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Original Article

Traditional Chinese medicine attenuates hospitalization and mortality risks in diabetic patients with carcinoma *in situ* in Taiwan

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ABSTRACT

Background: Diabetic patients are at high risk of developing cancer. Traditional Chinese medicine (TCM) has become increasingly popular as an adjuvant treatment for patients with chronic diseases, and some studies have identified its beneficial effect in diabetic patients with cancer. The purpoes of this study was to outline the potential of TCM to attenuate hospitalization and mortality rates in diabetic patients with carcinoma *in situ* (CIS).

Methods: A total of 6,987 diabetic subjects with CIS under TCM therapy were selected from the National Health Insurance Research Database of Taiwan, along with 38,800 of 1:1 sex-, age-, and index year-matched controls without TCM therapy. Cox proportional hazard analysis was conducted to compare hospitalization and mortality rates during an average of 15 years of follow-up.

Results: A total of 3,999/1,393 enrolled-subjects (28.62%/9.97%) had hospitalization/mortality, including 1,777/661 in the TCM group (25.43%/9.46%) and 2,222/732 in the control group (31.80%/10.48%). Cox proportional hazard regression analysis showed a lower rate of hospitalization and mortality for subjects in the TCM group (adjusted HR=0.536; 95% CI=0.367–0.780, $P<0.001$; adjusted HR=0.783; 95% CI=0.574–0.974, $P = 0.022$). Kaplan-Meier analysis showed that the cumulative risk of hospitalization and mortality in the case and control groups was significantly different (log rank, $P<0.001$ and $P = 0.011$, respectively).

Conclusions: Diabetic patients with CIS under TCM therapy were associated with lower hospitalization and mortality rates compared to those without TCM therapy. Thus, TCM application may reduce the burden of national medical resources.

1. Introduction

The International Diabetes Federation Diabetes Atlas estimated that the prevalence of diabetes among individuals aged 18–99 years would increase from 451 million in 2017 to 693 million by 2045.[1] Adults with type 2 diabetes mellitus (T2DM) also have an increased risk of cancer development[2] and cancer-related death compared to those without.[3] T2DM and cancer share many risk

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factors, such as aging, obesity, diet, and physical inactivity.[4, 5] Increased risk of death in patients with T2DM is specifically associated with cancers of the lung, breast, liver, and colorectum.[6, 7]

Although diabetes treatment has improved recently, patients with T2DM still have a high risk of cancer. In traditional Chinese medicine (TCM), herbs have played a significant role as an alternative and complementary medicine for centuries throughout Asian countries.[8] In Taiwan, TCM is popular as an adjuvant therapy for cancer, even in patients under standard therapy; particularly, it has been reported that various TCMs can control glucose metabolism by regulating the insulin signal transduction pathway in cancer patients with T2DM comorbidity.[9, 10]

Auxiliary TCM therapy has shown obvious benefit for cancer, diabetes, and comorbid patients in previous studies; in fact, it has been reported to reduce the risk or incidence of colorectal cancer and hepatocellular carcinoma. [11, 12] Recently, TCM has become increasingly popular as an adjuvant treatment for patients with chronic diseases[13, 14]; however, the relationship between TCM and the risk of carcinoma *in situ* (CIS) in patients with T2DM remains unknown. The aim of this study was to determine the potential of TCM therapy to attenuate the rate of hospitalization or mortality in T2DM patients with CIS, by using data from the Taiwan National Health Insurance Research Database (NHIRD) as a nationwide health insurance database.

2. Methods

2.1. Data sources

Diabetic patients with CIS were recruited from the outpatient Longitudinal Health Insurance Database (LHID) in Taiwan. We used data from the NHIRD to investigate whether TCM treatment can reduce hospitalization or mortality rate in diabetic patients with CIS over a 15-year period (2000–2015). The National Health Insurance (NHI) program was launched in Taiwan in 1995. As of June 2009, it had signed contracts with 97% of medical providers in Taiwan, with approximately 23 million beneficiaries, accounting for 99% of the total population in Taiwan.[15] The NHIRD uses codes from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to record diagnoses.[16] All diagnoses of T2DM and CIS were made by a board-certified medical specialist. The Bureau of NHI randomly reviews the records of one in 100 ambulatory care visits and one in 20 hospitalization claims to verify the accuracy of the diagnoses.[17] Multiple studies have proven the accuracy and effectiveness of NHIRD diagnosis.[18, 19]

