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# Integration of Chinese Herbal Medicine Therapy Improves Survival of Patients With Chronic Lymphocytic Leukemia

## *A Nationwide Population-Based Cohort Study*

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**Abstract:** Utilization of Chinese Medicine (CM) is not uncommon in patients with chronic lymphocytic leukemia (CLL). However, the current knowledge of the usage and efficacy of CM among CLL patients is limited. The aim of this study was to determine the impact of integrative Chinese Herbal Medicine (CHM) on the disease course of CLL and ascertain the herbal products most commonly prescribed to patients with CLL.

A Taiwanese nationwide population-based study involving the use of Western medicine and CM services provided by the National Health Insurance (NHI) was conducted.

An NHI Research Database-based cohort study was performed; the timeframe of the study was January 2000 to December 2010. The end of the follow-up period was defined as December 31, 2011.

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A total of 808 patients were diagnosed with CLL in Taiwan within the defined study period. After randomly matching for age and sex and excluding patients younger than 18 years of age, data from 616 patients were analyzed.

The 2 study groups both received standard of care treatment. In addition, 1 group also received CHM. Patients who were registered as receiving other forms of CM, such as acupuncture, were excluded.

Hazard ratios of mortality were used to determine the influence of CHM and the therapeutic potential of herbal products.

In total, 616 CLL patients were included in the analyses. We found that the HR associated with the adjunctive use of CHM was less than half when compared to the non-CHM group (0.43, 95% CI 0.33–0.55,  $P < 0.0001$ ) and that treatment-naïve patients who used CHM had the lowest HR. We also established that this association between reduction in HR and CHM was dose-dependent, and the longer CHM users received prescriptions, the lower the HR ( $P < 0.001$ ).

We supplied data from a relatively large population that spanned a significant amount of time. Our data suggests that the treatment of CLL with adjunctive CHM may have a substantial positive impact on mortality, especially for treatment-naïve patients. Further research is needed to confirm whether there is a direct causal relationship between CHM and the outcomes displayed.

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**Abbreviations:** CHF = congestive heart failure, CHM = Chinese Herbal Medicine, CKD = chronic kidney disease, CLL = chronic lymphocytic leukemia, CM = Chinese Medicine, COPD = chronic obstructive pulmonary disease, FCR = Fludarabine Cyclophosphamide Rituximab, ICD = International Classification of Diseases Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a hematologic malignancy which is characterized by clonal proliferation and accumulation of lymphoid B cells in the blood, bone marrow, lymph nodes, and spleen.<sup>1</sup> The fludarabine cyclophosphamide rituximab (FCR) chemoimmunotherapy regimen has become the standard first-line therapy, after decades of using chemotherapeutic agents alone.<sup>2</sup> Recent years have also been marked by the emergence of agents such as Idelalisib and Ibrutinib, which inhibit BCR signaling, and have shown positive results for both treatment-naïve and relapsed CLL patients.<sup>3–6</sup> Venetoclax (ABT-199) and chimeric antigen receptor T cells are examples of therapies that tackle CLL from different approaches, adding to the growing arsenal of options that physicians may choose from.<sup>7,8</sup> With all these new and

emerging drugs in the market, one might wonder whether any available therapies have been overlooked.

There are practically no published data concerning the efficacy of Chinese Medicine (CM) in the treatment of CLL. A case report from 2003 mentioned full remission in 1 patient, following the use of Chinese Herbal Medicine (CHM) alone.<sup>9</sup> Other cell-line and animal model studies have focused mainly on herbs or compounds from within the CHM pharmacopeia, that may be beneficial for CLL patients, for example, Indirubin, Curcumin, *Hedyotis diffusa*, and *Ganoderma lucidum* to name a few.<sup>10–13</sup> Clinical trials of CM in China have been steadily increasing in the past 30 years, and reviews have shown that 11% of these trials are on leukemia.<sup>14</sup> Unfortunately, these trials have not reached the standards required by science citation indexed journals and have thus failed to reach western readership. It is clear that much stronger evidence is needed before establishing any potential role that CM might have in the management of CLL.

CM has been regarded as a kind of complementary therapies in the Western countries. However, it has been one of the mainstream therapies in some Asian countries, such as Taiwan, Korea, and China.<sup>15,16</sup> Approximately 30% of Taiwanese sought CM service covered by the National Health Insurance (NHI) program.<sup>17</sup> This compulsory NHI was launched in 1995 and covered >99% of the Taiwanese population.<sup>18</sup> Ever since 1996, the NHI program has started to reimburse CM service provided by qualified Chinese medical doctors, including acupuncture, moxibustion, Chinese orthopedics and traumatology, and Chinese herbs.

