Prescription Pattern and Related Influence Factors of Chinese Herbal Medicine for Chronic Liver Diseases in Taiwan

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Chinese herbal medicine (CHM) is a commonly used complementary and alternative medicine for patients with chronic liver diseases in Taiwan. In order to identify how CHM is prescribed for patients with chronic liver diseases, the drug effectiveness was used to classify the herbal formulae. The aim of this study is to explore the prescription pattern of drug effectiveness and the factors that affect this pattern. The National Health Insurance (NHI) database was analyzed for the pharmacoepidemiology study. Traditional Chinese medicine (TCM) outpatients who were identified by Gastroenterology with chronic liver diseases in the year of 2008 were included. Statistics and data mining tools were employed to explore CHM prescription pattern and factors that affect the pattern in terms of drug effectiveness, respectively. Among the 43,119 subjects treated chronic liver diseases with CHM, herbal formulae that has the effect of He Jie (harmonize, 63.7%) and Qing Re Xie Huo (clear heat and drain fire, 40.8%) were most commonly prescribed. Subjects prescribed for formulae with the effects of Fa Biao (release exterior, 45.4 years) and Qu Feng (expel wind 52.0 years) were the youngest and eldest, respectively. Male were more commonly prescribed for Bu Yang (tonify and nourish), Qing Re Xie Huo, and Li Xue (regulate blood); female were more commonly prescribed for He Jie, Biao Li (exterior and interior), and Ren Zao (moisture dryness). This study shows the prescription pattern of CHM in terms of drug effectiveness for chronic liver diseases. Gender and age affect this pattern.

Key words: Chronic liver diseases, Chinese herbal medicine, pharmacoepidemiology, National Health Insurance, prescription pattern

Abbreviation: CHM, Chinese herbal medicine; TCM, traditional Chinese medicine; CLD, chronic liver disease; CCMP, Committee on Chinese Medicine and Pharmacy (CCMP); NHI, National Health Insurance; SH, single herbs; HF, herbal formula; CHAID, Chi-squared Automatic Interaction Detection

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Introduction

Chronic liver diseases (CLD) are a serious health problem worldwide^{1,2}. Because of efficient treatment in the conventional medicine remains limited. A portion of patients seek for complementary and alternative medicine including Chinese herbal medicine (CHM)^{3,4}. Therefore, the efficacy and the safety of CHM need more investigation.

The National Health Insurance (NHI) program in Taiwan is a universal system of compulsory health insurance. This system reimburses general healthcare expenditure, including CHM since 1996. All the claims for reimbursement are submitted in the database, available to researchers. Hence, large-scale surveys of the pharmacoepidemiology can be conducted with this NHI database.

Drug utilization and prescribing patterns of chronic hepatitis were explored to identify the potentially effective CHM by analyzing the NHI database for the whole year 2002⁵. The NHI database of TCM outpatients in Taipei for the whole 2004-2007 also was analyzed to identify the frequency and pattern of TCM prescriptions of chronic liver diseases⁶. But the prescription pattern of drug effectiveness and its affected factors remain to be further investigated.

Chinese medicine is a complex and historical practice with its own theory, diagnosis, treatment systems and pharmacology. The prescription of CHM is heavily dependent on physicians' experiences. Our result showed more than 300 single herbs (SH) or herbal formulae (HF) have been prescribed for patients with chronic liver disease in the year of 2008. To simplify the prescriptions, we classified the most frequently prescribed herbal formulae according to the drug effectiveness (Yi-Fang-Ji-Jie; Analytic Collection of Medical Recipes, 1682 A.D.) and the top ten were further analyzed.

The aim of this study is to survey the frequency and pattern of CHM used in patients who were identified by Gastroenterology with chronic liver diseases for the whole year 2008, and to determine the influence of genders and ages on the use of CHM in chronic liver diseases. The NHI database contains massive information, we therefore include statistical method and data mining concept to explore and discover the prescription pattern of CHM and its related influential factor from the NHI database.

Materials and Methods

Data sources

In this study, we analyzed the complete database of TCM claims of the year 2008 from the National Health Insurance Research Database. The TCM claims database comprises ambulatory care expenditures by visits plus details of ambulatory care orders. The records of ambulatory care expenditures by visits contain information of patients' gender, date of birth, the date of encounter, the medical care facility and specialty, and at most three diagnoses in coding of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The records of details of ambulatory care orders contain corresponding prescriptive orders and Chinese herbal drugs or formulae.