2.2. Study design and sampled participants

Our study had a retrospective, paired cohort design. Diagnoses of T2DM and CIS were selected according to codes ICD-9-CM 230.XX-234.XX (CIS) and ICD-9-CM 250.XX (T2DM), respectively, from January 1, 2000, to December 31, 2015. In addition, according to these ICD-9-CM codes, each enrolled patient had at least three outpatient visits for TCM therapy during the study period. Patients who received TCM therapy for less than thrice and those younger than 18 years were excluded.

The covariates include the Chalson Comorbidity Index (CCI) minus T2DM, gender, age, geographic area of residence (northern, central, southern, and eastern Taiwan), and level of residential urbanization (levels 1 to 4). The level of urbanization was determined according to population size and development level. Level 1 urbanization is defined as having a population of $>$ 1250,000 and a status of economic, cultural, metropolitan, and political development. Level 2 urbanization is defined as having a population of 500,000 to 1249,999 and an important role in the political system, culture, and economy. Urbanization levels 3 and 4 were defined as having populations of 149,999–499,999 and $<$149,999, respectively.[20]

2.3. Outcome measures

All study participants were tracked from the index date until hospitalization or mortality under the NHI program before the end of 2015.

2.4. Statistical analysis

All statistical analyses were performed using the SPSS software version 22 for Windows (SPSS Inc., Chicago, IL, USA). Chi-square tests and *t*-tests were used to evaluate the distributions of categorical and continuous variables, respectively. Multivariate Cox proportional hazards regression analysis was used to determine the risk of mortality or hospitalization among diabetic patients with CIS who received TCM therapy. Statistical analysis results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Differences in the risk of hospitalization or mortality between the groups with and without TCM therapy were estimated using the Kaplan-Meier method and log-rank test. Statistical significance was determined using a two-tailed test with a p value less than 0.05.

2.5. Ethics

Our research was conducted in accordance with the ethical code of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of the Tri-Service General Hospital (TSGH) approved our study and waived the need for individual written informed consent (TSGH IRB No.2–105–05–082).

3. Results

A total of 61,307 patients were enrolled in this study. After the exclusion of 14,482 patients, 46,825 subjects with cancer and T2DM were screened. From these patients, 8025 patients were assigned to the TCM therapy case group. Furthermore, we excluded 1038 patients who visited less than 3 times. From 38,800 patients of 1:1 sex-, age-, and index year-matched subjects without TCM therapy, 6987 were allocated to the comparison cohort (control) group (Fig. 1).

Overall, subjects with T2DM and CIS under TCM therapy were associated with lower rates of hospitalization and mortality compared to those without TCM therapy (adjusted HR=0.536, 95% CI=0.367–0.780, $P<0.001$; adjusted HR=0.783, 95% CI=0.574–0.974, $P = 0.022$). Fig. 2 and 3 show the results of Kaplan-Meier analysis for the cumulative risk of hospitalization and mortality in the case and control groups, respectively, revealing significant differences (log-rank test, $P<0.001$ and $P = 0.011$).

The baseline characteristics of the study included sex, age, comorbidities, geographical location, urbanization, level of care, and income (Supplementary Table 1). Of the 13,974 adult diabetic patients with CIS, 6978 (49.94%) were male, and 5257 (37.62%) were aged ge60 years. The mean age was 62.11 $\pm$ 18.47 years. There were no significant differences in sex, comorbidities, and covariates between the TCM and control groups after propensity score matching.

As shown in Table 1 and 2, at the end of follow-up, 3999 enrolled subjects (28.62%) were inpatients, including 1777 from the TCM group (25.43%) and 2222 from the control group (31.80%). Moreover, 1393 enrolled subjects (9.97%) had mortality, including 661 from the TCM group (9.46%) and 732 from the control group (10.48%). The TCM group was associated with a lower rate of hospitalization at the end of follow-up ($P<0.001$). There were no significant differences in sex, comorbidities, and covariates between the TCM and control groups at the end of follow-up.