All registration files and original claim data in the NHI program are registered in the Taiwanese NHI Research Database (NHIRD) and managed by National Health Research Institutes in Taiwan. In recent years, this database has played an increasing role in shedding light on the potential of CM on critical illnesses such as diabetes,<sup>19</sup> stroke,<sup>20</sup> and cancer.<sup>21</sup> Because CHM is more commonly provided to patients in Taiwan among the different modalities of treatments, we chose to focus on CHM. Also, 100% of the Chinese herbal products provided in the NHI program are manufactured by Good Manufacturing Practice (GMP)-certified pharmaceutical factories and 80% of them are manufactured by Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP-certified pharmaceutical factories. These Chinese herbal products are in the form of granules, including single-herb products (single Chinese herbs) or multiherb products (Chinese herbal formulas).<sup>21</sup>

Due to the complete lack of data on this topic, we used the NHIRD to conduct a nationwide population-based retrospective cohort study comparing the outcomes of CHM users and nonusers diagnosed with CLL.

## METHODS

### Database

As CM is part of the NHI policy in Taiwan, we used the National Health Insurance Research Database (NHIRD), to perform a nationwide population-based cohort study. The NHIRD contains information regarding each clinical visit and hospitalization incident of all its beneficiaries, as well as treatment received, and drugs or CHM prescribed. The NHIRD established a *Registry for Catastrophic Illnesses Patient Database* (RCIPD), including ~30 disease categories such as infantile cerebral palsy, cancer, and rheumatoid

arthritis.<sup>22</sup> The description of this database has been reported in our previous publications.<sup>21,22</sup> In brief, CLL patients who received comprehensive clinical and laboratory examinations, followed by regular review by hemato-oncologists commissioned by the National Health Insurance Administration, were granted for catastrophic illness certificates. Patients holding such certificates are free of co-payment. All diseases in the NHIRD are classified using the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM). For this study, we collected patient information through the RCPID file, which included the entire NHI records of all CLL (ICD-9-CM code: 204.1) patients in Taiwan. We then matched these patients corresponding information, including comorbidities, in the NHIRD inpatient and outpatient files.

### Study Population

We included all patients, aged 18 years and above, who were diagnosed with CLL between January 2000 and December 2010 in Taiwan. The end of follow-up period was defined as December 31, 2011. It should be noted that it is impossible to differentiate between CLL and the closely-related condition small lymphocytic lymphoma (SLL) based on ICD-9-CM 204.1 alone, and therefore, there is a high probability that this cohort contains patients with SLL as well. Both groups were age and sex matched. When analyzing the hazard ratio for comorbidities of these patients, the following ICD-9-CM codes were used: hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), congestive heart failure (CHF, ICD-9-CM 428), stroke (ICD-9-CM 430–438), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490–496), cirrhosis (ICD-9-CM 571), chronic kidney disease (CKD, ICD-9-CM 580–589), and anemia (ICD-9-CM 280–285).

### Statistical Analysis

In this study, SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis. For categorical variables, chi-square or fisher exact test was used to determine the statistical differences between 2 groups. For continuous variables, the independent *t* test was used. A Cox proportional hazard model, accounting for age, gender, urbanization level, and the comorbidities mentioned in the results, with a 95% confidence interval (CI), was used to estimate the hazard ratios (HR). For categorical covariates, Kaplan–Meier and log rank tests were performed. A *P* value <0.05 was considered statistically significant.

### Ethical Considerations

This study was conducted in accordance with the Helsinki Declaration. All of the datasets from the NHIRD were encrypted and de-identified to protect enrollee privacy. It was not possible to identify individual patients by any means. The Research Ethics Committee of China Medical University and Hospital approved this study (CMUH104-REC2-115).

