


The Association Between Different Patterns of Traditional Chinese Medicine Treatment and All-Cause Mortality Among Cancer Patients

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Shao-Yi Lu, MD¹, Jian-Jung Chen, MD, PhD², Jiann-I Pan, PhD³,
Zi-Xuan Fu, MS⁴, Jung-Lun Wu, MS¹, and Tsung-Cheng Hsieh, PhD¹

Abstract

Background: Cancer patients receiving Western medical treatment, frequently seek Traditional Chinese Medicine (TCM) to alleviate adverse effects and prolong survival. **Objective:** This study evaluated the association between the use of TCM and cancer survival rate. Research into the effect of TCM on patient survival is limited, this analysis focused on 3 patterns of TCM use. **Methods:** Three retrospective cohorts with different patterns of TCM use were selected from the National Health Insurance Research Database of Taiwan and analyzed. Patients with newly diagnosed cancer between 1997 and 2012 were classified into groups of prediagnosis, postdiagnosis, and continuous TCM use associated with awareness of cancer diagnosis. All demographic and clinical data were analyzed. **Results:** After propensity score matching, longevity of the postdiagnosis and continuous TCM user was significantly longer than the non-TCM user. The adjusted hazard ratios of death in postdiagnosis and continuous TCM use groups (0.59 and 0.61, respectively) were lower than the non-TCM use group. **Conclusion:** The analysis suggests that cancer patients using TCM in conjunction with Western medical treatment exhibited a higher survival rate than patients not using TCM treatment.

Keywords

malignancy, Chinese herbal products, traditional Chinese medicine, mortality rate, propensity score, hazard ratio

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Introduction

Incidences of all cancer types have been increasing on a global basis. Approximately 14 million newly diagnosed cases were recorded in 2012.¹ Globally, the number of new cases of cancer is expected to rise about 70% over the next 2 decades. In Taiwan, there were more than 99 000 patients diagnosed with cancer in 2013; an increase of around 2500 cases from 2012. Cancer is the second leading cause of death in the world, where nearly 1 in 6 deaths is due to cancer. The World Health Organization estimated that 84 million people would die of cancer between 2005 and 2015.²

Successful cancer treatment remains a challenge, not only for improving the survival rates but also for improving the quality of life. Conventional treatments include surgery, chemotherapy, and radiotherapy. Surgical resection is the first-line therapy for most early-stage cancer, while adjuvant therapy such as chemotherapy or radiotherapy are often implemented in the advanced stages.³ Complementary

or alternative medicine (CAM) is one of the few choices for cancer patients to improve quality of life, relieve adverse effects of conventional therapy, and to attempt extending survival time.⁴ The traditional Chinese medicine (TCM) practitioner focuses on changes in the symptoms in conjunction with knowledge of the clinical condition, rather than a single treatment plan or regimen to treat cancer patients. In Taiwan, many patients use TCM to alleviate

¹Institute of Medical Sciences, Tzu-Chi University, Hualien, Taiwan

²Department of Chinese Medicine, Taichung Tzuchi Hospital, Buddhist Tzuchi Medical Foundation, Taichung, Taiwan

³Institute of Medical Informatics, Tzu-Chi University, Hualien, Taiwan

⁴Department of MIS, Taichung Tzuchi Hospital, Buddhist Tzuchi Medical Foundation, Taichung, Taiwan

Corresponding Author:

Tsung-Cheng Hsieh, Institute of Medical Sciences, Tzu-Chi University, No. 701, Sec. 3, Zhongyang Road, Hualien 97004, Taiwan.
Email: tchsieh@mail.tcu.edu.tw



symptoms of both the cancer as well as side effects of conventional treatments.⁵ Recent research indicated more than 60% of children with cancer and more than 10% of adult cancer patients in Taiwan used TCM for their complementary treatment.^{6,7}

The current study accessed the National Health Insurance Research Database (NHIRD) to examine the differences of all-cause mortality between the TCM-use patients and non-TCM-use patients. The National Health Insurance (NHI) program provides insurance coverage to more than 99% of Taiwan's population, and the NHIRD constitutes the usage information of TCM and Western medical treatment of the insured population. TCM therapy has been shown to alleviate the adverse symptoms of conventional treatments such as nausea, vomiting, and fatigue.^{8,9} Other studies have shown conflicting results with regard to the effect of complementary TCM treatment reducing mortality of cancer patients.¹⁰⁻¹⁴

The purpose of this research was to evaluate the effect of adjuvant TCM therapy on survival rate in cancer patients. As research into patient survival and TCM use before or after cancer remains limited, this analysis focused on 3 patterns of TCM use.

Methods

Data Sources

Data were sourced from the NHIRD between 1997 and 2012. The datasets were provided by the Taiwan National Health Research Institute. The NHI is a compulsory health insurance program effective in Taiwan since 1995. TCM services, including herbal medicines, acupuncture, moxibustion, and chiropractic, have been covered by the NHI since 1996. The NHI has extended its coverage to virtually the entire population of Taiwan, ranging from 96.1% to 99.6% since its implementation.¹⁵ The database contains demographic variables, outpatient and inpatient visits, prescription details, and disease diagnoses based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). All cancer patients in the NHI program are registered with catastrophic illness and may then access the NHI approved therapies. This study was approved by the Research Ethics Committee of Hualien Tzu-Chi Hospital in Taiwan (IRB101-98).