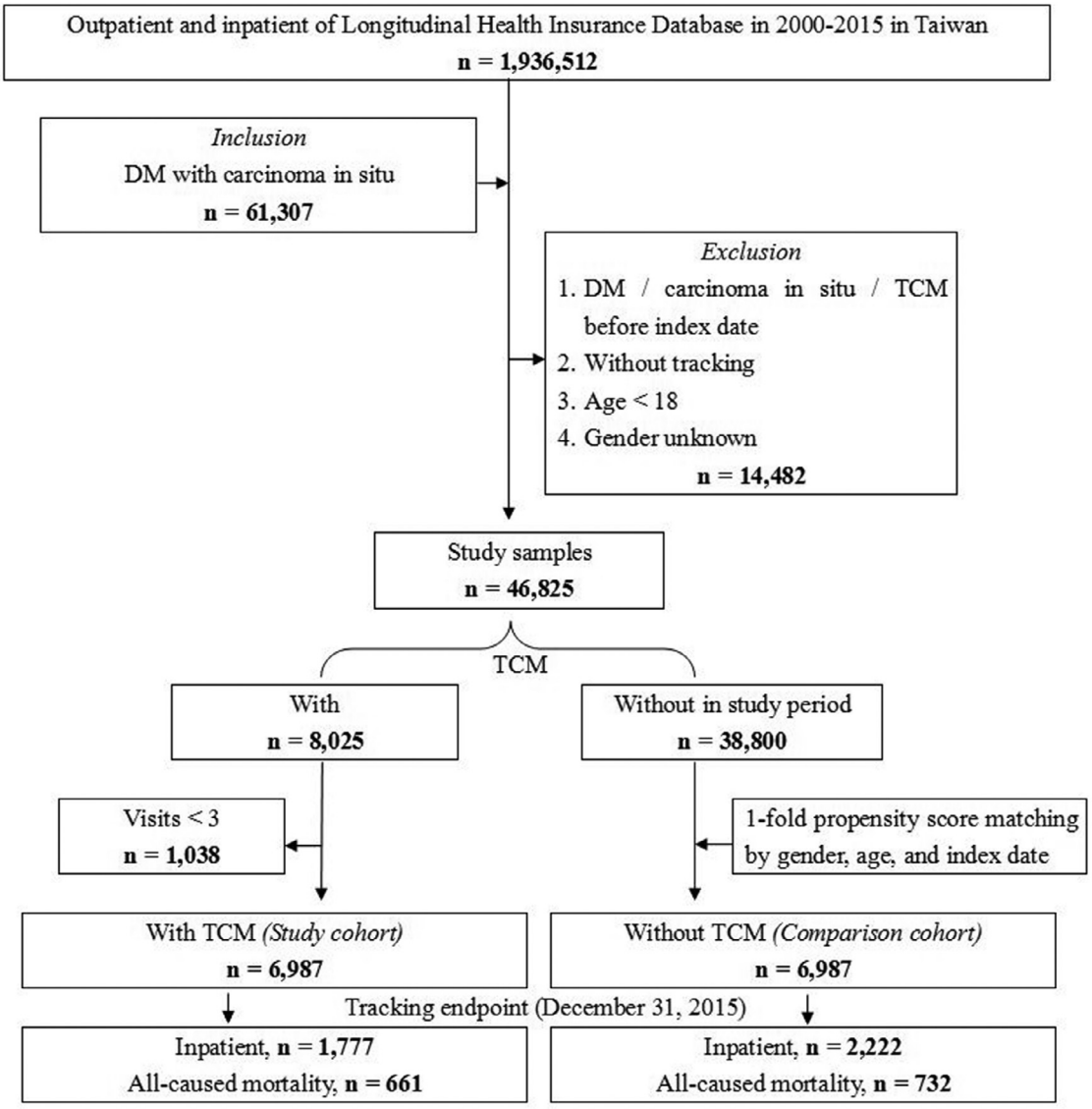

Fig. 1.. Flowchart of subject selection from the National Health Insurance Research Database in Taiwan. DM, Diabetes mellitus: ICD-9-CM 250; Carcinoma *in situ*: ICD-9-CM 230–234; TCM therapy: ≧ 90 days.