### Availability of Supporting Data

All data in the NHIRD are properly maintained by the National Health Research Institutes in Taiwan (<http://nhird.nhri.org.tw/en/index.html>) for research purpose only. Researchers who fulfill the requirements of conducting research, approved by an institutional review board and follow the Computer-Processed Personal Data Protection Law (<http://www.winklerpartners.com/?p=987>) and related regulations of

**TABLE 1.** Characteristics of Chronic Lymphocytic Leukemia Patients Differentiated According to Utilization of Chinese Medicine

	CHM				P Value
	No (N = 306)		Yes (N = 310)		
	n	%	n	%	
Gender*					0.9636
Female	111	36.27	113	36.45	
Male	195	63.73	197	63.55	
Age mean ± SD†(years)	69.64 (12.28)		66.48 (10.76)		0.0007
Age group‡					0.9430
18–39	2	0.65	2	0.65	
40–59	69	22.55	72	23.23	
≥60	235	76.80	236	76.13	
Urbanization level*,§					0.7167
1 (highest)	74	24.18	72	23.23	
2	84	27.45	92	29.68	
3	61	19.93	52	16.77	
4 (lowest)	87	28.43	94	30.22	
Number of comorbidities*					0.5875
<2	101	33.01	96	30.97	
≥2	205	66.99	214	69.03	
Comorbidities					
Hypertension*	190	62.09	165	53.23	0.0260
Diabetes*	88	28.76	93	30.00	0.7351
CHF*	28	9.15	26	8.39	0.7377
Stroke*	61	19.33	59	19.03	0.7774
COPD*	130	42.48	147	47.42	0.2182
Cirrhosis*	79	25.82	118	38.06	0.0011
Anemia*	85	27.78	92	29.68	0.6024
CKD*	56	18.30	62	20.00	0.5920
Treatment*					0.0142
Yes (received drug treatment)	209	68.30	239	77.10	
No (treatment-naive)	97	31.70	71	22.90	
Drug use					
Fludarabine*	36	11.76	41	13.23	0.5835
Rituximab*	26	8.50	27	8.71	0.9249
Cyclophosphamide*	100	32.68	115	37.10	0.2502
Chlorambucil*	169	55.23	196	63.23	0.0434
Baseline CCI score*					0.1140
0	146	47.71	173	55.81	
1	65	21.24	60	19.35	
≥2	95	31.05	77	24.84	
HSCT					
No	0	0	0	0	
Yes	0	0	1	100	
Follow time (mean in years)¶	2.67 (2.39)		4.59 (2.85)		

CHM included only Chinese Herbal Medicine, excluded acupuncture, and manual therapies.

CCI = Charlson Comorbidity Index, CHF = congestive heart failure, CHM = Chinese Herbal Medicine, CM = Chinese medicine, CKD = chronic kidney disorder, COPD = chronic obstructive pulmonary disease, HSCT = hematopoietic stem cell transplantation, HR = hazard ratio, SD = standard deviation.

\*Chi-square test.

†t-test.

‡Fisher-exact test.

§The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

¶Cessation of follow time was defined as expiration or end of study timeframe.

National Health Insurance Administration and National Health Research Institutes can apply for the datasets. All applications are reviewed for approval of data release.