Sample Population and Exposure Assessment

Selection criteria for analysis consisted of all patients newly diagnosed with malignancy (ICD-9-CM code: 140-208) from 1997 to 2012. This was refined as patients diagnosed with malignant neoplasm of trachea, bronchus, and lung (ICD-9CM: 162), malignant neoplasm of liver and intrahepatic bile ducts (ICD-9-CM: 155, except patients of liver

transplantation), and malignant neoplasm of colon, rectum, rectosigmoid junction, and anus (ICD-9-CM: 153-154).

The study defined TCM users based on patient frequency of TCM access. The TCM users are divided into 3 cohorts, including postdiagnosis (*B0A1*), prediagnosis (*B1A0*), and continuous (*B1A1*) TCM users. Cohort 1 consisted of a control group (*B0A0*, non-TCM users) and the *B0A1* group, which represented patients who initiated TCM use more than or equal to 6 times post cancer diagnosis within the following 6 months. Individuals who used TCM less than 6 times, who used TCM only before the diagnosis, or initiated TCM 6 months post cancer diagnosis were excluded. Cohort 2 was composed of a control (*B0A0*) and the *B1A0* group consisted of patients who used TCM more than or equal to 6 times within the 6 months prior to cancer diagnosis, but not during conventional cancer therapy. Individuals who used TCM less than 6 times or who used TCM only in the 6-month period prior to cancer diagnosis were excluded. Cohort 3 consisted of a control (*B0A0*) and the *B1A1* group, which consisted of patients who used TCM more than or equal to 6 times not only in the 6-month period prior to diagnosis, but also after the cancer diagnosis. Individuals who used TCM less than 6 times, or no TCM in the 6 months prior to or post diagnosis were excluded.

To reduce potential confounding factors, non-TCM users were selected by propensity score matching for gender, age, Charlson Comorbidity Index (CCI), diabetes, hypertension, hyperlipidemia, insurance premium (represents income level), and conventional therapies including surgery, chemotherapy, and radiotherapy. To avoid the effect of the time gap between the initial cancer diagnosis and TCM treatment, the time from initial diagnosis to TCM treatment was matched between *B0A1* and *B0A0* in cohort 1. For instance, if the enrolled *B0A1* patient used TCM treatment initially 30 days after cancer diagnosis, then the follow-up for a patient in the control group would also begin 30 days after cancer diagnosis. Based on the available sample size, cohort 1 (*B0A1* vs *B0A0*) allowed for a 1:4 case-control ratio, while cohort 2 (*B1A0* vs *B0A0*) and cohort 3 (*B1A1* vs *B0A0*) had a ratio of 1:1. Individuals who had died within 90 days post cancer diagnosis were excluded.

Outcome Assessment and Confounding Variables

The Registry for Catastrophic Illness Patients Database identified primary outcome as mortality from the registry files. Patients were followed from the index date to the date of death, date of withdrawal from the NHI system, or December 31, 2012. The index date was defined as the date of cancer diagnosis, except for the *B0A1* group. The index date of *B0A1* was determined as the date patients incorporated TCM treatment. Confounding variables included

gender, age, CCI, baseline comorbidities, and conventional cancer treatments (surgery, chemotherapy, and radiation therapy). Baseline comorbidities included diabetes mellitus (ICD-9-CM code: 250), hypertension (ICD-9-CM code: 401), and hyperlipidemia (ICD-9-CM code: 272). These diseases were determined by at least 2 outpatient visits or one inpatient visit at least 1 year prior to cancer diagnosis. Data regarding insurance premiums as a representative of economic status were also accessed.

Statistical Analysis

Demographic variables in conjunction with the cancer diagnosis between the cohorts were examined for appropriateness of comparison. The variables with a standard difference of >0.1 were deemed clinically meaningful. Hazard ratios (HRs) between treatment groups were estimated using Cox regression. The Kaplan-Meier method was used to assess the fraction of patients surviving 5-years postdiagnosis. The 2-tailed significance level was set at 0.01 in all statistical tests. All analyses were run using SAS statistical software version 9.3.

Results

Patient Data Selection

The flowchart in Figure 1 illustrates the differentiation criteria and process for categorizing the 3 cohorts. Cohort 1 (*B0A1* vs *B0A0*), cohort 2 (*B1A0* vs *B0A0*), and cohort 3 (*B1A1* vs *B0A0*). Cohort 1 compared postdiagnosis TCM users (*B0A1*) with non-TCM (*B0A0*) users. Cohort 2 represents the comparison of prediagnosis TCM users (*B1A0*) with non-TCM users. Cohort 3 constitutes continuous TCM users (*B1A1*) with non-TCM users. One-to-4 matching was performed for cohort 1 due to the small sample size of the *B0A1* group, whereas for cohorts 2 and 3, one-to-one matching was applied. After matching, 16 250 (3250:13 000), 20 806 (10 403:10 403), and 22 022 patients (11 011:11 011) constituted cohort 1, cohort 2, and cohort 3, respectively.