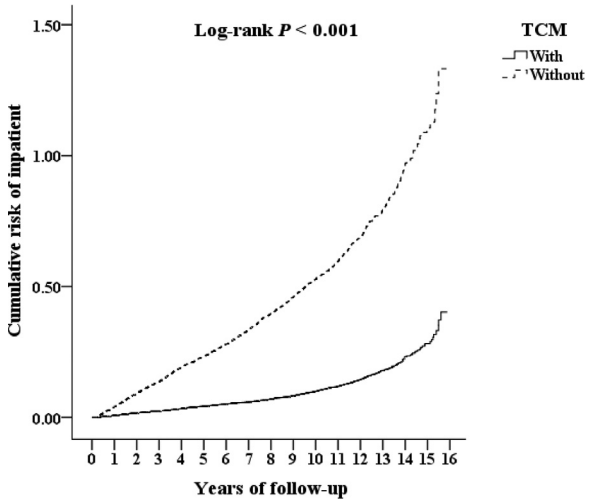

Fig. 2.. Kaplan-Meier analysis for cumulative risk of hospitalization in patients with DM and CIS, as stratified by TCM with log-rank test.

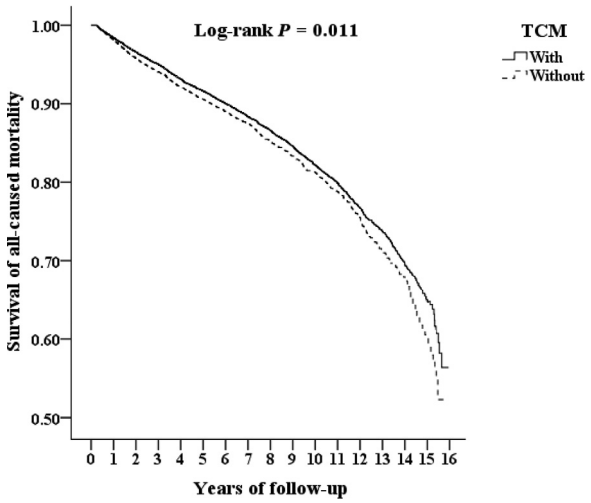

Fig. 3.. Kaplan-Meier survival analysis of all-cause mortality in patients with DM and CIS, as stratified by TCM with log-rank test.

Table 1
Characteristics of enrolled participants.

Variables	Total (n=16,050)		TCM group (n=8,025)		Control group (n=8,025)		*P*
	n	%	n	%	n	%	
Inpatient							<0.001
No	11445	71.31	5981	74.53	5464	68.09	
Yes	4605	28.69	2044	25.47	2561	31.91	
All-cause mortality							0.032
Absent	14426	89.88	7254	90.39	7172	89.37	
Present	1624	10.12	771	9.61	853	10.63	
Gender							0.999
Male	8004	49.87	4002	49.87	4002	49.87	
Female	8046	50.13	4023	50.13	4023	50.13	
Age (yrs)	61.71 ± 19.03		61.23 ± 18.80		62.19 ± 19.24		0.001
Age groups (yrs)							0.047
18–49	6927	43.16	3526	43.94	3401	42.38	
50–59	3082	19.20	1553	19.35	1529	19.05	
≥60	6041	37.64	2946	36.71	3095	38.57	
Low-income							0.017
No	15806	98.48	7922	98.72	7884	98.24	
Yes	244	1.52	103	1.28	141	1.76	
Catastrophic Illness							0.666
Absent	13153	81.95	6566	81.82	6587	82.08	
Present	2897	18.05	1459	18.18	1438	17.92	
CCI_R	0.73 ± 1.86		0.74 ± 1.88		0.71 ± 1.83		0.306
Season							0.911
Spring	4305	26.82	2168	27.02	2137	26.63	
Summer	4164	25.94	2076	25.87	2088	26.02	
Autumn	3939	24.54	1975	24.61	1964	24.47	
Winter	3642	22.69	1806	22.50	1836	22.88	
Location							<0.001
Northern Taiwan	6097	37.99	3085	38.44	3012	37.53	
Middle Taiwan	4065	25.33	2067	25.76	1998	24.90	
Southern Taiwan	4468	27.84	2233	27.83	2235	27.85	
Eastern Taiwan	1180	7.35	597	7.44	583	7.26	
Outlets islands	240	1.50	43	0.54	197	2.45	
Urbanization level							0.372
1 (the highest)	6025	37.54	3025	37.69	3000	37.38	
2	6164	38.40	3112	38.78	3052	38.03	
3	1842	11.48	889	11.08	953	11.88	
4 (the lowest)	2019	12.58	999	12.45	1020	12.71	
Level of care							<0.001
Hospital center	6478	40.36	3865	48.16	2613	32.56	
Regional hospital	5395	33.61	2511	31.29	2884	35.94	
Local hospital	4177	26.02	1649	20.55	2528	31.50	