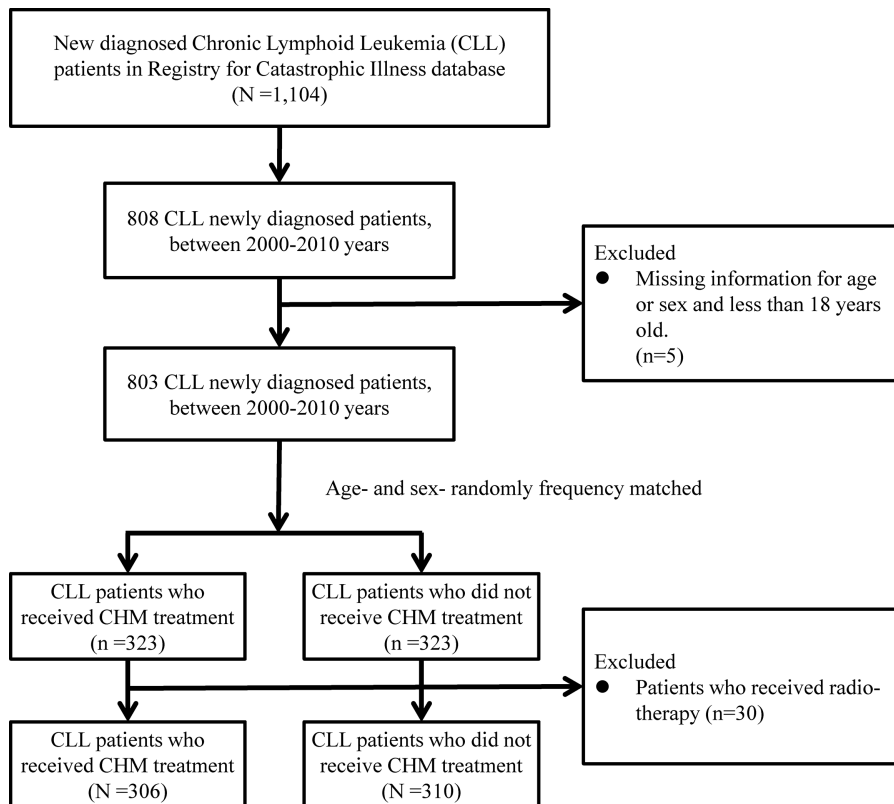
**RESULTS**

Of the total number of patients diagnosed with CLL between 2000 and 2011 who met our criteria, 616 were age- and sex-matched and included into our study, n = 306 in the non-CHM and n = 310 in the CHM group. (Table 1, Figure 1). In accordance with previous studies, the ratio of male to female patients in our cohort was ~2:1.<sup>23</sup> After age matching, the mean age of the non-CM group was 3.16 years greater than that of the CHM group (69.64 ± 12.28 vs 66.48 ± 10.76, respectively). Additionally, the NHIRD categorizes the level of urbanity based on the population density where the event occurred (people/km<sup>2</sup>). In this respect, we found that there was no significant difference between both groups. The prevalence of liver cirrhosis and hypertension was higher by 12.24% and lower by 8.86%, respectively, in non-CHM users. The percentage of treatment-naive patients in the non-CHM group was higher by 8.8% than the CHM group (P = 0.0142). Furthermore, chlorambucil was found to be prescribed 8% more in the CHM group. No significant differences were found in respect to the Charlson Comorbidity Index (CCI) or number of patients who received hematopoietic stem cell transplantation (HSCT). The mean follow-up time was 2.67 years for non-CHM users and 4.59 years for CM users (P < 0.0001).

After inserting age, gender, urbanization level, number of comorbidities, treatments, and drugs used into the regression model, CHM users had a much lower HR of mortality (0.43, 95% CI 0.33–0.55, P < 0.0001) compared to non-CHM group users (Table 2). Furthermore, in Table 2 the cohort was subgrouped according to standard of care treatment and it was shown that CHM users experienced a decrease of HR compared to non-CHM users, in both the treatment and treatment-naive subgroups (0.53, 95% CI 0.40–0.71, P < 0.0001, and 0.19, 95% CI 0.10–0.38, P < 0.0001, respectively). The difference in mortality between the subgroups was also illustrated through a Kaplan–Meier survival graph (Figure 2), which displayed a consistent difference in the mortality rate between the groups, in favor of the CHM users (P < 0.0001).

Table 3 reveals the distribution of CHM users according to their accumulated days of herbal prescriptions. Using patients with < 30 days of CHM use (including nonusers, n = 416) as the reference, it was observed that patients who accumulated between 30 and 180 days of herbal prescriptions (n = 141) experienced an HR of 0.57 (95% CI 0.42–0.79, P < 0.001). The risk of mortality of CHM users who had accumulated > 6 months of herbal prescriptions was lower still (HR 0.35, 95% CI 0.21–0.60, P < 0.001).

In Table 4, the HR of the 10 singleherb and multiherb products most commonly prescribed for the treatment of CLL are listed. With exception of 2 herbal products (*Scutellaria barbata*, Ping Wei San), all others were associated with significant reductions in HR.



**FIGURE 1.** Study population flowchart diagram. Of the total number of chronic lymphoid leukemia (CLL) patients registered in the NHIRD (n = 1104), 808 patients were diagnosed within the years 2000 to 2010. After excluding patients with missing information who were aged > 18 and after matching 1:1 by age and sex, both groups contained 323 patients. CLL = chronic lymphocytic leukemia, NHIRD = National Health Insurance Research Database.