Baseline Characteristics

The basic characteristics of cohort 1 (*B0A1* vs *B0A0*), cohort 2 (*B1A0* vs *B0A0*), and cohort 3 (*B1A1* vs *B0A0*) are delineated as gender, age, CCI score, baseline comorbidities, and use of conventional treatments (Table 1).

The mean days from initial diagnosis of cancer to TCM treatment was 51 days in cohort 1. The age distribution, gender, comorbidities, CCI, and the percentage of conventional treatments received were not clinically meaningful between the postdiagnosis TCM user (*B0A1*) and non-TCM user (*B0A0*) groups. However, the insurance premium of cohort 1 showed a slight difference (standard difference = 0.13),

and a higher male/female ratio with a greater age distribution in the 40+ years range.

In cohort 2, no clinically meaningful differences were observed between the prediagnosis TCM users (*B1A0*) and the control, regardless of age, gender, comorbidities, insurance premium, or the percentage use of conventional therapies. Similar to cohort 1, there was a greater male to female ratio, and an age distribution where slightly more than 90% of patients were in the 40+ years range. The median survival time was 1.9 years for prediagnosis TCM users (*B1A0*), and 3.4 years for non-TCM users.

In cohort 3, TCM users (*B1A1*) and controls (*B0A0*) showed similar characteristics as cohorts 1 and 2. Slightly more than 90% of patients were in the 40+ years age range. However, a larger portion of female to male patients was observed.

Cancer Type

Survival rates are highly dependent on the type of cancer. The 10 most common types of cancer in Taiwan account for 3 quarters of the mortality rate (Table 2.) In *B0A1* group, the frequency by type was 10.9% lung cancer, 11% liver cancer, 13.4% colorectal cancer, 15.4% breast cancer, and 11.9% oral cancer in *B0A1* group. In *B1A0* group, lung cancer was 18.5%, liver cancer 13.8%, colorectal cancer 13.3%, breast cancer 7.9%, and oral cancer 5.1% in frequency. As well as in *B1A1* group, the frequencies were 8.2% lung cancer, 12.9% liver cancer, 12.7% colorectal cancer, 16.9% breast cancer, and 6.4% oral cancer.

All-Cause Death Incidence

In cohort 1, there were 1105 deaths per 10 725 person-years in the postdiagnosis TCM user (*B0A1*) group; meaning the incidence rate was 103 cases per 1000 person-years. The control had a total 4297 deaths per 43 515 person-years, resulting in an incidence rate of 98.7 cases per 1000 person-years. The incidence ratio was 1.0 and exhibited no statistically significant different incidence of mortality in post-cancer diagnosis TCM users (*B0A1*) to non-TCM users (Table 3).

In cohort 2, a total 5574 deaths occurred in the prediagnosis TCM users (*B1A0*), and the incidence rate was 230.9 cases per 1000 person-years. The incidence ratio of 1.4 demonstrated a statistically significant higher incidence of mortality in prediagnosis TCM users (*B1A0*) compared with the controls.

In the continuous TCM users (*B1A1*) of the third cohort, the incidence rate was 69.3 per 1000 person-years, and the incidence rate of the control group was 163.2 per 1000 person-years. The incidence ratio of 0.7 exhibits a lower incidence of mortality in continuous TCM users (*B1A1*), and was statistically significant compared with the controls.

