



Study on the Prognosis Effect of Traditional Chinese Medicine Treatment in Patients with Diabetic Neuropathy – A Nationwide, Population-based Study in Taiwan

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Background: Diabetic neuropathy (DN) is one of the common chronic complications, leading to limb disability and increased risks of hospitalization and mortality. Traditional Chinese medicine (TCM) has been commonly applied in Taiwan as an adjunctive treatment to ameliorate diabetes-associated chronic complications, including neuropathy. **Aim:** We aimed to investigate whether the clinical treatment of DN combined with TCM can reduce the associated hospitalization and mortality using the National Health Insurance Research Database (NHIRD) of Taiwan. **Methods:** We selected 1,152 patients with DN who received TCM treatment as the study cohort group, and 4,940 patients with DN who did not receive TCM treatment from Taiwan NHIRD were further matched 1:1 for sex, age, and index year as the comparison cohort group. Cox proportional hazards analysis was performed to compare hospitalization and mortality during a mean follow-up period of 15 years. **Results:** A total of 687/225 enrolled patients (29.82%/9.77%) had hospitalization/mortality, including 298/97 in the TCM group (25.87%/8.42%) and 389/128 in the comparison group (33.77%/11.11%). Cox proportional hazard regression analysis showed a lower rate of hospitalization and mortality for patients in the TCM group (adjusted hazard ratio [HR] of 0.434, 95 confidence interval [CI] = 0.172–0.798, $P < 0.001$; adjusted HR of 0.689, 95 CI = 0.372–0.981, $P = 0.039$). The Kaplan–Meier analysis showed that the cumulative risk of hospitalization and mortality in the study and comparison cohort groups was significantly different (log-rank $P < 0.001$ and $P = 0.007$, respectively). **Conclusion:** Our results suggest that the application of TCM might be beneficial for patients with DN to lower the risks of hospitalization and mortality; however, further prospective cohort studies are still required to confirm our observations.

Key words: Diabetic neuropathy, traditional Chinese medicine, hospitalization and mortality

INTRODUCTION

Neuropathy is a common chronic complication of diabetes and one of the main causes of diabetic limb disability.¹ The prevalence can range from 7.5% at the time of diabetes diagnosis to 45%–60% after 20 years.² A survey in Taiwan showed that about 26.8% of patients with type 2 diabetes (T2D) had diabetic polyneuropathy (DN).³ Risk factors for DN

include age, gender (male), poorly controlled hyperglycemia, and fundus lesions.⁴ The longer the duration of diabetes, the greater the chance of neuropathy.

The most common form of DN is symmetrical diabetic peripheral neuropathy (DPN), which is usually sensory based.⁵ One review article showed that 10 years after diabetes diagnosis, about 20% of patients had pain and 33% had paresthesia.⁶ To ameliorate the diabetes-associated

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complications, including polyneuropathy, adequately glycemic control in patients with diabetes has been shown as the central dogma.⁷ For the treatment of diabetic neuropathy pain, the European Society of Neurology recommends drug treatment for polyneuropathy pain, while the therapeutic response still varies from person to person.⁸ Besides, diabetic cardiovascular autonomic neuropathy has been emphasized as an independent cause of sudden cardiac death based on the Rochester Diabetic Neuropathy Study.⁹ Therefore, diabetes-associated neuropathy not only caused limb pain and disability but also associated with the risk of cardiovascular death.

In Taiwan, traditional Chinese medicine (TCM) has been commonly applied for the treatment of chronic diseases, especially in the field of diabetes.¹⁰ Based on previous studies, TCM had been shown to have roles in the treatment of diabetes through stabilizing the blood glucose levels with the improvement of long-term glycemic control to a certain extent.¹¹ However, there are very limited reports examining the therapeutic benefits as combining TCM with ordinary glycemic control in patients with DN. Therefore, we utilized the Taiwan Health Insurance database to investigate whether the combination of clinical treatment of DN with TCM can reduce the associated hospitalization and mortality in patients with diabetes.