**TABLE 2.** Cox Proportional Hazard Regression With Hazard Ratios and 95% Confidence Intervals of Mortality Associated With CHM and Covariates Among Chronic Lymphocytic Leukemia Patients

Variable	Frequency of Mortality (n = 241)	Crude*			Adjusted†		
		HR	(95% CI)	P Value	HR	(95% CI)	P Value
CHM							
No	138	1	Reference		1	Reference	
Yes	103	0.44	(0.34–0.57)	<0.0001	0.43	(0.33–0.55)	<0.0001
Received treatment							
Non-CHM	98	1	Reference		1	Reference	
CHM	92	0.52	(0.39–0.70)	<0.0001	0.53	(0.40–0.71)	<0.0001
Treatment-naïve							
Non-CHM	40	1	Reference		1	Reference	
CHM	11	0.2	(0.10–0.40)	<0.0001	0.19	(0.10–0.38)	<0.0001

CHF = congestive heart failure, CHM = Chinese Herbal Medicine, CI = confidence interval, CKD = chronic kidney disorder, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

\*Relative hazard ratio.

†adjusted hazard ratio: mutually adjusted through Cox proportional hazard regression model for CHM use, age group, gender, urbanization level, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disorder, number of comorbidities (<2, ≥2), treatment and drugs used including fludarabine, rituximab, cyclophosphamide, and chlorambucil.

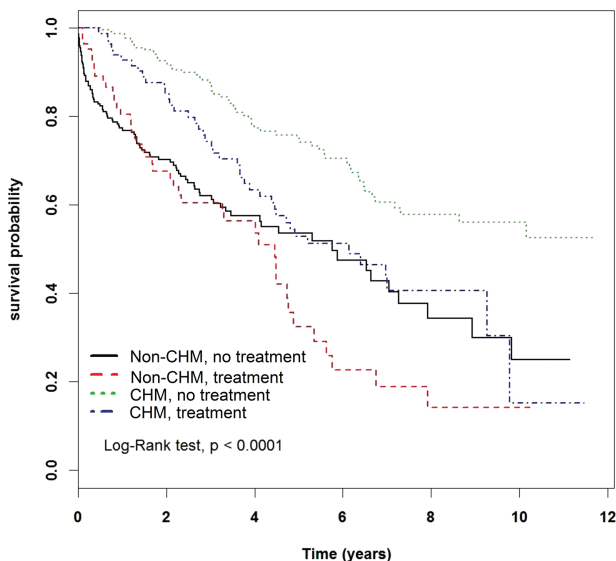
**DISCUSSION**

Our study is the first to comprehensively include leukemia patients from a period of 10 years and illustrate their utilization of Western medicine and CHM in Taiwan. Furthermore, we have found that integrative CHM therapy may be beneficial for patients with CLL. In Italy, it was reported that the rate of CLL patients seeking Complementary and Alternative Medicine (CAM) was 16%;<sup>24</sup> a different study in Germany reported rates of 44%.<sup>25</sup> Additionally, 6.9% of these German patients stated that they had used acupuncture, but the therapy most commonly used in these 2 studies was vitamin supplementation. No thorough data exists regarding the use of CM among patients

in western countries, let alone of CLL patients, yet it is clear that the Taiwanese rates of utilization are comparatively high. During our analyses, we discovered that between 2000 and 2011, approximately half of the CLL patients in Taiwan made use of the CM offered in the NHI program. Furthermore, during the exclusion process, we found that 98% of the CM users among CLL patients received CHM and only very few of them received acupuncture treatment alone. This is not surprising when taking into account the fact that CM in Asia emphasizes the use of herbs, and as much as 85% of the CM treatments carried out within the Taiwanese NHI program are CHM.<sup>17</sup> We only mention this because acupuncture has become the popular modality of complementary therapies, as perceived by patients or physicians, in the west.<sup>26,27</sup> From our results, however, it is evident that Taiwanese CM physicians perceive herbs as an indispensable part of treatment.

Our most significant finding was the reduced risk of mortality associated with the utilization of CHM among CLL patients (0.4243, 95% CI 0.3233–0.5455,  $P < 0.0001$ ). This was also reflected by a follow-up time that was longer by 42% in the CHM group than in the non-CHM group. In addition, in Table 3, it was demonstrated that the reduction in risk had a direct relation to the length of time CHM was directly related to the length of use of CHM. When examining the accumulated use of CHM, users in the “30 to 180 days” group were at less risk than those in the “<30 days” group, and the same was true for patients in the “>180 days” compared to the “30 to 180 days” group ( $P < 0.001$ ). The fact that this improvement was dose-dependent strengthens the possibility of a causal relation between CHM and a decrease in HR. This reduction in HR is quite significant. For the sake of comparison, the trials from the German CLL study group published in 2010 showed that treatment-naïve patients on the FCR regimen versus FC alone had an overall survival (OS) HR of 0.61 (95% CI 0.41–0.91,  $P = 0.017$ ).<sup>2</sup>

One of the limitations of this study was that we had no information regarding the levels of fitness and health of patients. For example, these would be taken into consideration when choosing between a regimen of FCR, fludarabine plus



**FIGURE 2.** Kaplan–Meier curves of overall survival in patients with chronic lymphoid leukemia according to use of Chinese Herbal Medicine (CHM) and standard treatment. CHM = Chinese Herbal Medicine, Treatment = Western medical treatment.

