and Welfare Data Science Center, Department of Statistics, Ministry of Health and Welfare, Taiwan. Requests to access the datasets should be directed to <https://dep.mohw.gov.tw/DOS/np-2497-113.html>.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Kaohsiung Medical University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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AUTHOR CONTRIBUTIONS

Conceptualization, H-LL, M-YL, and Y-WC; methodology, M-YL, C-JC, S-JH, and M-HY; writing—original draft preparation, H-LL, C-HT and Y-HW; writing—review and editing, M-YL, M-HY, and Y-WC; supervision, C-JC, M-HY, and S-JH. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2021.573145/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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