MATERIALS AND METHODS

Data sources

Diabetic patients with DN were recruited from the Taiwan Outpatient Longitudinal Health Insurance Database. We used data from the National Health Insurance Research Database (NHIRD) to investigate whether TCM treatment could reduce hospitalization or mortality in T2D with DN over 15 years (2000–2015). In 1995, Taiwan launched the National Health Insurance (NHI) program. As of June 2009, it had contracted with 97% of Taiwan's medical providers, with a population of about 23 million, or 99% of Taiwan's total population.¹² The NHIRD uses codes from the International Classification of Diseases, 9th edition, clinically revised (ICD-9-CM), to record diagnoses. All diagnoses in T2D with DN are made by medical professionals certified by a specialist physician. The NHI randomly reviewed records of every 100 outpatient visits, and every 20 inpatient claims to verify diagnostic accuracy.¹³ Previous research has demonstrated the accuracy and validity of NHIRD diagnosis.^{14–16}

Study design and sampled participants

Our study used a retrospective paired cohort design. From

January 1, 2000, to December 31, 2015, the diagnosis of T2D and DN was selected according to codes ICD-9-CM 250.XX (T2D) and ICD-9-CM 250.6 or 357.2 (DN), respectively. According to these ICD-9-CM codes, each enrolled patient had a record of at least three outpatient clinic visits during the study period, and patients who received fewer than three TCM treatments and were <18 years old were excluded. The covariates include the Charlson comorbidity index minus T2D, level of care, gender, and age.¹⁵

Outcome measures

According to the NHI program, all the study participants were tracked from the index date to hospitalization or death until the end of 2015.

Statistical analysis

All statistical analyses were performed using the SPSS software version 22 for Windows (SPSS Inc., Chicago, IL, USA). The 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 T2D with DN 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 $P < 0.05$.

Ethics

Our research was performed in accordance with the World Medical Association Code of Ethics (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 (TSGHIRB No. E202316013).

RESULTS

We included 8294 patients with DN and excluded 2005 patients with DN who had received TCM treatment before 2000, those who had no follow-up records, who were less than 18 years old, and whose gender could not be identified, and finally included 6289 patients with DN. Among them, 1349 received TCM treatment, and 4,940 did not receive TCM treatment. Then, 197 outpatients who received TCM treatment were further excluded due to < 3 times of follow-up with the remaining 1152 received TCM treatment. We further performed 1:1 propensity score matching by sex, age, and index year

to select patients who did not receive TCM treatment as the comparison cohort group. Among the 1152 patients with DN and treated with TCM, there are 298 patients were hospitalized and 97 died. In the matched comparison cohort group (patients with DN who did not receive TCM treatment), there were 389 patients hospitalized and 128 died, as shown in Figure 1. In Figures 2 and 3, we further performed the Kaplan–Meier analysis to evaluate the cumulative risk of hospitalization and death. We observed that patients with DN who received TCM treatment had significantly lower cumulative risk for hospitalization and death (log-rank $P < 0.001$ and $P = 0.007$, respectively) compared to patients with DN who did not receive TCM treatment.

We also compared the characteristics between 1152 patients with DN who received and did not receive TCM treatment at the time of admission as shown in Table 1. There were 672 (58.33%) males and 480 (41.67%) females, and the average age was 51.06 years and 51.1 years, respectively. The disease severity averaged 0.96, with no statistically significant difference between the two groups. A higher proportion

of DN patients receiving TCM treatment were in medical centers ($P < 0.001$). Table 2 presented the characteristics of these two groups at the end of the study, 298 (25.87%) DN patients who received TCM treatment were hospitalized, and 389 (33.77%) patients who did not receive TCM were hospitalized ($P < 0.001$). All-cause mortality in patients who received TCM treatment was 8.2% (97 deaths), whereas there were 128 deaths (11.11%) in the comparison group ($P = 0.03$). Again, we observed that more DN patients who received TCM treatment were treated in medical centers ($P < 0.001$). There are no significant statistical differences in gender, age, and disease severity between patients with or without TCM treatment.