Currently, the hospitalizations for TCM care are not recruited in NHI in Taiwan. Therefore, all TCM were provided only in ambulatory clinics within the coverage of NHI. For privacy protection, the identification data of patients and institutions had been scrambled cryptographically to attain anonymity.

Study design

The concept of disease entities in TCM is different from those in western medicine. For the sake of the efficient management for the Committee on Chinese Medicine and Pharmacy (CCMP), the diagnostic terms used in TCM have also been modified to fit into ICD-9-CM system since 2002. In this study, a single diagnostic code 571 of ICD-9-CM from the TCM claims database of the year 2008 was chosen to investigate the usage of TCM for chronic liver diseases.

Statistical analysis and Data Mining

We first carry out the descriptive statistical analysis of the database to investigate the characteristics and medical utilization patterns among patients who has been prescribed CHMs at least once. Also, we characterize the number of total CHM (including SH and HF) prescribed for subjects with chronic liver diseases during the year of 2008.

We choose the 23 most frequently prescribed HFs from the previous analysis and classify them into 10

categories by drug effectiveness according to Yi-Fang-Ji-Jie. An initial statistical analysis used to observe, respectively, the mean ages of the subjects' age for the 10 categories of drug effectiveness. We also applied the decision tree procedure, Chi-squared Automatic Interaction Detection (CHAID), to investigate the influence among the 10 categories of drug effectiveness, subjects' age and gender. All of the above analyses are performed using the PASW 18.0 software package.

Results

Among the valid beneficiaries of the NHI at the end of 2008 in Taiwan, 43,119 subjects (28691 male and 14418 female) had ever used CHM claimed chronic liver diseases (ICD-9-571) during the year 2008. The mean age was 46.9 (\pm 13.8) years (male 45.5 (\pm 13.3) and female 49.6 (\pm 14.3) years, respectively). CHM use for chronic liver diseases peaked at the age of 40s, followed by the 30s and 50s (Table 1).

The number of total CHM prescriptions (including

in Taiwan during 2008							
Age (years)	number of patients		Male	Male		Female	
0-9	37	0.1 %	15	0.1 %	22	0.2 %	
10-19	736	1.7 %	501	1.7 %	235	1.6 %	
20-29	4,309	10.0 %	3,053	10.6 %	1,256	8.7 %	
30-39	8,759	20.3 %	6,572	22.9 %	2,287	15.2 %	
40-49	11,673	27.1 %	8,334	29.0 %	3,339	23.1 %	
50-59	10,496	24.3 %	6,442	22.5 %	4,054	28.1 %	
60-69	4,751	11.0 %	2,518	8.8 %	2,233	15.5 %	
70-79	2,016	4.7 %	1,061	3.7 %	955	6.6 %	
80-89	330	0.8 %	190	0.7 %	140	1.0%	
90-99	12	0.0 %	5	0.0 %	7	0.0 %	
total	43,119	100.0	28,691	100.0	14,528	100.0	

Table 1. Frequency distribution of the gender and age for the CHM use in patients with chronic liver diseases in Taiwan during 2008

SH and HF) for one subject with chronic liver diseases during the year of 2008 has a mean of 10 (\pm 9.2), a median of 7 and a mode of 6. Figure 1A shows that the frequency for the number of total CHM prescription for one subject with chronic liver diseases. The number of total CHM prescription (including SH and HF) a physician made for subjects with chronic liver diseases during the year of 2008 has a mean of 42 (\pm 41), a median of 29 and a mode of 6. Figure 1B shows that the frequency for the number of total CHM prescription a physician made for subjects with chronic liver diseases.



Figure 1. Frequency of the number of total CHM presription (A) for one subject (B) a physician made for subjects with chronic liver diseases during the year of 2008.

Among TCM prescriptions of chronic liver diseases, Jia Wei Xiao Yao San (19.3 %) was the most commonly prescribed Chinese herbal formulae for subjects with chronic liver diseases, followed by Xiao Chai Hu Tang (also called Sho Saiko To [TJ-9] in Japan) (14.4 %), Long Dan Xie Gan Tang (12.3 %), Yin Chen Wu Ling San (11.2 %), Chai Hu Ching Gan Tang (6.4%), Chai Hu Shu Gan Tang (6.3 %), Gan Lu Yin (6.0%), Gan Lu Xiao Du Dan (5.7%), Xue Fu Zhu Yu Tang (5.0 %), Da Chai Hu Tang (4.8 %) etc. (Table 2).

