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Complementary Chinese Herbal Medicine Therapy Improves Survival of Patients With Pancreatic Cancer in Taiwan: A Nationwide Population-Based Cohort Study

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Abstract

Background: Pancreatic cancer is a difficult-to-treat cancer with a late presentation and poor prognosis. Some patients seek traditional Chinese medicine (TCM) consultation. We aimed to investigate the benefits of complementary Chinese herbal medicine (CHM) among patients with pancreatic cancer in Taiwan. **Methods:** We included all patients with pancreatic cancer who were registered in the Taiwanese Registry for Catastrophic Illness Patients Database between 1997 and 2010. We used 1:1 frequency matching by age, sex, the initial diagnostic year of pancreatic cancer, and index year to enroll 386 CHM users and 386 non-CHM users. A Cox regression model was used to compare the hazard ratios (HRs) of the risk of mortality. The Kaplan-Meier curve was used to compare the difference in survival time. **Results:** According to the Cox hazard ratio model mutually adjusted for CHM use, age, sex, urbanization level, comorbidity, and treatments, we found that CHM users had a lower hazard ratio of mortality risk (adjusted HR = 0.67, 95% CI = 0.56-0.79). Those who received CHM therapy for more than 90 days had significantly lower hazard ratios of mortality risk than non-CHM users (90- to 180-day group: adjusted HR = 0.56, 95% CI = 0.42-0.75; >180-day group: HR = 0.33, 95% CI = 0.24-0.45). The survival probability was higher for patients in the CHM group. Bai-hua-she-she-cao (Herba Oldenlandiae; *Hedyotis diffusa* Spreng) and Xiang-sha-liu-jun-zi-tang (Costus and Chinese Amomum Combination) were the most commonly used single herb and Chinese herbal formula, respectively. **Conclusions:** Complementary Chinese herbal therapy might be associated with reduced mortality among patients with pancreatic cancer. Further prospective clinical trial is warranted.

Keywords

Chinese herbal medicine, complementary and alternative medicine, National Health Insurance Research Database, pancreatic cancer, traditional Chinese medicine

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Introduction

Pancreatic cancer is a type of gastrointestinal tumor that often has a poor prognosis.[1] The incidence of pancreatic cancer has risen in recent years. Pancreatic cancer is the fourth leading cause of cancer-related death in the United States among both men and women.[2] According to national statistical data, pancreatic cancer was the eighth leading cause of cancer-related death in Taiwan in 2013.[3]

Pancreatic cancer occurs in men more often than in women. The causes of pancreatic cancer include smoking, alcohol consumption, chronic pancreatitis, and age. Pancreatic cancer can lead to nonspecific epigastric pain, back pain, weight loss, progressive jaundice, unexplained pancreatitis or diabetes, and chronic diarrhea. The treatments include surgery, chemotherapy, and radiotherapy. Surgery is possibly the only method known to cure the disease, but pancreatic cancer patients are often diagnosed in the late stages of the disease, resulting in a poor prognosis.[1] The median survival is only 5 to 6 months, indicating the importance of finding other treatments to address this unmet need.

One earlier study showed the improved prognosis of pancreatic cancer patients who take traditional Chinese medicine (TCM).[4] In that study, the authors also found that heat-clearing, diuresis-promoting, and detoxification herbs had a better efficacy. A phase II study demonstrated that a Chinese herbal formula, PHY906, has synergistic antitumor activity with capecitabine in patients with advanced pancreatic cancer who were previously treated with gemcitabine-based regimens.[5] However, current information about the clinical treatment for patients with pancreatic cancer is very limited.

In Taiwan, the National Health Insurance (NHI) program was launched in 1995, and the health insured rate of the whole population is 99.6% as of 2015.[6] The National Health Insurance Administration deidentified all of the registration files and claims data, and sent the datasets to the National Health Research Institutes to construct a National Health Insurance Research Database (NHIRD) for scientific research. It provides data on the insured population's TCM and Western medical treatment use. As a result, this database can provide nationwide population-based information. The database has been used to survey the utilization of TCM for various diseases such as stroke,[7] fractures,[8] rheumatoid arthritis,[9] diabetes mellitus,[10] and cancer.[11] Previous studies also revealed that complementary Chinese herbal medicine improved survival in patients with gastric cancer,[12] acute myeloid leukemia,[13] and chronic myeloid leukemia.[14] However, few studies have reported on the benefit of complementary utilization of Chinese herbal medicine (CHM) in patients with pancreatic cancer. CHM treatment is part of the NHI program. Many people in Taiwan take complementary Chinese medicine to treat their disease; accordingly, we used the NHIRD to investigate patients with pancreatic cancer. As it is a population-based database, an analysis of its data may lead to a better understanding of the adjunctive CHM use in pancreatic cancer from a nationwide perspective.

Materials and Methods

Data Sources

Our study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115). It was designed as a matched-cohort study. All data were acquired from the database maintained by the National Health Research Institutes. We used ambulatory and inpatient medical records for cancer care linked with the Registry for Catastrophic Illness Patients Database (RCIPD) for the period from 1997 to 2010 to identify study subjects for follow-up until the end of 2011.

The RCIPD is part of the NHIRD, which enrolled all of the patients with catastrophic illness proven by pathological, laboratory, and clinical diagnoses by specialists and reviewed by the National Health Insurance Administration regularly. All registered cancer patients are issued catastrophic illness certificates and are free of copayments to visit TCM or Western medical doctors for cancer-related treatment. Therefore, it is a comprehensive database to survey all pancreatic cancer patients in Taiwan.