We further analyzed the factors affecting the Cox regression of hospitalization and all-cause mortality as shown in Table 3. Among hospitalized patients, we saw patients with DN who received TCM treatment had an adjusted HR of 0.434 (95 CI = 0.172–0.798, $P < 0.001$), with a lower proportion of hospitalizations. While males had adjusted HR 1.565 (95 CI = 1.372–1.765, $P < 0.001$), patients with older age ≥ 60

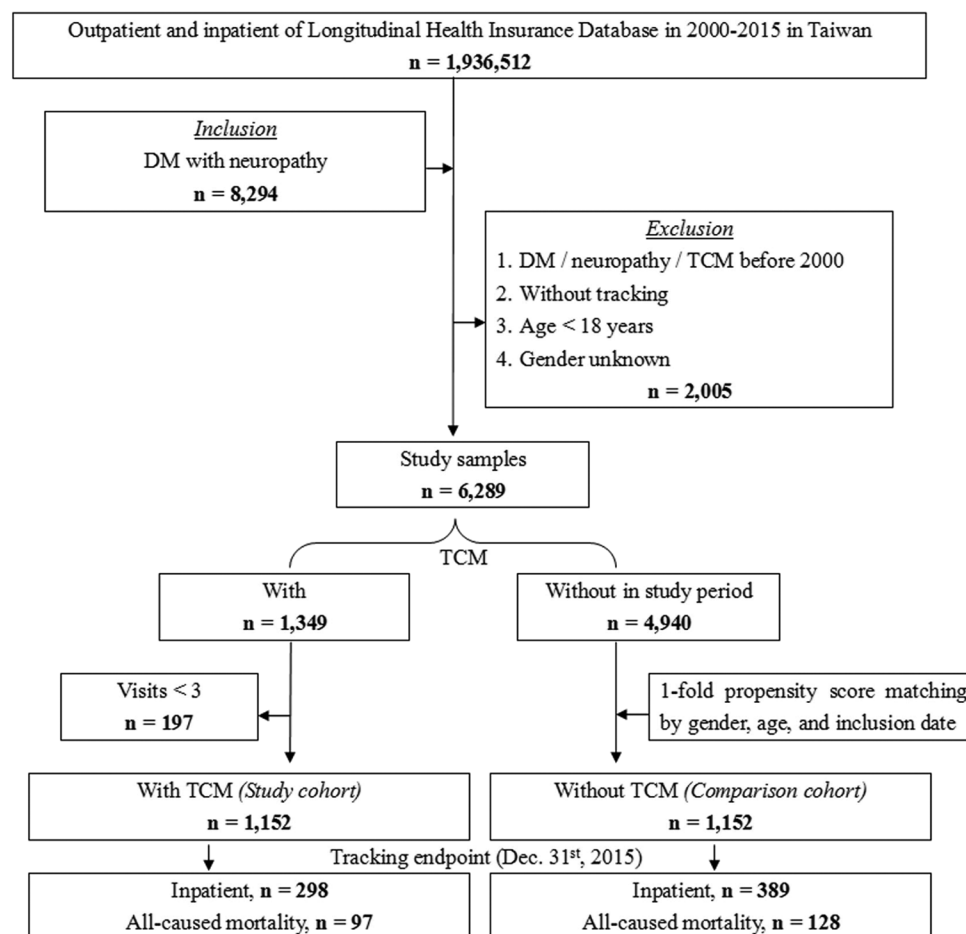


Figure 1: The flowchart of the study

Table 1: Characteristics of the study in the baseline

Variables	TCM			P
	Total, n (%)	With, n (%)	Without, n (%)	
Total	2304	1152 (50.00)	1152 (50.00)	
Gender				
Male	1344 (58.33)	672 (58.33)	672 (58.33)	0.999
Female	960 (41.67)	480 (41.67)	480 (41.67)	
Age (years)	51.08±19.25	51.06±19.24	51.10±19.27	0.960
Age groups (years)				
18–49	1106 (48.00)	553 (48.00)	553 (48.00)	0.999
50–59	442 (19.18)	221 (19.18)	221 (19.18)	
≥60	756 (32.81)	378 (32.81)	378 (32.81)	
Catastrophic illness				
Without	1895 (82.25)	941 (81.68)	954 (82.81)	0.513
With	409 (17.75)	211 (18.32)	198 (17.19)	
CCI_R	0.96±1.01	0.98±1.02	0.94±1.00	0.342
Level of care				
Hospital center	1007 (43.71)	620 (53.82)	387 (33.59)	<0.001
Regional hospital	783 (33.98)	382 (33.16)	401 (34.81)	
Local hospital	514 (22.31)	150 (13.02)	364 (31.60)	