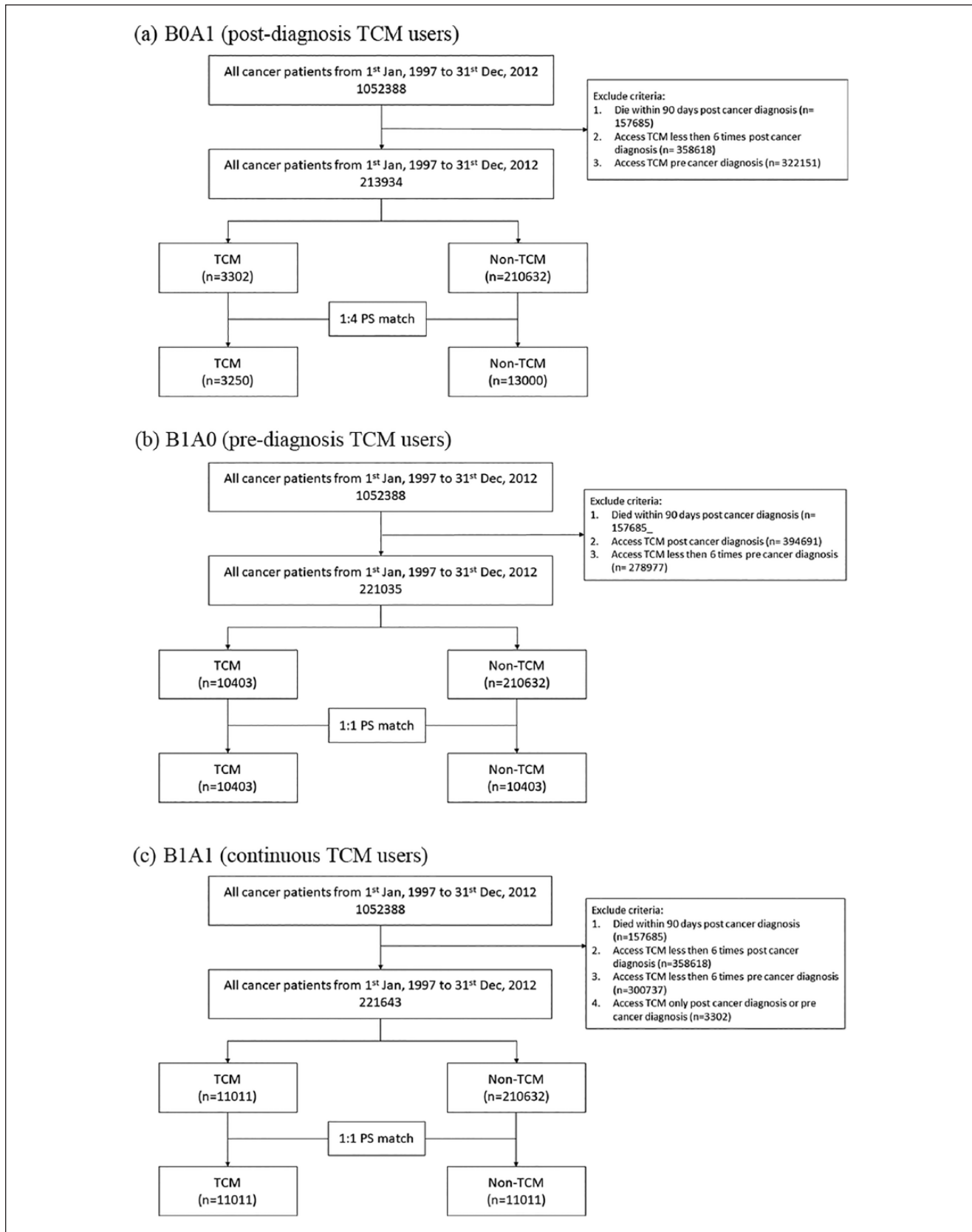


Figure 1. Flowchart of study design: (a) postdiagnosis, (b) prediagnosis, (c) continuous traditional Chinese medicine (TCM) users.

Table 1. Demographic Characteristics of All Cancer Patients by Pattern of TCM Treatment Use.

Variables	TCM (B0A1)	Control (B0A0)	Standardized Difference	TCM (B1A0)	Control (B0A0)	Standardized Difference	TCM (B1A1)	Control (B0A0)	Standardized Difference
N	3250	13 000		10 403	10 403		11 011	11 011	
Gender, n (%)									
Female	1425 (43.8)	5716 (44)	0.00	4997 (48)	5030 (48.4)	0.01	6178 (56.1)	6130 (55.7)	-0.01
Male	1825 (56.2)	7284 (56)		5406 (52)	5373 (51.6)		4833 (43.9)	4881 (44.3)	
Age (years), mean ± SD	56.0 ± 15.0	55.7 ± 14.6	0.02	61.8 ± 15.0	61.9 ± 16.4	0.00	59.9 ± 14.1	59.8 ± 17.1	0.00
≤40, n (%)	418 (12.9)	1649 (12.7)	0.00	827 (7.9)	903 (8.7)	0.05	904 (8.2)	1268 (11.5)	0.16
Age group (years), n (%)									
41-50	730 (22.5)	3053 (23.5)		1501 (14.4)	1413 (13.6)		1966 (17.9)	1687 (15.3)	
51-60	768 (23.6)	3247 (25)		2080 (20)	1988 (19.1)		2505 (22.7)	2258 (20.5)	
61-70	697 (21.4)	2675 (20.6)		2394 (23)	2340 (22.5)		2593 (23.5)	2330 (21.2)	
>70	637 (19.6)	2376 (18.3)		3601 (34.6)	3759 (36.1)		3043 (27.6)	3468 (31.5)	
CCI, mean ± SD	5.9 ± 3.4	5.8 ± 3.4	0.03	7.6 ± 3.7	7.6 ± 3.7	0.00	6.0 ± 3.1	5.9 ± 3.3	0.01
Diabetes mellitus, n (%)	749 (23)	2930 (22.5)	0.01	2601 (25)	2553 (24.5)	0.01	3423 (31.1)	3381 (30.7)	0.01
Hypertension, n (%)	1340 (41.2)	5295 (40.7)	0.01	5049 (48.5)	5043 (48.5)	0.00	6043 (54.9)	6111 (55.5)	-0.01
Hyperlipidemia, n (%)	772 (23.8)	2988 (23)	0.02	2632 (25.3)	2622 (25.2)	0.00	4168 (37.9)	4125 (37.5)	0.01
Chemotherapy, n (%)	1452 (44.7)	5811 (44.7)	0.00	4494 (43.2)	4483 (43.1)	0.00	3057 (27.8)	3029 (27.5)	0.01
Radiation therapy, n (%)	886 (27.3)	3567 (27.4)	0.00	2766 (26.6)	2674 (25.7)	0.02	1983 (18)	1951 (17.7)	0.01
Insurance premium, n (%)									
Dependent	855 (26.3)	3054 (23.5)	0.13	3261 (31.3)	3087 (29.7)	0.08	3210 (29.2)	3058 (27.8)	0.04
0-19 100	759 (23.4)	3448 (26.5)		2314 (22.2)	2656 (25.5)		2466 (22.4)	2586 (23.5)	
19 100-42 000	1350 (41.5)	5690 (43.8)		4407 (42.4)	4247 (40.8)		4697 (42.7)	4775 (43.4)	
>42 000	286 (8.8)	808 (6.2)		421 (4)	413 (4)		638 (5.8)	592 (5.4)	
Days from initial diagnosis to treatment, mean ± SD	51.4 ± 38.1	51.6 ± 38.1	-0.01						
Median survival (years)	NA ^a	NA ^a		1.9	3.4		NA ^a	NA ^a	