The demographic information in the database includes International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, age, sex, clinical data, hospitalization records, outpatient records, and prescribed drugs and dosages. Our study acquired the data on pancreatic cancer patients from the RCIPD according to ICD-9-CM code 157. There were 18 487 patients with pancreatic cancer in the database. We excluded patients who were less than 20 years old, diagnosed as having acute myocardial infarction, or withdrew from the NHI program during the follow-up period. Among them, 13 943 patients were newly diagnosed from January 1, 1997 to December 31, 2010 with complete information and followed until the end of 2011 (Figure 1). We defined CHM users as those had used CHM for more than 30 days. Additionally, the main reason for them to visit the TCM doctors should be pancreatic cancer. The index date was defined as the first time that patients received CHM treatment. The immortal time was defined as the period from the initial diagnosis of pancreatic cancer to the index date. Finally, to evaluate the benefits of the adjunctive use of CHM, we used 1:1 frequency matching by age (per 5 years), sex, initial diagnostic year of pancreatic cancer, and index year to compare the 2 groups. Patients who died within 30 days of the index date were excluded. We followed the

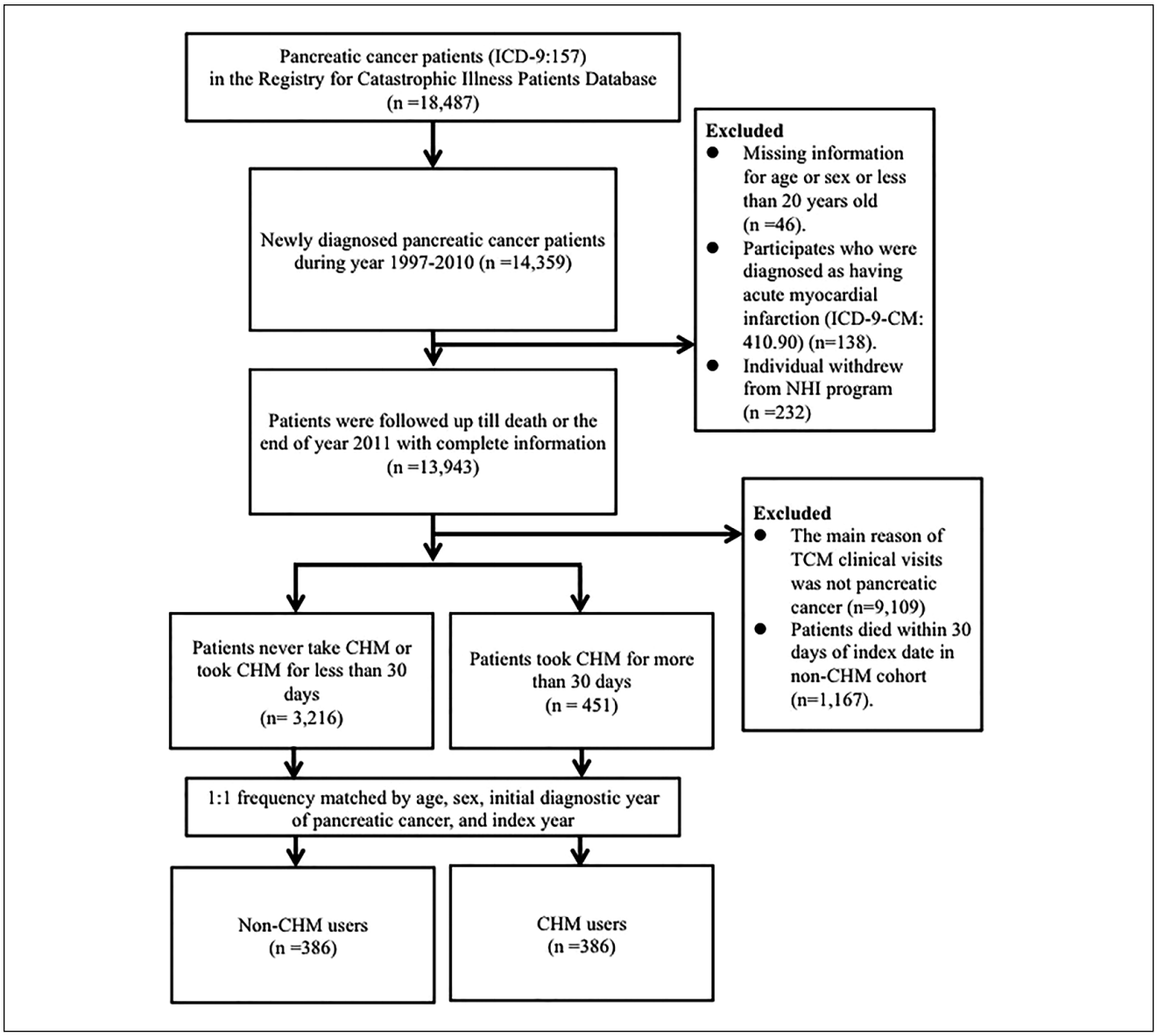

Figure 1. Recruitment flowchart of subjects from the Registry for Catastrophic Illness Patients Database (RCIPD) of the National Health Insurance Research Database (NHIRD) during the period 1997-2010 in Taiwan. CHM, Chinese herbal medicine; TCM, traditional Chinese medicine.

included patients until the event of death or the end of the study period (December 31, 2011).