P=Chi-square/Fisher's exact test on category variables and *t*-test on continue variables. TCM=Traditional Chinese Medicine; CCI=Charlson comorbidity index

had adjusted HR 1.372 (95 CI = 1.114–1.578, $P < 0.001$), and those with higher disease severity had adjusted HR 1.240 (95 CI = 1.112–1.309, $P < 0.001$), indicating male, aging, and concurrent disease severity are all notable factors to cause a higher rate of hospitalization. Similar findings were also observed in all-cause mortality; patients with DN who received TCM treatment had an adjusted HR of 0.689 (95 CI = 0.372–0.981, $P = 0.039$) and had a lower mortality rate. While male patients had adjusted HR 1.422 (95 CI = 1.209–1.786, $P < 0.001$), individuals with older age ≥ 60 had adjusted HR 1.574 (95 CI = 1.246–1.998, $P < 0.001$), and patients with higher disease severity had adjusted HR 1.367 (95 CI = 1.287–1.483, $P < 0.001$), pointing out male, aging, and disease severity as factors contributing to higher all-cause mortality. Besides, level of care is also a notable factor associated with hospitalization and all-cause mortality. Patients who were followed in hospital centers or regional hospitals presented an increased risk for hospitalization and all-cause mortality compared to those followed in local hospitals.

Based on the results shown in Table 3, we found that TCM, gender, age, disease severity, and level of care are all significant factors associated with the risk of hospitalization and all-cause mortality. To understand whether the lower hospitalization in patients who received TCM is dependent on or independent

Table 2: Characteristics of the study in the endpoint

Variables	TCM			P
	Total, n (%)	With, n (%)	Without, n (%)	
Total	2304	1152 (50.00)	1152 (50.00)	
Inpatient				
Without	1617 (70.18)	854 (74.13)	763 (66.23)	<0.001
With	687 (29.82)	298 (25.87)	389 (33.77)	
All-cause mortality				
Without	2079 (90.23)	1055 (91.58)	1024 (88.89)	0.030
With	225 (9.77)	97 (8.42)	128 (11.11)	
Gender				
Male	1344 (58.33)	672 (58.33)	672 (58.33)	0.999
Female	960 (41.67)	480 (41.67)	480 (41.67)	
Age (years)	61.57±20.46	61.68±19.74	61.96±21.17	0.361
Age groups (years)				
18–49	1060 (46.01)	523 (45.40)	537 (46.61)	0.334
50–59	440 (19.10)	211 (18.32)	229 (19.88)	
≥60	804 (34.90)	418 (36.28)	386 (33.51)	
Catastrophic illness				
Without	1891 (82.07)	939 (81.51)	952 (82.64)	0.480
With	413 (17.93)	213 (18.49)	200 (17.36)	
CCI_R	1.01±1.12	1.01±1.14	1.00±1.1	0.831
Level of care				
Hospital center	1000 (43.40)	618 (53.65)	382 (33.16)	<0.001
Regional hospital	748 (32.47)	342 (29.69)	406 (35.24)	
Local hospital	556 (24.13)	19 (16.67)	364 (31.60)	

P: Chi-square/Fisher's exact test on category variables and *t*-test on continue variables. CCI=Charlson comorbidity index; TCM=Traditional Chinese Medicine

from other significant factors (gender, age, disease severity, and level of care), we further stratified the data based on these factors to evaluate the effect of TCM as presented in Table 4. First, we illustrated that total patients with DN who received TCM treatment had a lower hospitalization rate adjusted HR 0.434 (95 CI = 0.172–0.798, $P < 0.001$). Then, we evaluated the beneficial effect of TCM treatment by stratifying the data to different groups of gender, age, disease severity, and level of care. Notably, we observed that patients with DN who received TCM treatment persistently maintained lower hospitalization rate (all $P < 0.001$) regardless of gender, age, disease severity, and level of care, indicating TCM treatment as an important and independent factor contributing to the decreased risk of hospitalization in patients with DN. Then, we performed the same analysis in Table 5 to evaluate whether the overall beneficial effect of TCM on all-cause mortality (adjusted HR 0.689 (95 CI = 0.372–0.981, $P = 0.039$)) is dependent on or independent from other significant factors. Again, we observed