Abbreviations: TCM, traditional Chinese medicine; CCI, Charlson Comorbidity Index; NA, not available.

^aNot available because the corresponding survival probability was greater than 50% during the whole 5-year observation period.

Table 2. The 10 Leading Causes of Cancer Death in Taiwan.^a

Variables	TCM (B0A1)	Control (B0A0)	TCM (B1A0)	Control (B0A0)	TCM (B1A1)	Control (B0A0)
Cancers of trachea, bronchus, and lung	355 (10.9)	1523 (11.7)	1928 (18.5)	1466 (14.1)	903 (8.2)	1028 (9.3)
Cancers of liver and intrahepatic bile ducts	357 (11)	1815 (14)	1433 (13.8)	1163 (11.2)	1422 (12.9)	1247 (11.3)
Cancers of colon, rectum, and anus	435 (13.4)	1366 (10.5)	1383 (13.3)	1665 (16)	1403 (12.7)	1630 (14.8)
Cancer of breast (female)	502 (15.4)	1587 (12.2)	822 (7.9)	1014 (9.7)	1861 (16.9)	1316 (12)
Cancer of oral cavity	386 (11.9)	1409 (10.8)	528 (5.1)	842 (8.1)	700 (6.4)	921 (8.4)
Cancer of prostate	104 (3.2)	243 (1.9)	325 (3.1)	328 (3.2)	695 (6.3)	403 (3.7)
Cancer of stomach	173 (5.3)	634 (4.9)	566 (5.4)	661 (6.4)	308 (2.8)	542 (4.9)
Cancer of pancreas	52 (1.6)	222 (1.7)	273 (2.6)	185 (1.8)	56 (0.5)	149 (1.4)
Cancer of esophagus	57 (1.8)	439 (3.4)	230 (2.2)	260 (2.5)	71 (0.6)	181 (1.6)
Cancer of ovary	64 (2)	225 (1.7)	146 (1.4)	177 (1.7)	203 (1.8)	188 (1.7)
Others	765 (23.5)	3537 (27.2)	2769 (26.6)	2642 (25.4)	3389 (30.8)	3406 (30.9)

Abbreviation: TCM, traditional Chinese medicine.

^aData are presented as number (percentage).

Table 3. Incidence (1000 Person-Years) and Incidence Ratio of Mortality for Cancer Patients With and Without TCM Treatment.

Comparison	TCM			Control (B0A0)			Ratio ^c (99% CI)
	PY	Event ^a	Rate ^b (99% CI)	PY	Event ^a	Rate ^b (99% CI)	
B0A1 vs B0A0	10 725.0	1105	103.0 (95.0–111.0)	43 515.0	4297	98.7 (94.9–102.6)	1.0 (1.0–1.1)
B1A0 vs B0A0	24 145.0	5574	230.9 (222.9–238.8)	28 645.0	4674	163.2 (157.0–169.3)	1.4 (1.3–1.5) ^d
B1A1 vs B0A0	40 895.0	2832	69.3 (65.9–72.6)	3602.0	3807	105.7 (202.3–1110.1)	0.7 (0.6–0.7) ^d

Abbreviations: TCM, traditional Chinese medicine; PY, total person-years.

^aEvent indicates number of events.

^bRate indicates incidence.

^cRatio indicates incidence ratio.

^dStatistically significant at $P < .01$.

Table 4. HR for All Causes Mortality in Patients With Cancer Receiving TCM Treatment in the Stratification of After (B0A1), Before (B1A0), and Continuous (B1A1) Use Pattern.

Variables	B0A1		B1A0		B1A1	
	HR (99% CI)	<i>P</i>	HR (99% CI)	<i>P</i>	HR (99% CI)	<i>P</i>
Group	0.59 (0.54–0.65)	<.001	1.68 (1.60–1.72)	<.001	0.61 (0.58–0.66)	<.001
Age, years	1.01 (1.01–1.02)	<.001	1.01 (1.01–1.02)	<.001	1.02 (1.01–1.02)	<.001
Gender	1.87 (1.73–2.01)	<.001	1.27 (1.21–1.34)	<.001	1.52 (1.43–1.63)	<.001
CCI	1.14 (1.13–1.15)	<.001	1.11 (1.10–1.12)	<.001	1.17 (1.15–1.18)	<.001

Abbreviations: HR, hazard ratio; TCM, traditional Chinese medicine; CCI, Charlson Comorbidity Index; CI, confidence interval.