Order	Formulae	Drug effectiveness	Number	of prescription
1	Jia Wei Xiao Yao San	He Jie	37,990	(19.3 %)
2	Xiao Chai Hu Tang	He Jie	28,226	(14.4 %)
3	Long Dan Xie Gan Tang	Qing Re Xie Huo	24,189	(12.3 %)
4	Yin Chen Wu Ling San	Li Shi	22,058	(11.2 %)
5	Chai Hu Ching Gan Tang	Qing Re Xie Huo	12,598	(6.4%)
6	Chai Hu Shu Gan Tang	He Jie	12,374	(6.3%)
7	Gan Lu Yin	Ren Zao	11,714	(6.0%)
8	Gan Lu Xiao Du Dan	Qing Re Xie Huo	11,245	(5.7%)
9	Xue Fu Zhu Yu Tang	Li Xue	9,783	(5.0%)
10	Da Chai Hu Tang	Biao Li	9,523	(4.8%)
11	Yi Guan Decoction	Bu Yang	8,416	(4.3%)
12	Yin Chen Hao Tang	Li Shi	8,289	(4.2%)
13	Ping Wei San	Xiao Dao	7,672	(3.9%)
14	Liu Wei Di Huang Wan	Bu Yang	7,215	(3.7%)
15	Zhi Bai Di Huang Wan	Bu Yang	6,725	(3.4%)
16	Xiang Sha Liu Jun Zi Tang	Xiao Dao	6,695	(3.4%)
17	Qi Ju Di Huang Wan	Bu Yang	6,057	(3.1%)
18	Si Ni San	He Jie	5,254	(2.7%)
19	Ji Sheng Shen Qi Wan	Bu Yang	3,255	(1.7%)
20	Chai Hu Gui Zhi Tang	Biao Li	2,291	(1.2%)
21	Shao Yao Gan Cao Tang	He Jie	2,157	(1.1%)
22	Ge Gen Tang	Fa Biao	1,684	(0.9%)
23	Du Huo Ji Sheng Tang	Qu Feng	1,668	(0.8%)

 Table 2. Classify the most commonly used formulae according to the "drug effectiveness". The top 23 used formulae for chronic liver diseases were divided into 10 groups according to the drug effectiveness.

The most frequently prescribed herbal formulae were classified into 10 categories of drug effectiveness, defined in Yi-Fang-Ji-Jie (Table 3). The mean of the patients' age by the ten formula categories, respectively, are shown in Figure 2. Subjects prescribed for Qu Feng (expel wind) are the eldest (52 years) while prescribed for Fa Biao (release exterior) are the youngest (45 years).

According the decision tree procedure, we fed the PASW software package 18.0 the information of all the subjects' gender and age. The system automatically grouped the gender before the age, which means

Name (English Pin-Yin)	Name	Number of prescription	
He Jie	Harmonize	86,001 (34.8 %)	
Qing Re Xie Huo	Clear Heat and Drain Fire	48,032 (19.4 %)	
Bu Yang	Tonify and Nourish	31,668 (12.8 %)	
Li Shi	Resolve Dampness	30,347 (12.3 %)	
Xiao Dao	Eliminate and Guide	14,367 (5.8 %)	
Biao Li	Exterior & Interior	11,814 (4.8 %)	
Ren Zao	Moisture Dryness	11,714 (4.7 %)	
Li Xue	Regulate Blood	9,783 (4.0 %)	
Fa Biao	Release Exterior	1,684 (0.7 %)	
Qu Feng	Expel Wind	1,668 (0.7 %)	

Table 3. The English Pin-Yin and translated names of drug effectiveness as defined in Yi-Fang-Ji-Jie.



Figure 2. The average age of patients prescribed CHM with different drug effectiveness.

gender affects the prescription pattern more than age. After the nodes of gender, the system grouped the age of subjects into three classes: subjects' age less or equal to 42.701, between 42.701 and 54.288, and more than 54.288 (Figure 3).



Figure 3. Decision tree for drug effectiveness.