Table 3: Factors of prognosis using Cox regression

Variables	Prognosis					
	Inpatient			All-cause mortality		
	AHR	95% CI	<i>P</i>	AHR	95% CI	<i>P</i>
TCM						
Without	Reference			Reference		
With	0.434	0.172–0.798	<0.001	0.689	0.372–0.981	0.039
Gender						
Male	1.565	1.372–1.765	<0.001	1.422	1.209–1.786	<0.001
Female	Reference			Reference		
Age groups (years)						
18–49	Reference			Reference		
50–59	1.154	1.030–1.289	<0.001	1.230	1.114–1.378	<0.001
≥60	1.372	1.114–1.578	<0.001	1.574	1.246–1.998	<0.001
Catastrophic illness						
Without	Reference			Reference		
With	1.702	1.433–2.101	<0.001	2.035	1.554–2.897	<0.001
CCI_R	1.240	1.112–1.309	<0.001	1.367	1.287–1.483	<0.001
Level of care						
Hospital center	2.892	2.101–3.452	<0.001	2.773	2.008–3.386	<0.001
Regional hospital	1.776	1.245–2.013	<0.001	1.860	1.435–2.241	<0.001
Local hospital	Reference			Reference		

AHR: Adjusted variables listed in the table. Location had multicollinearity with urbanization level. CI=Confidence interval; CCI=Charlson comorbidity index; AHR=Adjusted hazard ratio; TCM=Traditional Chinese Medicine

that patients with DN who received TCM treatment persistently presented lower all-cause mortality rate (all $P < 0.05$) regardless of gender, age, disease severity, and level of care, supporting TCM treatment as an independent factor contributing to the decreased risk of all-cause mortality in patients with DN. Furthermore, we also evaluated the interactions between the level of care and other variables (gender, age, and disease severity) as shown at the bottom of Tables 4 and 5, which are all nonsignificant.

DISCUSSION

Our results based on the health insurance database disclosed that the treatment of DN with diabetic medicine combined with TCM treatment will have lower hospitalization and mortality. About 1 year after starting the treatment with TCM, it is gradually seen that patients will have a lower hospitalization rate. Regarding the all-cause mortality, it seems that after 8 years of treatment with TCM, a lower mortality rate begins to be seen. During the 15 years of follow-up, TCM decreased by around 56.6% hospitalization rate with adjusted HR = 0.434 (CI = 0.172–0.798, $P < 0.001$) and attenuated around 31.1% mortality rate with adjusted

HR = 0.689 (CI = 0.372–0.981, $P = 0.039$) compared with those without TCM treatment. This is the first study to investigate the hospitalization and mortality rates among patients with DN treated with diabetic medicine combined with TCM treatment.

In our data, it is easy to understand that DN patients with older age, higher severity of illness, and not received concomitant TCM would have higher rates of hospitalization and all-cause mortality. However, we also observed that male DN patients would have higher hospitalization rates and all-cause mortality. Actually, previous research had found males with diabetes are more vulnerable to encounter diabetes neuropathy¹⁷ and more commonly to be hospitalized due to diabetic neuropathy,¹⁸ which are in line with our results, and we further disclosed that there is a higher mortality rate in males with diabetic neuropathy.