Hazard Ratio and 5-Year Survival

A Cox proportional hazard model was used to adjust the patient covariate variable, and the HRs for mortality are shown in Table 4. Compared with non-TCM users, postdiagnosis patients (B0A1) and continuous (B1A1) TCM users showed a lower risk of death, 0.59 (HR 99% confidence interval (CI) = 0.54–0.65, $P < .001$) and 0.61 (HR 99%

CI = 0.58–0.66, $P < .001$), respectively. Pre-cancer diagnosis TCM users (B1A0) showed a high risk of death at 1.68 (HR 99% CI = 1.60–1.72, $P < .001$). Moreover, advanced age, male gender, and high CCI score were significantly related to an increased risk of death from cancer.

The Kaplan-Meier survival curves for both the postdiagnosis TCM users (B0A1, Figure 2a), cohort 1, and the continuous TCM use group (B1A1, Figure 2c), cohort 3 exhibits

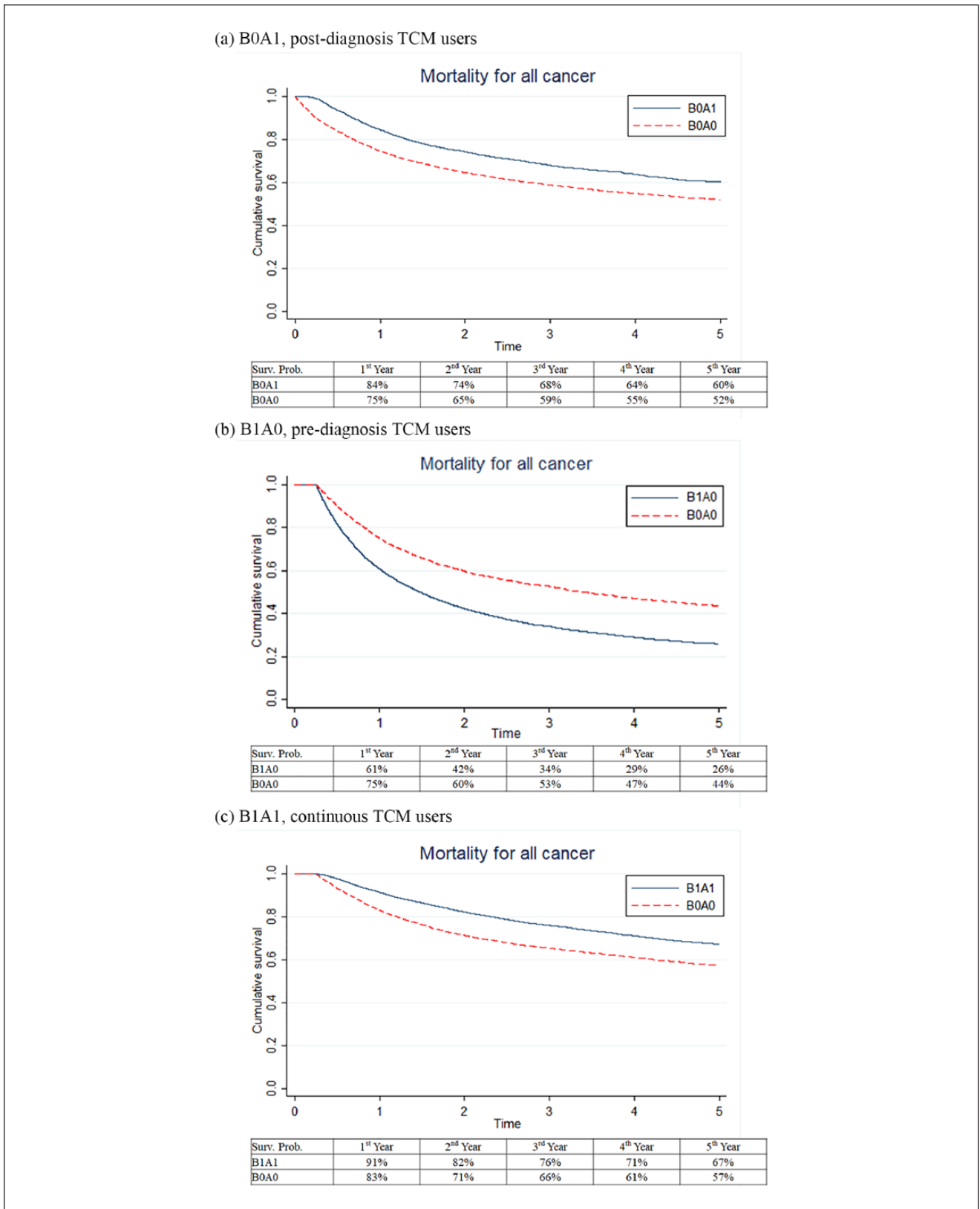


Figure 2. Kaplan-Meier survival curves for cancer patients receiving traditional Chinese medicine (TCM) treatment use stratified by use pattern: (a) postdiagnosis, (b) prediagnosis, (c) continuous TCM users.

Table 5. Subgroup Analysis for HR of Death in Patients With Different Types of Cancer Receiving TCM Treatment.