Study Variables

We classified the patients into 6 groups by age: 20-29, 30-39, 40-49, 50-59, 60-69, and more than 70 years. Urbanized residence areas were divided into 4 levels as in a previous study.[15] We defined level 1 as the highest urbanization level and level 4 as the lowest urbanization level. The comorbidity of these patients were determined by ICD-9-CM codes: diabetes mellitus (DM, 290), prior myocardial infarction (412), angina pectoris (413.9), arrhythmia (427), chronic heart failure (CHF, 428), chronic kidney disease (CKD, 581-586), upper gastrointestinal bleeding (578.9), acute pancreatitis (577.0), chronic pancreatitis (577.1), intestinal obstruction (560.9), sepsis (038.x, 054.5, 003.1, 022.3), cachexia (799.4), peritonitis (567.9), hematemesis (578.0), hemoptysis (786.3), edema (782.3), jaundice (782.4), nausea and vomiting (787.0), hypertension (401-405), hyperlipidemia (272), stroke (430-438), chronic obstructive pulmonary disease (COPD, 491, 492, 494, 496), liver diseases (570, 571, 573.3, 573.8, 573.9, 070), renal dialysis (V45.1, V56), alcoholism (291, 303, 305.00-305.03, 790.3, and V11.3), tobacco

use (305.1), and obesity (278 and A183). We also identified the patients who received total pancreatectomy (treatment code: 75410B and 75411B), partial pancreatectomy (treatment code: 75404B, 75405B, 75412B, and 75415B-75417B), or other pancreatectomy (treatment code: 75406B-75409B, 75413B, and 75414B).

Statistical Analysis

We used the chi-square test or Fisher's exact test to identify the differences between CHM and non-CHM groups for categorical variables. We also used *t* tests to differentiate the mean age between the two groups. Cox proportional hazard regression analysis was performed to estimate crude and adjusted hazard ratios (HRs) of CHM use, age, sex, urbanization level, comorbidity, conventional treatment, and specific drugs used. We also evaluated the differences in survival time using Kaplan-Meier curves. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA), and we considered a $P < .05$ as statistically significant.

Complementary Chinese Herbal Medicine

We tried to identify the most common herbal formulas and single herbs prescribed to the CHM group patients. Next, we calculated the adjusted hazard ratios (mutually adjusted for age, sex, urbanization level, comorbidity, and Western medical treatment) of the CHM mentioned above. Full botanical names comply with the International Plant Names List (IPNI; http://www.ipni.org) and The Plant List (http://www.theplantlist.org/).[16]

Results

Overall, there were 451 patients with pancreatic cancer who received CHM treatment for more than 30 days after being diagnosed with pancreatic cancer (Figure 1). We performed 1:1 frequency matching by age, sex, initial diagnostic year of pancreatic cancer, and index year. There were 386 patients in both CHM and non-CHM user groups. The percentages of patients with comorbidities in the 2 groups were similar (Table 1). The percentages of patients receiving different types of pancreatectomy in the 2 groups were also similar. However, CHM users had a higher percentage of receiving radiotherapy (39.9% vs 31.35%) or chemotherapy (70.21% vs 59.59%) than non-CHM users.

According to the Cox hazard ratio model mutually adjusted for CHM use, age, sex, urbanization level, comorbidity, treatment, and drug used, we found that CHM users had a lower hazard ratio of mortality risk (adjusted HR = 0.67, 95%CI = 0.56-0.79) (Table 2). The mortality risk in the 50- to 59-year-old group was lower than that of the patients more than 70 years old (adjusted HR = 0.73, 95% CI = 0.57-0.93). Patients receiving radiotherapy also had a lower hazard ratio (adjusted HR = 0.78, 95% CI = 0.64-0.94).

Based on the Kaplan-Meier curves, we found that the survival probability was higher for patients in the CHM group than for those in the non-CHM group (Figure 2). Both female and male CHM users had lower mortality risks (women: adjusted HR = 0.66, 95% CI = 0.5-0.86; men: adjusted HR = 0.63, 95% CI = 0.5-0.79) (Table 3). Of the patients aged from 40 to 69 years, the mortality risk of CHM users is also lower than non-CHM users.

We classified CHM users into 3 subgroups according to the number of days they used CHM, namely, a 30- to 90-day group, 90- to 180-day group, and >180-day group. On the basis of the Cox hazard ratio model, we found that the mortality risk in CHM users who received CHM treatment for more than 90 days was significantly lower than non-CHM users (90- to 180-day group: adjusted HR = 0.56, 95% CI = 0.42-0.75; >180-day group: HR = 0.33, 95%CI = 0.24-0.45). This indicated that adjunctively taking CHM for more than 90 days had benefits on the survival of pancreatic cancer patients (Table 4).

Our study showed that there were 386 patients with pancreatic cancer who used CHMs after being diagnosed with pancreatic cancer. We identified the most commonly used single herb as Bai-hua-she-she-cao (Herba Oldenlandiae, *Hedyotis diffusa* Spreng) (Table 5). In addition, the most commonly used Chinese herbal formula was Xiang-sha-liu-jun-zi-tang (Costus and Chinese Amomum Combination).

Discussion

Our study is the first nationwide study investigating the benefits of complementary CHM among patients with pancreatic cancer. This matched-cohort study was based on a database, RCIPD, which enrolled all the pancreatic cancer patients during the years 1997-2010 to compare the differences between CHM users and non-CHM users in Taiwan. We found that patients who used CHM for more than 90 days had lower mortality risk than those in the non-CHM group. Our study is in accordance with a previous study published by Tianjin Medical University Cancer Hospital, China. In that study, the hazard ratio of mortality risk was 0.419 and the median overall survival was 19 months for patients with TCM treatment versus 8 months for those without TCM treatment.[4]

The cancer statistics in the United States indicated that advances have been very slow for pancreatic cancer, for which the 5-year survival is only 8%.[2] Our Kaplan-Meier survival curve suggested that the 5-year survival among non-CHM users was similar to that of the US cancer statistics. We found that the overall survival probability of CHM users was higher.