P indicates Chi-square test or Fisher exact test for categorical variables, and *t*-test for continuous variables.

The factors associated with hospitalization and mortality according to Cox regression analysis are shown in Table 2. Cox proportional hazard regression analysis revealed a lower rate of hospitalization and mortality for the TCM group ($P<0.001$ and $P = 0.022$, respectively).

Cox regression analysis also revealed (Table 3) that TCM treatment reduced hospitalization risk regardless of gender (male or female), age group (18–49, 50–59, ≥ 60), income (high or low), catastrophic illness (with or without), season (spring, summer, autumn, winter), urbanization level (level 1, 2, 3, or 4), or hospital level (hospital center, regional hospital, local hospital). The results of the Cox regression analysis in Table 4 are most of the above variables, and the results of the sub-stratified analysis also indicate that the use of TCM therapy will reduce the risk of mortality.

Table 5 shows prognosis factors in different TCM subgroups, which indicate TCM usage in the population, including the types of TCM treatment, such as herbal formulae, acupuncture, TCM traumatology, or combinations of herbal formulae. The TCM group showed reduced risks of hospitalization (adjusted HR=0.536, 95% CI=0.367–0.780, $P<0.001$) and mortality (adjusted HR=0.783, 95% CI=0.574–0.974, $P = 0.022$). The definitions and detailed information on the herbal formula are described in Supplementary Tables 2 and 3.

4. Discussion

Our present study revealed that T2DM patients with CIS under TCM therapy were associated with lower hospitalization and mortality rates compared to those without TCM therapy. The overall adjusted HRs were 0.543 for hospitalization ($P<0.001$) and 0.793 for mortality ($P = 0.025$), even after adjusting for comorbidities and other covariates. Kaplan-Meier analysis revealed that the TCM case group had a significantly lower 15-year risk of hospitalization and mortality than the controls. This study is the first nationwide, population-based study to indicate that T2DM patients with CIS under TCM therapy were associated with lower hospitalization and mortality risks.

In Taiwan, diabetics can freely choose between Western medicine and TCM to treat diabetes-related symptoms or to alleviate the side effects of anti-diabetic drugs.[21] TCM has been used in Taiwan for hundreds of years, with a high number of patients who use anti-diabetic drugs and TCM concomitantly.[22] Although TCM therapy is based on syndrome differentiation rather than blood sugar level, previous studies have shown that TCM has a blood sugar-lowering effect.[23] However, whether TCM can help reduce the risk of cancer in diabetic patients remains unclear.

Our present findings are approximately consistent with previous research results. Previous studies have shown that patients

Table 2
Factors of prognosis according to Cox regression analysis.