Our reports found that patients with diabetic neuropathy who were treated with TCM had lower hospitalization and mortality rates; however, the underline mechanisms are still ambiguous. One research showed that the use of TCM treatment can improve the blood circulation of T2D, thereby alleviating ischemia and hypoxia of nerve tissue and improving the syndrome of neuropathy.¹⁹ The pathogenesis of DN may include metabolic factors, lack of myo-inositol,

Table 4: Factors of inpatient stratified by variables listed in the table using Cox regression

Stratified	TCM					
	Events		With versus without (reference)			
	With	Without (reference)	Adjusted HR	95% CI	95% CI	P
Total	298	389	0.434	0.172	0.798	<0.001
Gender						
Male	182	222	0.463	0.187	0.853	<0.001
Female	116	167	0.395	0.155	0.726	<0.001
Age groups (years)						
18–49	131	172	0.428	0.169	0.782	<0.001
50–49	53	75	0.433	0.173	0.799	<0.001
≥60	114	142	0.441	0.175	0.809	<0.001
Catastrophic illness						
Without	240	320	0.428	0.171	0.764	<0.001
With	58	69	0.445	0.180	0.823	<0.001
Level of care						
Hospital center	161	130	0.440	0.182	0.804	<0.001
Regional hospital	89	138	0.435	0.174	0.797	<0.001
Local hospital	48	121	0.424	0.165	0.785	<0.001

Interaction (level of care × gender), $P=0.832$. Interaction (level of care × age groups), $P=0.727$. Interaction (level of care × catastrophic illness), $P=0.544$. AHR: Adjusted for the variables listed in Table 3. CI=Confidence interval; TCM=Traditional Chinese Medicine; AHR=Adjusted hazard ratio

Table 5: Factors of all-cause mortality stratified by variables listed in the table using Cox regression

Stratified	TCM					
	Events		With versus without (reference)			
	With	Without (reference)	Adjusted HR	95% CI	95% CI	P
Total	97	128	0.689	0.372	0.981	0.039
Gender						
Male	57	75	0.690	0.371	0.984	0.036
Female	40	53	0.685	0.368	0.977	0.024
Age groups (years)						
18–49	42	58	0.672	0.334	0.969	0.011
50–49	18	26	0.677	0.362	0.970	0.029
≥60	37	44	0.698	0.375	0.995	0.046
Catastrophic illness						
Without	78	106	0.674	0.368	0.973	0.022
With	19	22	0.691	0.375	0.990	0.040
Level of care						
Hospital center	53	43	0.691	0.377	0.974	0.024
Regional hospital	28	45	0.684	0.368	0.965	0.015
Local hospital	16	40	0.672	0.362	0.961	0.011

Interaction (level of care × gender), $P=0.317$. Interaction (level of care × age groups), $P=0.262$. Interaction (level of care × catastrophic illness), $P=0.118$. AHR: Adjusted for the variables listed in Table 3. CI=Confidence interval; AHR=Adjusted hazard ratio; TCM=Traditional Chinese Medicine

decreased activity of sodium/potassium ion ATPase in nerve cell membrane, accumulation of abnormal monosaccharide alcohol metabolism (polyol pathway) affecting nerve function,

hyperglycemia stimulation aldose reductase activity with sorbitol (sorbitol) accumulation, osmolar changes, and so on.^{20,21} Whether TCM treatment may benefit the outcome

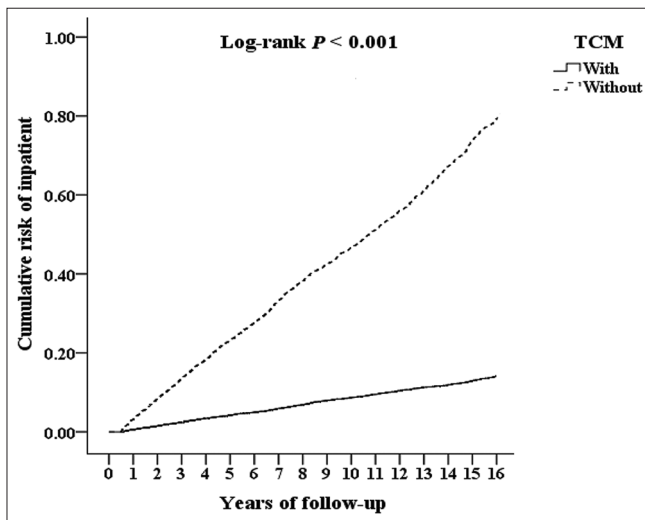


Figure 2: Kaplan–Meier for cumulative risk of inpatients among DM with neuropathy aged 18 and over stratified by traditional Chinese medicine with log-rank test

of patients with DN through their mechanisms still requires further basic studies to uncover.