Table 1. Characteristics of Patients With Pancreatic Cancer According to Their Use of Chinese Herbal Medicine.

	Patients With Pancreatic Cancer (n = 790)				
	Non-CHM User (n = 386)		CHM User (n = 386)		
Variable	n	%	n	%	*P*
Sex					.99[a]
Female	168	43.52	168	43.52	
Male	218	56.48	218	56.48	
Age, y, mean ± SD	63.60 ± 12.03		62.79 ± 10.98		.3911[b]
Age-group, y					.99[a]
20-29	1	0.26	1	0.26	
30-39	7	1.81	7	1.81	
40-49	32	8.29	32	8.29	
50-59	127	32.9	127	32.9	
60-69	105	27.2	105	27.2	
>70	114	29.53	114	29.53	
Urbanization level[c]					.1919[a]
1 (highest)	99	25.65	110	28.5	
2	116	30.05	114	29.53	
3	49	12.69	63	16.32	
4 (lowest)	122	31.61	99	25.65	
Comorbidity					
DM	159	41.19	165	42.75	.6617[a]
Type I DM	4	1.04	5	1.3	.99[d]
Type II DM	148	38.34	151	39.12	.8246[a]
Hypertension	194	50.26	209	54.15	.2798[a]
Hyperlipidemia	109	28.24	158	40.93	.0002[a]
Prior myocardial infarction	1	0.26	2	0.52	.99[c]
Angina pectoris	23	5.96	30	7.77	.3191[a]
Arrhythmia	38	9.84	55	14.25	.0602[a]
CHF	23	5.96	15	3.89	.1832[a]
CKD	46	11.92	58	15.03	.2059[a]
Renal dialysis	1	0.26	0	0	—
Liver diseases	153	39.64	208	53.89	<.0001[a]
Upper gastrointestinal bleeding	22	5.7	14	3.63	.1721[a]
Acute pancreatitis	28	7.25	37	9.59	.2434[a]
Chronic pancreatitis	20	5.18	26	6.74	.3616[a]
Intestinal obstruction	9	2.33	2	0.52	.0636[d]
Sepsis	31	8.03	16	4.15	.024[a]
Cachexia	16	4.15	10	2.59	.2313[a]
Peritonitis	4	1.04	1	0.26	.3734[d]
Hematemesis	0	0	1	0.26	—
Hemoptysis	3	0.78	5	1.3	.7251[d]
Edema	37	9.59	30	7.77	.3708[a]
Jaundice	39	10.1	41	10.62	.8133[a]
Nausea and vomiting	17	4.4	24	6.22	.2612[a]
Ascites	14	3.63	4	1.04	.029[d]
Depression	23	5.96	38	9.84	.0454[a]
Anxiety	56	14.51	81	20.98	.0185[a]
Stroke	51	13.21	50	12.95	.9150[a]
COPD	76	19.69	77	19.95	.9281[a]
Alcoholism	0	0	1	0.26	—
Tobacco use	1	0.26	4	1.04	.3734[d]
Obesity	4	1.04	3	0.78	.99[d]

(continued)

Table 1. (continued)

Variable	Patients With Pancreatic Cancer (n = 790)				
	Non-CHM User (n = 386)		CHM User (n = 386)		
	n	%	n	%	*P*
Treatment					
Radiotherapy	121	31.35	154	39.9	.0131[a]
Chemotherapy	230	59.59	271	70.21	.002[a]
Surgery					
Total pancreatectomy	1	0.26	1	0.26	.99[d]
Partial pancreatectomy	9	2.33	12	3.11	.5069[a]
Other pancreatectomy	1	0.26	3	0.78	.624[d]
Drug used					
Statin	12	3.11	26	6.74	.0199[a]
Gemcitabine	206	53.37	251	65.03	.001[a]
Paclitaxel	1	0.26	1	0.26	.99[d]
Tegafur	35	9.07	37	9.59	.8045[a]
Irinotecan	3	0.78	1	0.26	.624[d]
Oxaliplatin	4	1.04	7	1.81	.5459[d]
5-Fluorouracil	136	35.23	159	41.19	.0885[a]
Leucovorin	125	32.38	137	35.49	.3617[a]
Capecitabine	2	0.52	5	1.3	.451[d]
Cisplatin	61	15.8	87	22.54	.0174[a]
Interval between the initial diagnosis of pancreatic cancer and the index date, days, mean (median)	156 (68)		141 (52)		.4263[b]
Follow-up time, years, mean (median)	0.74 (0.25)		1.25 (0.71)		

Abbreviations: CHM, Chinese herbal medicine; DM, diabetes mellitus; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.
[a]Chi-square test.
[b]*t* test.
[c]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.
[d]Fisher's exact test.

Table 2. Cox Model With Hazard Ratios and 95% Confidence Intervals of Mortality Associated With Chinese Herbal Medicine and Covariates Among Patients With Pancreatic Cancer.