Type of Cancer	B0A1		B1A0		B1A1	
	TCM:Control	HR (99% CI)	TCM:Control	HR (99% CI)	TCM:Control	HR (99% CI)
Lung cancer	284:1136	0.70 (0.56–0.87) ^a	1842:1842	1.31 (1.18–1.45) ^a	784:784	0.78 (0.66–0.94) ^a
Liver cancer	309:1236	0.73 (0.59–0.92) ^a	1378:1378	1.49 (1.32–1.70) ^a	1296:1296	0.56 (0.48–0.65) ^a
Colorectal cancer	391:1564	0.83 (0.65–1.07)	1315:1315	1.44 (1.23–1.69) ^a	1299:1299	0.77 (0.64–0.94) ^a

Abbreviations: HR, hazard ratio; TCM, traditional Chinese medicine; CI, confidence interval.

^aStatistically significant at $P < .01$.

better survival curves than controls without the use of TCM (log-rank test: $P < .05$). The 5-year survival probabilities for cohort 1 were 60% for postdiagnosis TCM users (B0A1) and 52% for the control. For cohort 3, the 5-year survival probabilities were 67% for continuous TCM users (B1A1) and 57% for non-TCM users. However, compared with the non-TCM users, the prediagnosis TCM users (B1A0, Figure 2), cohort 2 exhibited a lower survival estimate, for those who ceased TCM use after the cancer diagnosis. The 5-year survival probability of the prediagnosis TCM users (B1A0) was 26%, and 44% for the control.

Subgroup Analysis

To further investigate the effect of TCM on patients, 3 cancer types were selected to conduct subgroup analysis. Cancer of the trachea, bronchus, and lung (lung cancer); cancer of the liver and intrahepatic bile ducts (liver cancer); and cancer of the colon, rectum, and anus (colorectal cancer) were chosen as these were the 3 leading causes of cancer death in Taiwan in 2016. Propensity score matching was performed with 1:4 case-control ratio selected for the B0A1 group, and 1:1 ratio for both the B1A0 and the B1A1 groups.

Among lung cancer patients, there were 284, 1842, and 784 cases using TCM enrolled in the B0A1, the B1A0, and the B1A1 groups, respectively (Table 5). The HR of B0A1 was 0.70 (99% CI = 0.56–0.87, $P < .001$), HR of B1A1 was 0.78 (99% CI = 0.66–0.94, $P < .001$), and an increased risk of death from B1A0 (HR = 1.31, 99% CI = 1.18–1.45, $P < .001$) group after adjusting for covariates. For liver cancer patients, risk of death was lower in both B0A1 (HR = 0.73, 99% CI = 0.59–0.92, $P < .001$) and B1A1 (HR = 0.56, 99% CI = 0.48–0.65, $P < .001$) groups, and higher in B1A0 (HR = 1.49, 99% CI = 1.32–1.70, $P < .001$). The results of the colorectal cancer subgroup analysis showed reduced risk of death in cohorts 1 and 3 (B0A1 [HR = 0.83, 99% CI = 0.65–1.07, $P = .057$], B1A1 [HR = 0.77, 99% CI = 0.64–0.94, $P < .001$]), but a higher risk in cohort 2, B1A0 (HR = 1.44, 99% CI = 1.23–1.69, $P < .001$).

Discussion

The use of CAM for cancer is widespread and the interest in pursuing this form of adjunct therapy has increased globally from 25% to almost 50%.¹⁶ In the United States, 10% to more than 60% of cancer patients have used CAM.¹⁷ In Canada, more than 80% of all women with breast cancer use CAM.¹⁸ In Germany, 50.1% of breast cancer patients, and 44% of gynecological cancer patients used CAM.¹⁹

TCM modalities in conjunction with standard western medical practice include acupuncture and herbalism. TCM has long been accepted in Taiwan and covered by the NHI program since 1996. Previous research demonstrated that cancer patients use TCM as their preferred CAM therapy in Taiwan.^{7,20–23} Therefore, the TCM therapy has been the most accepted and dominant option among cancer patients who received CAM treatment.

The effect of TCM treatment on patient survival of various cancer types has been reported for gastric cancer,¹⁰ liver cancer,²² head and neck cancer,²³ breast cancer,²⁴ lung cancer,^{12,25,26} prostate cancer,¹¹ myeloid leukemia,²¹ and pancreatic cancer.²⁷ The literature to date supports the effectiveness of TCM for alleviating chemotherapy, radiotherapy, and surgery-induced side effects. However, there is limited evidence to suggest TCM efficacy as a treatment for cancer.^{13,14,28} The present research suggests that TCM treatment is positively associated with increased cancer survival rates. Multiple mechanisms of action are associated with TCM in cancer treatment, including (1) immunomodulation,^{29,30} (2) altered inflammation response,^{31,32} (3) angiogenesis suppression,^{33–35} and (4) microenvironment modification.³⁶ A significant proportion of TCM research focuses on botanical preparations; however, TCM is often a combination of techniques that have been shown to alter immune response and anti-inflammatory effect.^{37–40} Due to the multiplicity of interventions available within TCM, this study focused on botanical/herbal medication and acupuncture.