Regarding the current therapeutic strategies for DN, we are still largely depending on glycemic control through prescribing oral or injectable hypoglycemic agents. In addition, pregabalin or duloxetine has been proven to relieve diabetic peripheral neuropathy pain (DPNP).²² Although tricyclic antidepressants are useful in the treatment of neuropathy pain, they are currently not DPNP drugs approved by the Food and Drug Administration of the Ministry of Health and Welfare of Taiwan.^{23,24} Meanwhile, the side effects of these DPNP drugs should be taken into consideration as well. Therefore, the application of TCM for patients with DN will be another suitable choice, and our data provided supportive evidence for its beneficial effects on clinical utilization.

TCM treats disease and enhances health through unique theoretical practices that include herbal medicine, acupuncture, nutrition, and other nondrug treatments.²⁵ The main TCM theories include “Yin” and “Yang” and the five elements to describe the role of Qi and blood in relation to bodily functions and activities and the role of body fluids and the differential diagnosis of syndromes.²⁶ T2D is a chronic disease, and TCM and modern medicine have their own advantages and disadvantages in the treatment of diabetes.²⁷ It is feasible to combine the advantages of both to break through the bottleneck of diabetes treatment. The concept of “Yin and Yang” is at the core of TCM philosophy, and one of the main goals is to balance the role of “Qi” in the body, not only for treating secondary manifestations but also for treating chronic complications like diabetes-associated neuropathy.²⁸ A recent study by Meyer-Hamme *et al.* using acupuncture for DPN in

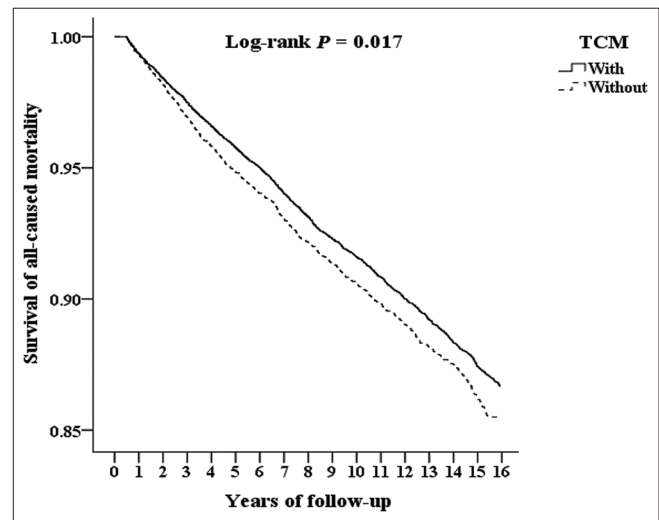


Figure 3: Kaplan–Meier for the survival of all-cause mortality among DM with neuropathy patients aged 18 and over stratified by traditional Chinese medicine with log-rank test

patients with T2D found a significant improvement in DPN symptoms, possibly due to the improved structural nerve regeneration after acupuncture treatment.²⁹ Another study found that the use of integrated traditional Chinese and Western medicine in the treatment of chronic complications of diabetes is more effective than unilateral treatment of the disease or syndrome.³⁰ Exploring the cause may be a threat to diabetic complications, and early diagnosis is necessary. Because not all DN can be treated with the recommended in the guidelines and can achieve effective symptom improvement, DN patients in Taiwan are sometimes referred to Chinese medicine clinics for a combination of TCM and diabetic medicine.

Our research still has several limitations. First of all, the research method is to use the ICD-9 or ICD-10 codes on the health insurance database for identifying patients with relevant diagnoses as the inclusion criteria; however, it lacks patients’ blood biochemical reports for evaluating the general disease status, including glycemic control. Furthermore, we can only explore the correlation between research purposes, and the discussion of causality cannot be explained through this research method.

CONCLUSION

This is the first report to support the beneficial effects of hospitalization and mortality rates in DN patients who are treated with diabetic medicine combined with TCM. However, further prospective cohort studies or basic research are still required to confirm our observations and explore the potential underpinned mechanisms mediated by TCM in patients with DN.

Acknowledgments

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Data availability statement

The data of this study are available from the corresponding author under reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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