Variable	Patients With Pancreatic Cancer						
	No. of Death (n = 633)	Crude[a]			Adjusted[b]		
		HR	(95% CI)	*P*	HR	(95% CI)	*P*
CHM used (reference = non-CHM user)							
Non-CHM user	320	1.00	Reference		1.00	Reference	
CHM user	313	0.63	(0.54-0.74)	<.0001	0.67	(0.56-0.79)	<.0001
Sex							
Female	271	1.00	Reference		1.00	Reference	
Male	362	1.08	(0.92-1.26)	.3527	1.05	(0.88-1.24)	.5882
Age group, y							
20-29	1	0.34	(0.05-2.44)	.2837	0.35	(0.05-2.56)	.2993
30-39	10	0.52	(0.27-0.98)	.0433	0.52	(0.27-1.03)	.0592
40-49	53	0.83	(0.62-1.13)	.2449	0.85	(0.6-1.23)	.3925
50-59	202	0.73	(0.6-0.89)	.0017	0.73	(0.57-0.93)	.0111

(continued)

Table 2. (continued)

Variable	No. of Death (n = 633)	Patients With Pancreatic Cancer					
		Crude[a]			Adjusted[b]		
		HR	(95% CI)	*P*	HR	(95% CI)	*P*
60-69	177	0.98	(0.79-1.2)	.8092	0.95	(0.75-1.19)	.6401
>70	190	1.00	Reference		1.00	Reference	
Urbanization level							
1 (highest)	174	1.00	Reference		1.00	Reference	
2	181	0.99	(0.8-1.22)	.9293	1.07	(0.85-1.33)	.5679
3	90	0.89	(0.69-1.14)	.3574	0.90	(0.68-1.18)	.432
4 (lowest)	188	1.22	(1-1.51)	.0542	1.28	(1.02-1.6)	.0317
Comorbidity (reference = no comorbidity)							
DM	265	1.07	(0.92-1.26)	.3795	1.04	(0.88-1.24)	.6256
Hypertension	326	1.03	(0.88-1.2)	.7112	0.92	(0.76-1.1)	.3573
Hyperlipidemia	215	0.95	(0.8-1.12)	.509	1.05	(0.86-1.27)	.6296
Prior myocardial infarction	2	0.65	(0.16-2.58)	.5369	0.75	(0.18-3.12)	.6915
Angina pectoris	43	1.06	(0.78-1.45)	.6983	1.07	(0.76-1.5)	.7115
Arrhythmia	75	1.05	(0.82-1.33)	.7102	1.12	(0.85-1.47)	.4254
CHF	32	0.97	(0.68-1.39)	.8872	0.83	(0.56-1.22)	.3385
CKD	87	0.95	(0.76-1.19)	.6735	0.98	(0.77-1.26)	.8772
Renal dialysis	1	0.96	(0.14-6.84)	.9687	0.71	(0.1-5.23)	.7333
Liver diseases	294	0.84	(0.72-0.98)	.025	0.87	(0.73-1.03)	.0984
Upper gastrointestinal bleeding	29	0.98	(0.68-1.43)	.9267	1.18	(0.79-1.76)	.4256
Acute pancreatitis	52	0.82	(0.62-1.09)	.1724	0.76	(0.54-1.05)	.0983
Chronic pancreatitis	38	0.89	(0.64-1.23)	.4699	0.92	(0.64-1.33)	.6649
Intestinal obstruction	8	1.38	(0.68-2.79)	.3763	1.19	(0.56-2.54)	.6467
Sepsis	41	1.39	(1.01-1.91)	.042	1.41	(1-1.99)	.0488
Cachexia	21	1.74	(1.12-2.7)	.0129	1.54	(0.97-2.46)	.0698
Peritonitis	4	0.95	(0.35-2.54)	.916	1.00	(0.35-2.82)	.9988
Hematemesis	1	5.87	(0.82-41.97)	.0776	8.71	(1.18-64.58)	.0342
Hemoptysis	7	1.12	(0.53-2.36)	.7661	1.02	(0.47-2.22)	.9549
Edema	57	1.32	(1-1.73)	.0488	1.30	(0.96-1.77)	.0923
Jaundice	64	0.89	(0.69-1.15)	.3645	0.87	(0.66-1.14)	.2972
Nausea and vomiting	34	1.10	(0.78-1.56)	.5737	1.12	(0.78-1.6)	.5495
Ascites	16	2.22	(1.35-3.66)	.0017	1.76	(1.03-3)	.039
Depression	51	0.96	(0.72-1.27)	.7656	1.01	(0.73-1.4)	.9394
Anxiety	111	0.93	(0.76-1.14)	.4865	0.91	(0.72-1.16)	.441
Stroke	86	1.13	(0.9-1.42)	.2918	0.95	(0.73-1.23)	.7032
COPD	131	1.18	(0.98-1.43)	.0861	1.15	(0.93-1.43)	.2035
Alcoholism	1	1.34	(0.19-9.53)	.7699	3.43	(0.44-26.83)	.2401
Tobacco use	3	1.09	(0.35-3.4)	.8764	1.60	(0.49-5.19)	.4339
Obesity	6	1.18	(0.53-2.63)	.6943	1.68	(0.6-4.68)	.322
Treatment							
Radiotherapy	231	0.82	(0.7-0.97)	.0192	0.78	(0.64-0.94)	.0078
Chemotherapy	433	1.21	(1.02-1.44)	.0261	1.25	(0.82-1.9)	.3042
Surgery							
Total pancreatectomy	1	0.54	(0.08-3.82)	.5346	1.08	(0.14-8.22)	.9378
Partial pancreatectomy	15	0.54	(0.32-0.9)	.0184	0.59	(0.35-1)	.0491
Other pancreatectomy	2	0.34	(0.08-1.35)	.1257	0.41	(0.1-1.67)	.2133
Drug used							
Statin	22	0.45	(0.3-0.69)	.0003	0.45	(0.28-0.71)	.0005
Gemcitabine	400	1.22	(1.04-1.44)	.0178	1.26	(0.86-1.83)	.2372

(continued)

Table 2. (continued)