Variables	Inpatient			All-cause mortality		
	Adjusted HR	95% CI	*P*	Adjusted HR	95% CI	*P*
TCM						
No	Reference			Reference		
Yes	0.543	0.372, 0.79	<0.001	0.793	0.581, 0.986	0.025
Gender						
Male	1.563	1.089, 1.788	0.001	1.246	1.033, 1.452	0.017
Female	Reference			Reference		
Age groups (yrs)						
18–49	Reference			Reference		
50–59	1.351	1.124, 1.587	<0.001	1.482	1.203, 1.675	<0.001
≥60	1.864	1.489, 2.161	<0.001	2.011	1.593, 2.764	<0.001
Low-income						
No	Reference			Reference		
Yes	1.206	0.878, 1.786	0.197	1.331	1.006, 1.576	0.043
Catastrophic Illness						
Absent	Reference			Reference		
Present	1.896	1.435, 2.298	<0.001	2.135	1.379, 3.010	<0.001
CCI_R	1.156	1.101, 1.218	<0.001	1.167	1.124, 1.229	<0.001
Season						
Spring	Reference			Reference		
Summer	1.026	0.524, 1.564	0.489	1.165	0.735, 1.672	0.329
Autumn	1.186	0.598, 1.601	0.421	1.271	0.777, 1.786	0.301
Winter	1.279	0.672, 1.675	0.384	1.389	0.892, 1.834	0.283
Urbanization level						
1 (the highest)	2.264	1.615, 2.863	<0.001	1.994	1.480, 2.397	<0.001
2	2.006	1.589, 2.811	<0.001	1.873	1.376, 2.285	<0.001
3	1.723	1.206, 2.240	<0.001	1.564	1.189, 1.906	<0.001
4 (the lowest)	Reference			Reference		
Level of care						
Hospital center	2.989	1.382, 4.487	<0.001	2.251	1.713, 3.065	<0.001
Regional hospital	1.843	1.246, 2.183	<0.001	1.972	1.334, 2.843	<0.001
Local hospital	Reference			Reference		

Location had multi-collinearity with urbanization level.
Adjusted variables are listed in the table.
CI, confidence interval; HR, hazard ratio.

Table 3
Factors of hospitalization stratified according to variables by Cox regression.

	TCM group			Control group *(Reference)*			TCM *vs.* Control *(Reference)*		
Stratified variables	Events	PYs	Rate (per 10^5 PYs)	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	*P*
Total	2044	66789.68	3060.35	2561	67858.94	3774.01	0.543	0.372, 0.790	<0.001
Gender									
Male	1065	33304.25	3197.79	1331	33879.62	3928.62	0.545	0.374, 0.796	<0.001
Female	979	33485.43	2923.66	1230	33979.32	3619.85	0.541	0.370, 0.783	<0.001
Age groups (yrs)									
18–49	502	29378.25	1708.75	603	28757.33	2096.86	0.54	0.368, 0.782	<0.001
50–59	321	12925.44	2483.47	389	1,927.08	3009.19	0.553	0.379, 0.803	<0.001
≥60	1221	24485.99	4986.52	1569	26174.53	5994.38	0.557	0.384, 0.811	<0.001
Low-income									
No	1918	65932.45	2909.04	2386	66666.50	3579.01	0.523	0.368, 0.780	<0.001
Yes	126	857.23	14698.51	175	1192.44	14675.79	0.677	0.459, 0.925	<0.001
Catastrophic Illness									
Absent	1135	54650.23	2076.84	1567	55668.97	2814.85	0.494	0.338, 0.714	<0.001
Present	909	12139.45	7487.98	994	12189.97	8154.24	0.611	0.428, 0.899	<0.001
Season									
Spring	529	18042.33	2931.99	630	18067.94	3486.84	0.573	0.391, 0.826	<0.001
Summer	526	17278.96	3044.16	642	17658.22	3635.70	0.567	0.387, 0.818	<0.001
Autumn	506	16438.25	3078.19	623	16605.28	3751.82	0.541	0.369, 0.785	<0.001
Winter	483	15030.14	3213.54	666	15527.50	4289.16	0.502	0.344, 0.727	<0.001
Urbanization level									
1 (the highest)	598	25175.66	2375.31	633	25157.34	2516.16	0.637	0.435, 0.928	0.001
2	671	25798.23	2600.95	735	25804.28	2848.36	0.618	0.422, 0.899	<0.001
3	202	7397.22	2730.76	246	8038.90	3060.12	0.594	0.410, 0.870	<0.001
4 (the lowest)	573	8418.57	6806.38	947	8858.42	10690.39	0.425	0.303, 0.627	<0.001
Level of care									
Hospital center	1025	32143.25	3188.85	843	22131.17	3809.11	0.567	0.400, 0.822	<0.001
Regional hospital	640	20898.22	3062.46	907	24389.91	3718.75	0.55	0.384, 0.806	<0.001
Local hospital	379	13748.21	2756.72	811	21337.86	3800.76	0.483	0.328, 0.709	<0.001

CI, confidence interval; HR, hazard ratio (adjusted for variables listed in Table 2); PYs, Person-years.