**TABLE 3.** Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With Cumulative Use of Days of Chinese Herbal Medicine Among Chronic Lymphocytic Leukemia Patients

	n	Frequency. of Mortality	Hazard Ratio (95% CI)	
			Crude	Adjusted
Non-CM users or CHM users <30 days	416	177	1 (reference)	1 (reference)
CHM users (>= 30 days) ‡				
30–180 days	141	49	0.58 (0.42–0.80)***	0.57 (0.42–0.79)***
>180 days	59	15	0.35 (0.21–0.60)***	0.35 (0.21–0.60)***
P for trend			<0.0001	<0.0001

Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, gender, urbanization level, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disorder, number of comorbidities (<2, ≥2), treatment and drugs used including fludarabine, rituximab, cyclophosphamide, and chlorambucil.

CHM = Chinese herbal medicine, CHM = Chinese Medicine, CI = confidence interval, HR = hazard ratio.

\*P < 0.05.

\*\*P < 0.01.

\*\*\*P < 0.001.

**TABLE 4.** Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With Cumulative Use of Herbal Formulas Among Chronic Lymphocytic Leukemia Patients

TCM Prescription	Mortality		Hazard Ratio (95% CI)		
	n	Frequency	Crude	Adjusted	
Non-Chinese Herbal Medicine group	306	138		1 (reference)	
Single-herb products					
Pin yin nomenclature	Scientific name				
Bai Hua She She Cao	<i>Hedyotis diffusa</i>	29	11	0.52 (0.28–0.97)*	0.48 (0.25–0.90)*
Yan Hu Suo	<i>Corydalis yanhusuo</i>	50	10	0.21 (0.11–0.40)***	0.22 (0.11–0.42)***
Bei Mu	<i>Fritillaria thunbergii</i>	56	19	0.40 (0.24–0.64)***	0.37 (0.23–0.61)***
Huang Qin	<i>Scutellaria baicalensis</i>	49	12	0.28 (0.16–0.51)***	0.29 (0.16–0.52)***
Dan Shen	<i>Salvia miltiorrhiza</i>	50	14	0.34 (0.19–0.59)***	0.34 (0.20–0.60)***
Ban Lan Gen	<i>Isatis tinctoria</i>	31	10	0.42 (0.22–0.79)***	0.40 (0.21–0.77)**
Ge Gen	<i>Pueraria lobata</i>	53	14	0.27 (0.16–0.47)***	0.27 (0.15–0.48)***
Ban Zhi Lian	<i>Scutellaria barbata</i>	12	6	0.72 (0.32–1.64)	0.77 (0.33–1.80)
Ju Hua	<i>Chrysanthemum morifolium</i>	23	8	0.39 (0.19–0.81)**	0.41 (0.20–0.84)*
Huang Qi	<i>Astragalus membranaceus</i>	46	11	0.26 (0.14–0.49)***	0.26 (0.14–0.49)***
Multiherb products					
Pin yin nomenclature	Scientific name				
Zhi Bo Di Huang Wan	–	37	6	0.19 (0.08–0.43)***	0.21 (0.09–0.47)***
Ma Zi Ren Wan	–	16	3	0.19 (0.06–0.60)**	0.19 (0.06–0.59)**
Shen Ling Bai Zhu San	–	18	5	0.29 (0.12–0.71)**	0.29 (0.12–0.71)**
Bu Zhong Yi Qi Tang	–	37	16	0.56 (0.34–0.95)*	0.55 (0.32–0.93)*
San Zhong Kui Jian Tang	–	18	5	0.39 (0.16–0.95)*	0.38 (0.15–0.93)*
Zhi Gan Cao Tang	–	42	12	0.32 (0.18–0.59)***	0.30 (0.17–0.55)***
Ping Wei San	–	36	16	0.58 (0.35–0.98)*	0.60 (0.35–1.01)
Gui Pi Tang	–	37	16	0.57 (0.34–0.96)*	0.54 (0.32–0.91)*
Jia Wei Xiao Yao San	–	42	5	0.15 (0.06–0.36)***	0.17 (0.07–0.41)***
Du Huo Ji Sheng Tang	–	43	8	0.20 (0.10–0.40)***	0.19 (0.09–0.39)***

Crude HR represented relative hazard ratio; adjusted HR represented adjusted hazard ratio: mutually adjusted for age group, gender, urbanization level, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disorder, number of comorbidities (<2, ≥2), treatment and drugs used including fludarabine, rituximab, cyclophosphamide, and chlorambucil.