The usage pattern of TCM and its association with survival rates has not previously been investigated. This is the first nationwide cohort study to assess the association between survival rate of cancer patients and TCM usage

pattern. This retrospective cancer study is a population-based TCM pharmacoepidemiological analysis: the primary finding is that postdiagnosis and continuous TCM treatment use are associated with a significant decrease in HR of all cancer types. This finding remained true even with the exclusion of individuals expiring within 90 days post cancer diagnosis. The crude HRs were statistically significant, and remained consistent after adjusting for age, gender, comorbidities, monthly income, and use of conventional therapy. Patients from TCM-use groups of the B0A1 (post-diagnosis use) and the B1A1 (continuous use) exhibited a lower HR when compared with non-TCM users within a 5-year follow-up period.

Of particular interest is the B1A0 (prediagnosis use) group, which exhibited a higher risk of mortality than the control group. This may be due to delayed diagnosis in the B1A0 group, or an artefact of poor compliance to follow-up. Consistent outpatient TCM treatments are crucial for TCM treatment to be effective, as such, loss of follow-up is a plausible reason for the increased mortality. The potential for positive effect via TCM intervention is dependent on the duration of the therapy and skill of the practitioner. While TCM is not a proven curative therapy for any cancers, the extended therapy may potentiate a positive outcome due to placebo effect. Late-stage colon cancer patients reported protective effects of TCM⁴¹; however, no sustained effect on survival was noted. Cancer prevention using TCM is supported by multiple fields of research including: cell studies, animal studies, and clinical trials.^{42,43} Botanical extracts, herbal preparations, multiple antioxidant sources, including regular ginseng ingestion prior to cancer diagnosis was associated with significantly improved overall and disease-free survival.⁴⁴ The literature is vast with studies demonstrating the positive effect of TCM treatment. TCM appears to have a significant impact in the prevention of relapse, metastasis, radiation injury prevention, chemotherapy-induced adverse effects, and other negative pharmacologically induced side effects.⁴⁵ The chemical complexity of TCM preparations must not be underestimated, as the compounds encompassing TCM prescriptions, in conjunction with acupuncture remains largely unknown. The current research suggests increased longevity for patients that accessed TCM prior to cancer diagnosis and continued in conjunction with western medical interventions. A similar positive effect exists for postdiagnosis TCM treatment and is comparable to findings in other studies.^{7,21,25} This analysis of the national cancer data suggests TCM treatment is a viable therapy for reducing mortality of cancer patients. Based on the current analysis, and subgroup investigation, TCM appears to be more effective for treating specific cancers. The data implies that TCM shows the greatest efficacy for treating liver cancer, followed by lung cancer and colorectal malignancy. TCM enhanced survival in liver, lung, and colorectal malignancy patients for both

postdiagnosis and continuous TCM use groups. A similar effect was found in all-cancer analysis. This study showed that patients undergoing chemotherapy or radiotherapy were at higher risk of mortality, which is in agreement with other research. In general, patients receiving either of these treatment modalities will exhibit advanced disease stages. Patients with stage III-IV cancer undergoing chemotherapy are at greater risk of suffering adverse effects due to immunosuppression. Opportunistic infections as a result of cancer treatment, and subsequent side effects may contribute to cancer progression and mortality.⁴⁶⁻⁴⁸ Notwithstanding the adverse effects of conventional treatment, the higher mortality rate may be associated with advanced stages of disease at the time of diagnosis. This study found that a higher CCI corresponded with higher risk of mortality. By contrast, hypertension and hyperlipidemia showed a lower risk of death. Based on the NHI database, patients with poor health status, regular exercise, or chronic disease were more likely to access TCM clinics.⁴⁹ The TCM treatment of comorbidities may explain the more frequent access to TCM clinical services and its beneficial effects.

This research is based on the NHIRD data from the NHI program, which covers over 99% of the Taiwanese population. This ensures that the study is representative of the general population of Taiwan. Unfortunately, several limitations exist, which may account for some of the conflicting results. Some datasets were not available, or were nonexistent, so that potential confounding variables remain unknown. Because of access restrictions to the NHI database or limited data, variables including performance status of patients, biochemical data, and cancer clinical stage, were not available. Patient medication compliance data were not accessible.

Conclusions

TCM adjuvant treatment appears to benefit cancer patients of all ages. Longevity and survival rates increased for all cancer types, regardless of the stage of cancer or Western medical intervention. The current study provides a strong basis for further research into the biochemical mechanisms of TCM therapy for cancer patients

Author Contributions

Shao-Yi Lu and Tsung-Cheng Hsieh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Shao-Yi Lu, Tsung-Cheng Hsieh
Acquisition of data: Jiann-I Pan, Zi-Xuan Fu, Jung-Lun Wu, Tsung-Cheng Hsieh

Analysis and interpretation of data: Shao-Yi Lu, Jain-Jung Chen, Tsung-Cheng Hsieh

Statistical analysis of data: Jung-Lun Wu, Tsung-Cheng Hsieh

Drafting the article: Shao-Yi Lu

Revising the article critically for important intellectual content: Shao-Yi Lu and Tsung-Cheng Hsieh.

Declaration of Conflicting Interests

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