Table 4
Factors of all-cause mortality stratified according to variables by Cox regression.

	TCM group			Control group *(Reference)*			TCM *vs.* Control *(Reference)*		
Stratified	Events	PYs	Rate (per 10^5 PYs)	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	95% CI	*P*
Total	771	85626.75	900.42	853	86991.00	980.56	0.793	0.581, 0.986	0.025
Gender									
Male	391	42701.31	915.66	431	43381.62	993.51	0.796	0.584, 0.992	0.042
Female	380	42925.44	885.26	422	43609.38	967.68	0.789	0.571, 0.981	0.017
Age groups (yrs)									
18–49	211	37662.25	560.24	239	36867.25	648.27	0.743	0.553, 0.921	0.001
50–59	159	16572.35	959.43	173	16573.21	1043.85	0.797	0.582, 0.989	0.031
≥60	401	31392.15	1277.39	441	33550.54	1314.43	0.839	0.612, 1.048	0.074
Low-income									
No	748	84527.52	884.92	819	85462.69	958.31	0.792	0.578, 0.983	0.020
Yes	23	1099.23	2092.37	34	1528.31	2224.68	0.811	0.586, 0.990	0.041
Catastrophic Illness									
Absent	577	70063.51	823.54	670	71403.09	938.33	0.735	0.519, 0.903	<0.001
Present	194	15563.24	1246.53	183	15587.91	1173.99	0.917	0.671, 1.189	0.301
Season									
Spring	169	23131.26	730.61	199	23161.25	859.19	0.734	0.538, 0.911	0.003
Summer	197	22150.98	889.35	222	22633.74	980.84	0.783	0.572, 0.972	0.027
Autumn	181	21074.63	858.85	191	21289.30	897.16	0.827	0.606, 1.028	0.086
Winter	224	19269.88	1162.44	241	19906.71	1210.65	0.829	0.608, 1.033	0.104
Urbanization level									
1 (the highest)	293	32276.25	907.79	304	32251.14	942.60	0.832	0.609, 1.035	0.117
2	299	33024.25	905.40	324	33083.24	979.35	0.797	0.583, 0.991	0.043
3	66	9483.11	695.97	79	10306.21	766.53	0.782	0.571, 0.978	0.012
4 (the lowest)	113	10843.14	1042.13	146	11350.41	1286.30	0.699	0.501, 0.864	<0.001
Level of care									
Hospital center	366	41209.84	888.14	271	28373.25	955.12	0.803	0.587, 0.993	0.044
Regional hospital	234	26786.59	873.57	295	31264.11	943.57	0.800	0.584, 0.989	0.029
Local hospital	171	17630.32	969.92	287	27353.64	1049.22	0.789	0.572, 0.975	0.018

CI, confidence interval; HR, hazard ratio (adjusted for variables listed in Table 2); PYs, Person-years.

with T2DM have a relatively high risk of cancer.[5, 24] and one systematic review has established that cancer risk in patients with diabetes is three times that in the average person.[25] One study showed that incorporating TCM into diabetes treatment helped reduce the risk of breast cancer.[26] Moreover, a systematic review of individual patient data from 97 prospective studies showed that adults with diabetes have an increased risk of cancer death compared to adults without diabetes (HR=1.25; 95% CI=1.19–1.31).[3] Further, based on the findings that TCM can reduce cancer risk, long-term population-based cohort studies on the effect of TCM on cancer risk in T2DM patients may be useful for allocating medical resources and establishing fact-based policies for the treatment of cancer in patients with T2DM.