Variable	No. of Death (n = 633)	Patients With Pancreatic Cancer					
		Crude[a]			Adjusted[b]		
		HR	(95% CI)	*P*	HR	(95% CI)	*P*
Paclitaxel	2	0.56	(0.14-2.23)	.4081	0.59	(0.14-2.46)	.4663
Tegafur	58	0.83	(0.63-1.08)	.1645	0.74	(0.55-0.99)	.0448
Irinotecan	3	0.93	(0.3-2.9)	.903	0.63	(0.18-2.24)	.4795
Oxaliplatin	10	0.88	(0.47-1.64)	.6762	0.77	(0.35-1.67)	.5067
5-Fluorouracil	258	1.08	(0.92-1.27)	.3426	0.98	(0.67-1.45)	.9301
Leucovorin	231	1.06	(0.9-1.24)	.4986	1.10	(0.75-1.63)	.6216
Capecitabine	6	1.02	(0.46-2.29)	.9528	1.13	(0.42-3.07)	.807
Cisplatin	127	0.89	(0.73-1.08)	.2392	0.84	(0.67-1.06)	.1384

Abbreviations: CHM, Chinese herbal medicine; DM, diabetes mellitus; CHF, congestive heart failure; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
[a]Crude HR represents relative hazard ratio.
[b]Adjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity (as in the list of Table 2), treatment (as in the list of Table 2) and drug used (as in the list of Table 2) in Cox proportional hazard regression.

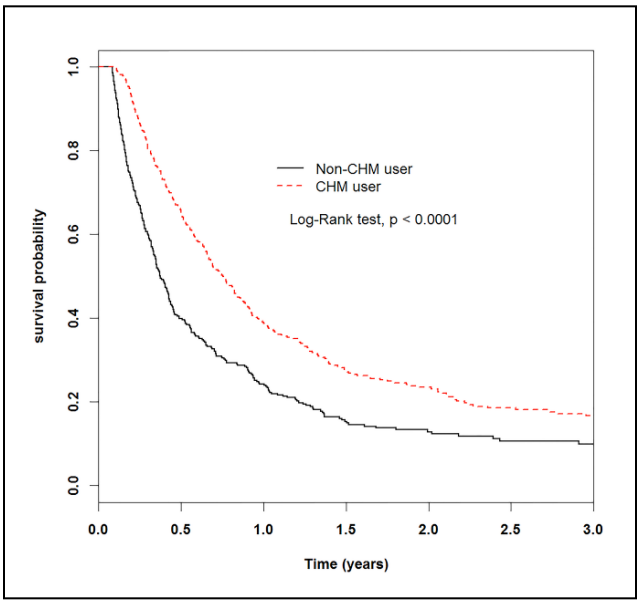

Figure 2. Kaplan-Meier curves of survival rate in pancreatic cancer patients of CHM and non-CHM group. CHM, Chinese herbal medicine.

Previous studies usually showed a preference of using TCM in women.[15,17] However, in the current study in pancreatic cancer, there was no obvious tendency of more female CHM users. This is probably because of the fact that the incidence rate of pancreatic cancer is higher in males.[18]

Our study not only showed that adjunctive Chinese herbal therapy had the potential to improve survival but also identified some candidate herbs and formulas deserving further investigation. The most commonly used Chinese herb was Bai-hua-she-she-cao (Herba Oldenlandiae; *Hedyotis diffusa* Spreng). In recent studies, one indicated that Bai-hua-she-she-cao could suppress tumor angiogenesis in vivo via inhibition of Sonic hedgehog signaling in colorectal cancer.[19] Another found that the novel cyclotides in Bai-hua-she-she-cao had anticancer activity.[20] Ban-zhi-lian (Herba Scutellariae Barbatae; *Scutellaria barbata* D Don) could promote the tumor inhibition rate of 5-fluorouracil, which is often prescribed to pancreatic cancer patients. It could also extend the survival time and elevate immune function in H22 tumor-bearing mice.[21] Cryptotanshinone, one of the constituents of Dan-shen (Radix Salviae Miltiorrhizae; *Salvia miltiorrhiza* Bunge) could exert anticancer effects by inducing apoptosis and cell cycle arrest via inhibition of the STAT3 signaling pathway in human pancreatic cell line.[22] Shen-qu (Medicated Leaven; Massa Medicata Fermentata) could help with digestion by its diverse bacterial and fungal communities.[23] Recent studies on the human microbiome have highlighted how perturbations of commensal bacterial populations can influence the interplay between inflammation and microbiome in the context of pancreatic carcinogenesis.[24] Shen-qu appeared to be a commonly prescribed herb for pancreatic cancer patients implying that further studies toward this direction are needed. It is noteworthy that the common herb, Huang-qin (Radix Scutellariae; *Scutellaria baicalensis* Georgi), is one of the major herbs of a Chinese herbal formula PHY906, which has been shown to be a safe and feasible salvage therapy for advanced pancreatic cancer in a phase II clinical trial.[5]

The most common Chinese herbal formula was Xiang-sha-liu-jun-zi-tang (Costus and Chinese Amomum Combination). In a meta-analysis of randomized controlled trials, Xiang-sha-liu-jun-zi-tang was found to improve the symptom of dyspepsia.[25] Pancreatic cancer patients often

Table 3. Incidence Rates, Hazard Ratios, and Confidence Intervals of Mortality for Patients Stratified by Demographic Characteristics, Comorbidity, Treatment, and Drug Used.