Discussion

Shimizu *et al* (2007) reported chronic hepatitis B appears to progress more rapidly in males than in female. They suggested the greater progression of hepatic fibrosis and HCC in men and postmenopausal women may be due, at least in part, to lower production of estradiol and a reduced response to the action of estradiol⁷. In this study, we described the prescription pattern of CHM in the chronic liver diseases by analyzing the NHI database and found that the pattern was dependent on the gender and age of subjects.

The prescription patterns of CHM for liver diseases of 2002 and 2004-2007 (population from Taipei city only), respectively, have been reported^{5,6}. Despite the differences of population, these two studies had similar results. In our study, the top 6 formulae are exactly the same compared with the previous studies, but with different orders.

The frequency of histogram on the CHM usage for one subject showed skewness to the left with tails on the right. This explains that 6 to 10 CHM usage is the most prescribed for one subject as the state of one's illness in a year (Figure 1A). This result is consistent to the clinical observations for CHM usage. In terms of clinics, the frequency of histogram on the CHM prescriptions by a physician in the whole year has a wide range differences among the mean, median and mode (a mean of 42 (\pm 41), a median of 29 and a mode of 6) (Figure 1B), which explains most of physicians have to grasp many prescriptions for his own subjective judgement (Zheng differentiation; TCM syndromes) depending on patient's condition.

The drug effectiveness versus age results showed

that subjects prescribed for Qu Feng are the eldest while prescribed for Fa Biao are the youngest (Figure 2). Du Huo Ji Sheng Tang is the only formulae belongs to the effectiveness of Qu Feng but not regularly used for liver diseases, which is usually used for treating low back or knee problems, for example, osteoarthritis, rheumatic arthritis, and sciatica⁸. This explains why the mean age for subjects prescribed for Qu Feng are the eldest.

In order to find clues of how the prescriptions of CHM for chronic liver diseases are made, we speculate that gender, age and climate may affect the prescription. The results demonstrated that gender and age are factors that affect the prescription pattern. In the decision tree analysis, we attempted to identify if exterior environment (eg, temperature or humidity) also affects the prescription by analyzing the months of visit or climate seasons of visit. However, the decision tree didn't show conclusive results in the month of visit, which might due to the geographic region of Taiwan that lies in subtropical/ tropical weather.

Xiao Chai Hu Tang is also a well known treatment in Japanese Kampo medicine (Sho-saiko-to, TJ-9) to treat liver diseases. A prospective study has shown its benefit on the prevention of developing HCC in cirrhosis patients, particularly in patients without HBs antigen^{9,10}. Three flavonoids, baicalein, viscidulin III, and baicalin in TJ-9 were found to be the main active compounds on hepatic fibrosis in rats¹¹. Rat *in vivo* studies have also show Yin Chen Hao Tang (Inchinko-to, TJ-135) protect liver cells from apoptosis¹² and prevent liver fibrosis^{13,14}. Most of above results remain in animal tests. Despite the advantage of western medicine in treating chronic liver diseases (CLD), there is a remarkable subjects seeking helps from complementary and alternative medicine. Therefore, a large-scale database survey of pharmacoepidemiology and drug used pattern in treating CLD is needed for efficacy and safety.

In this study, we provide the prescription pattern of CHM in the chronic liver diseases by analyzing the NHI database and suggest that the pattern depends upon the gender and age of subjects. The related TCM syndromes, used dosage and therapeutic effect in CLD remain to be further explored.

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台灣慢性肝病使用之中藥處方類型和相關影響 因子研究

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中藥是我國慢性肝病患者普遍使用之輔助醫療的藥物。為了鑑別用於治療慢性肝病中藥處 方如何調配,本研究用藥物的有效性作為中藥處方分類標準,探討藥物有效性之處方類型及影 響此類型之因子。使用國家健保資料庫分析 2008 年中醫門診用於治療慢性肝病的資料進行分 析藥物流行病學研究。經統計分析顯示在 2008 年間有 43,119 慢性肝病患者曾經使用中藥治療, 中藥處方中最普遍使用的處方是和解(harmonize, 63.7%)和清熱瀉火(40.8%)。較年輕(45.4 歲)和較年長(52.0歲)患者分別以發表和驅風處方為主。男性患者的處方以補陽、清熱瀉火 和理血藥為主;女性患者開的處方以和解表裡和潤燥作用為主。本研究顯示用於治療慢性肝病 的中藥處方類型受性別和年紀的影響。

關鍵字:慢性肝病、中藥、藥物流行病學、國家健康保險、處方類型

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