CI = confidence interval.

\*P < 0.05.

\*\*P < 0.01.

\*\*\*P < 0.001.

cyclophosphamide, or fludarabine alone.<sup>28</sup> Thus, the type of treatments may provide indirect insight into the levels of fitness and health of the patients. One seemingly suspicious finding in our study was that the CHM group and the non-CHM group had a follow-up time of 4.59 and 2.67 years, respectively. At first glance, we assumed that this was suggestive of an error in analyses, as western CLL patients often achieve much longer survival durations than these. However, it is important to note that life expectancy in Taiwan in 2011 was 75.94 for males and 82.60 for females, and was even lower during the preceding decade.<sup>29</sup> As the majority of patients in this cohort were male and roughly the age of 70, the follow-up times found are not inconceivable.

It has been shown that ~90% of newly diagnosed CLL patients suffer from 1 or more comorbidities.<sup>30</sup> However, thus far the only relation established between comorbidities and overall survival in CLL was reported in a recent analysis of the CLL4 and CLL5 trials, which showed that patients who suffered from 2 comorbidities or more had lower survival rates than those with <2.<sup>31</sup> Therefore, we chose to adjust our regression model according to this <2/≥2 cut point and found that the HR associated with the use of CHM was lower in both cases ( $P < 0.001$ , Table 2). We experimented with adjusting our regression model for the diseases in Table 1 and according to the Charlson Comorbidity Index. The differences in HR between the adjustment methods were negligible and the HR of the CHM group remained low in all cases.

An additional point of note is the homogeneity of our population. It has already been established that the disease course of CLL differs between ethnic groups.<sup>32</sup> Although studies have shown that CLL is on the rise in Taiwan, the prevalence of this disease is higher in Western countries. However, Taiwanese patients display much poorer survival rates than their American counterparts.<sup>23,33</sup> In a study conducted in the UK, Asian CLL patients' time-to-first-treatment was significantly shorter and overall survival rates lower when compared to those of Caucasians.<sup>34</sup> These differences make it difficult to infer the benefit that other ethnic groups would have from CHM treatment.

One further point to note is that the NHIRD does not contain information regarding performance status, staging, genetic mutations, molecular markers, and organ toxicity which all may confer to a favorable or unfavorable outcome. These are irreplaceable, however, we showed that the differences in baseline CCI score of patients from both groups was not significant and that in both groups, virtually the same amount of patients received HSCT.

An additional contribution of this study is the list of single-herb and multiherb products presented in Table 4. The prescription process of CHM differs from that of biomedicine in that there is not a 1:1 relationship between prescription and disorder, and the treatment of CLL may vary according to the symptoms and signs displayed by the patient. Although some of the herbs presented, for example, *Hedyotis diffusa* and *Salvia miltiorrhiza*, have been researched in the context of leukemia, other herbs such as *Corydalis yanhusuo* have not. Thus, the products listed in Table 4 may be used in future basic and clinical research.

Taking these limitations into consideration, this study has presented a reduction in the hazard ratio of CLL patients who received CHM. It is impossible to rule out certain influences such as patient motivation in this type of retrospective study; however, the results showed that reduction in HR was dose-

dependent, and challenging the notion that the reduced HR was a result of other factors.

In conclusion, we supplied data including western medicine and CHM from a relatively large population that spanned over a significant amount of time. Overall, we can report novel data concerning the treatment of CLL with adjunctive CHM, which may have a substantial positive impact on the management of this disease, especially for treatment-naïve patients. Alternative therapies and change of the social and environmental setting may have positive impact on health and course of diseases.<sup>35</sup> Further research is needed to substantiate whether this relationship holds true in non-Asian patients as well, and prospective studies are needed to confirm the causal relationship between CHM and the outcomes displayed.

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