	Chinese Herbal Medicine Used						Compared With Non-CHM User	
	Non-CHM User (n = 386)			CHM User (n = 386)				
Variables	Event	Person Years	IR	Event	Person years	IR	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Total	320	286	1119.33	313	483	647.46	0.63 (0.54-0.74)***	0.67 (0.56-0.79)***
Sex								
Female	137	118	1159.66	134	204	655.96	0.62 (0.48-0.78)***	0.66 (0.5-0.86)**
Male	183	168	1090.92	179	279	641.25	0.64 (0.52-0.79)***	0.63 (0.5-0.79)***
Age group, y								
20-29	1	0	2148.53	0	2	0	—	—
30-39	4	14	276.44	6	13	478.28	0.96 (0.27-3.46)	—
40-49	26	22	1155.85	27	45	601.29	0.56 (0.32-0.97)*	0.19 (0.06-0.68)*
50-59	103	107	965.33	99	198	500.63	0.62 (0.47-0.82)***	0.55 (0.4-0.77)***
60-69	92	64	1428.76	85	102	830.76	0.57 (0.42-0.76)***	0.52 (0.36-0.74)***
>70	94	77	1215	96	124	777.28	0.71 (0.53-0.94)*	0.8 (0.57-1.14)
Urbanization level								
1 (highest)	81	76	1060.37	93	146	636.6	0.67 (0.5-0.91)**	0.62 (0.44-0.88)**
2	95	75	1259.94	86	153	563.12	0.55 (0.41-0.74)***	0.55 (0.39-0.77)***
3	39	50	775.14	51	79	646.42	0.75 (0.49-1.14)	0.64 (0.32-1.28)
4 (lowest)	105	84	1253.23	83	106	785.1	0.63 (0.47-0.84)**	0.63 (0.45-0.88)**
Comorbidity[b]								
No	37	37	998.91	28	47	594.66	0.61 (0.37-1.00)	0.62 (0.33-1.16)
Yes	283	249	1137.25	285	436	653.16	0.64 (0.54-0.75)***	0.64 (0.54-0.76)***
Treatment[c]								
No	105	126	832.24	69	167	412.81	0.58 (0.43-0.79)***	0.62 (0.43-0.9)*
Yes	215	160	1346.1	244	316	771.48	0.62 (0.51-0.74)***	0.61 (0.5-0.74)***
Drug used[d]								
No	117	134	872.75	77	147	524.02	0.66 (0.49-0.88)**	0.62 (0.44-0.87)**
Yes	203	152	1337.04	236	336	701.37	0.59 (0.49-0.71)***	0.65 (0.53-0.8)***

Abbreviations: IR, incidence rates per 1000 person-years; CHM, Chinese herbal medicine; DM, diabetes mellitus; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

[a]Adjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity, treatment, and drug used in Cox proportional hazard regression.

[b]Comorbidities included the following: DM, prior myocardial infarction, angina pectoris, arrhythmia, CHF, CKD, upper gastrointestinal bleeding, acute pancreatitis, chronic pancreatitis, intestinal obstruction, sepsis, cachexia, peritonitis, hematemesis, hemoptysis, edema, jaundice, nausea and vomiting, ascites, alcoholism, tobacco use, obesity, hypertension, hyperlipidemia, depression, anxiety, stroke, COPD, liver diseases, and renal dialysis.

[c]Treatment included the following: radiotherapy, chemotherapy, surgery (total pancreatectomy, partial pancreatectomy, and other pancreatectomy).

[d]Drug use included the following: statin, gemcitabine, paclitaxel, tegafur, irinotecan, oxaliplatin, 5-fluorouracil, leucovorin, capecitabine and cisplatin.

*$P < .05$. **$P < .01$. ***$P < .001$.

suffer from gastrointestinal symptoms, which might explain why the formula was prescribed the most often. The other formulas, such as Shen-ling-bai-zhu-san (Ginseng and Bai-zhu Atractylodes Formula) and Ping-wei-san (Cang-zhu Atractylodes and Magnolia Formula) are also often used for gastrointestinal discomforts in TCM.[26,27] Jia-wei-xia-yao-san was also the commonly used formula. It can relieve anxiety and improve insomnia,[28] which are often symptoms that cancer patients experience. Liao et al. also indicated that Jia-wei-xia-yao-san and chai-hu-shu-gan-tang improved survival in patients with liver cancer.[29] In another study, Jia-wei-xia-yao-san was found to be effective in reducing mortality in patients with advanced breast cancer.[30]

The limitations of this study need to be mentioned. The RCPID did not provide detailed information regarding pathological types, staging, and the results of the clinical examinations. In addition, the RCPID did not provide the information about whether the tumors were resectable or not. In order to reduce the bias, we tried to identify the patients who received surgeries of different types of pancreatectomy by treatment codes. In our study, the numbers of the patients who received different types of pancreatectomy in both cohorts were similar. We also included these factors in the analysis of mortality risk to reduce the bias. The second limitation is that the RCPID did not provide the data about lifestyles, such as smoking, alcohol drinking, or food

Table 4. Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With the Cumulative Use (in Days) of Chinese Herbal Medicine Among Patients With Pancreatic Cancer.

No. of CHM Days	n	Death Events (n = 661)	Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
			Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]
Non-CHM user	386	320	1.00 (reference)	1.00 (reference)	—	—
CHM user (CHM ≥30 days)						
30-90 days	238	204	0.87 (0.73-1.04)	0.89 (0.74-1.07)	1.00 (reference)	1.00 (reference)
90-180 days	79	63	0.54 (0.41-0.70)***	0.56 (0.42-0.75)***	0.57 (0.43-0.76)***	0.54 (0.39-0.74)***
>180 days	69	46	0.31 (0.23-0.43)***	0.33 (0.24-0.45)***	0.31 (0.23-0.44)***	0.26 (0.18-0.37)***
P for trend			<.0001	<.0001	<.0001	<.0001

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval.
[a]Crude HR represents relative hazard ratio.
[b]Adjusted HR represents adjusted hazard ratio: mutually adjusted for CHM use, age, sex, urbanization level, comorbidity (as in list of Table 2), treatment (as in list of Table 2), and drug used (as in list of Table 2) in Cox proportional hazard regression.
*$P < .05$. **$P < .01$. ***$P < .001$.