Our findings are similar to those previous studies. For example, a population-based cohort study revealed a reduced risk of colorectal cancer in patients with T2DM who were treated with TCM,[11] and a case-control study of TCM products showed a decrease in breast cancer risk in women with T2DM.[26] Although the mechanism by which T2DM increases the risk of cancer is still unclear, antidiabetic drugs, such as metformin, are believed to prevent cancer development, and their efficacies have been evaluated in clinical trials.[27, 28] In addition, the mechanism of TCM in reducing the risk of CIS in T2DM patients remains unclear.

A recent systematic review and meta-analysis study has proposed a possible association between endothelial nitric oxide synthase gene polymorphism and susceptibility to prostate cancer.[29] Several studies have shown that TCM may reduce the risk of cancer. One study has confirmed that TCM can reduce the risk of endometrial cancer in patients with estrogen receptor-positive breast cancer, indicating that its antiproliferative effect is achieved through inhibition of the MGMT protein.[7, 30] Moreover, diabetes increases the risk of various cancers via various mechanisms, such as the insulin/IGF-I signaling pathway and the effect of hyperinsulinemia on other hormones.[2] Chronic intestinal inflammation is considered the most important mechanism leading to the pathogenesis of colorectal cancer.[11, 31] One possible mechanism of TCM in reducing cancer risk is its anti-inflammatory properties.[32] In addition, our study showed that TCM therapy reduced the risk of hospitalization and mortality in diabetic patients with CIS regardless of sex, age, income, catastrophic illness, season, urbanization degree, and hospital level.

We also described prognosis factors in various TCM subgroups. As presented in Table 5, herbal formulae resulted in more significant effects compared to that of acupuncture or TCM traumatology. The distribution of the herbal formulae is detailed in Supplementary Table 3. Jia-Wei-Xiao-Yao-San (Augmented Rambling Powder) and Shu-Jing-Huo-Xue-Tang (Channel-Coursing Blood-Quickening Decoction) are two of the most commonly used Chinese herbal products for female breast cancer patients in Taiwan.[33]

The present study had several limitations. First, our analyses did not consider disease duration, disease severity, and other patient parameters. Moreover, because the pathophysiological mechanism is not fully understood, other factors such as complications may explain the increase in hospitalization and mortality risks. Finally, a longer follow-up period may be necessary to clarify hospitalization and mortality risks in diabetic patients with CIS.

In conclusion, diabetic patients with CIS under TCM therapy were associated with lower hospitalization and mortality rates compared to those without TCM therapy. Thus, TCM therapy may reduce the burden of national medical resources. This effect of TCM therapy may be attributed to its anti-inflammatory properties, endothelial nitric oxide, and antiproliferative effects.

Conflict of interest

The authors declare no conflict of interest.

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Ethical statement

The Institutional Review Board of the Tri-Service General Hospital (TSGH) approved our study and waived the need for individual written informed consent (TSGH IRB No.2-105-05-082).

Data availability

The data associated with this study cannot be made available due to legal or ethical reasons as it contains sensitive information.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100831.

CRediT authorship contribution statement

Li-Jen Tsai: Conceptualization, Writing – original draft. **Chi-Hsiang Chung:** Data curation, Formal analysis. **Chien-Jung Lin:** Conceptualization. **Sheng-Chiang Su:** Conceptualization. **Feng-Chih Kuo:** Conceptualization. **Jhih-Syuan Liu:** Conceptualization. **Kuan-Chan Chen:** Conceptualization. **Li-Ju Ho:** Conceptualization. **Chih-Chun Kuo:** Conceptualization. **Chun-Yung Chang:** Conceptualization. **Ming-Hsun Lin:** Conceptualization. **Nain-Feng Chu:** Conceptualization. **Chien-Hsing Lee:** Conceptualization. **Chang-Hsun Hsieh:** Conceptualization. **Yi-Jen Hung:** Conceptualization. **Po-Shiuan Hsieh:** Conceptualization. **Fu-Huang Lin:** Conceptualization. **Chieh-Hua Lu:** Writing – original draft, Writing – review & editing. **Wu-Chien Chien:** Writing – review & editing.

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