Table 5. Hazard Ratios and 95% Confidence Intervals of Mortality Risk Associated With the Use of Most Common Chinese Herbal Medicine for Patients With Pancreatic Cancer.

CHM Prescription	Mortality		Hazard Ratio (95% CI)	
	n	No. of Events	Crude[a]	Adjusted[b]
Non-CHM user	386	320	1.00 (reference)	1.00 (reference)
CHM user				
Single herbs[c]				
Bai-hua-she-she-cao; Herba Oldenlandiae; *Hedyotis diffusa* Spreng	112	90	0.62 (0.49-0.78)***	0.69 (0.53-0.90)**
Shen-qu; Medicated Leaven; *Massa Medicata Fermentata*	91	73	0.61 (0.47-0.79)***	0.60 (0.45-0.79)***
Huang-qin; Radix Scutellariae; *Scutellaria baicalensis* Georgi	91	70	0.63 (0.48-0.81)***	0.72 (0.54-0.96)*
Ban-zhi-lian; Herba Scutellariae Barbatae; *Scutellaria barbata* D Don	89	75	0.61 (0.47-0.79)***	0.68 (0.51-0.90)**
Dan-shan; Radix Salviae Miltiorrhizae; *Salvia miltiorrhiza* Bunge	80	61	0.50 (0.38-0.66)***	0.55 (0.40-0.74)***
Huang-qi; Radix Astragali; *Astragalus membranaceus, Astragalus henryi, Astragalus hoantchy*	80	62	0.59 (0.45-0.78)***	0.65 (0.48-0.88)**
Chai-hu; Radix Bupleuri; *Buplerurm chinense* DC, *Bupleurum scorzonerifolium* Willd.	76	57	0.61 (0.46-0.81)***	0.70 (0.52-0.96)*
Da-huang; Radix et Rhizoma Rhei; *Rheum palmatum* L., *R tanguticum* Maxim et Reg, *R officinale* Baill.	75	62	0.79 (0.60-1.04)	0.88 (0.66-1.18)
Xiang-fu; Cyperus Rhizome; *Cyperus rotundus* L.	59	40	0.46 (0.33-0.65)***	0.46 (0.32-0.65)***
Hai-piao-xiao; Os Sepiae seu Sepiellae; *Sepia pharaonis, Sepia maindroni* de Rochedbrune, *Sepia esculenta* Hoyle	39	29	0.57 (0.39-0.84)**	0.59 (0.39-0.88)*
Chinese herbal formulas[d]				
Xiang-sha-liu-jun-zi-tang; Costus and Chinese Amomum Combination	106	83	0.63 (0.49-0.80)***	0.72 (0.55-0.94)*
Shen-ling-bai-zhu-san; Ginseng and Bai-zhu Atractylodes Formula	87	70	0.61 (0.47-0.79)***	0.65 (0.49-0.87)**
Ping-wei-san; Cang-zhu Atractylodes and Magnolia Formula	85	67	0.61 (0.47-0.80)***	0.66 (0.49-0.88)**
Xiao-chai-hu-tang; Minor Bupleurum Decoction	85	72	0.66 (0.51-0.86)**	0.71 (0.54-0.95)*
Gui-pi-tang; Ginseng and Longan Combination	76	66	0.67 (0.51-0.87)**	0.67 (0.50-0.90)**
Jia-wei-xia-yao-san; Bupleurum & Three Peony Formula	71	56	0.55 (0.41-0.73)***	0.61 (0.44-0.85)**
Ban-xia-xie-xin-tang; Pinellia Combination	63	52	0.60 (0.45-0.81)***	0.65 (0.47-0.90)**
Bao-he-wan; Tangerine and Chinese Hawthorn Formula	61	49	0.66 (0.49-0.90)**	0.74 (0.53-1.04)
Chai-hu-shu-gan-tang; Bupleurum and Cyperus Formula	55	35	0.42 (0.30-0.60)***	0.45 (0.31-0.65)***
Huo-hsiang-cheng-chi-San; Patchouli Formula	34	23	0.44 (0.29-0.68)***	0.50 (0.31-0.79)**

Abbreviation: CHM, Chinese herbal medicine.
[a]Crude HR represents relative hazard ratio.
[b]Adjusted HR represents adjusted hazard ratio: mutually adjusted for site-CHM use, age, sex, urbanization level, comorbidity (as in the list of Table 2), treatment (as in the list of Table 2) and drugs used (as in the list of Table 2) in Cox proportional hazard regression.
[c]Single herbs are listed in pin-yin name, Chinese *Materia Medica* name, and botanical name.
[d]Chinese herbal formulas are listed in pin-yin name and English name.
*$P < .05$. **$P < .01$. ***$P < .001$.

and dietary factors. We have tried our best to acquire the information of illnesses resulting from these personal habits and lifestyles. Patients diagnosed as having alcoholism, tobacco use, or obesity were similar in both cohorts (Table 1). It is also important to mention that only randomized controlled clinical trials can prove definite clinical efficacy. Our nationwide matched-cohort study can provide some hints for the design of future clinical trials.

Conclusion

In summary, adjunctive Chinese herbal medicine may have benefits in reducing mortality rate in pancreatic cancer patients. Bai-hua-she-she-cao and Xiang-sha-liu-jun-zi-tang appeared to be the most commonly used single herb and Chinese herbal formula for the treatment of pancreatic cancer patients. Future pharmacological investigations or clinical trials to validate these findings are warranted.

Authors' Note

This study was based in part on data from the National Health Insurance Research Database, provided by the National Health Insurance Administration, Ministry of Health and Welfare, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

Declaration of Conflicting Interests

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