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Association of traditional Chinese medicine body constitution and moderate-to-severe cancer-related fatigue in cancer patients

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ABSTRACT

Background and purpose: Fatigue is one of the most prevalent adverse events reported by cancer patients. The aim of this study was to investigate the association between traditional Chinese medicine body constitution (TCMBC) and moderate-to-severe cancer-related fatigue in cancer patients.

Materials and methods: A cross-sectional study was conducted on cancer patients recruited from a regional hospital in southern Taiwan. The association between TCMBC, measured using the Constitution in Chinese Medicine Questionnaire (CCMQ) and moderate-to-severe cancer-related fatigue (based on the Taiwanese version of the Brief Fatigue Inventory score ≥ 4) was evaluated using multiple logistic regression analysis.

Results: Of the 170 participants, 37 (21.8%) had moderate-to-severe fatigue. Yang-deficiency (adjusted odds ratio [aOR] = 3.55, 95% confidence interval [CI] = 1.50–8.40) and Qi-deficiency (aOR = 2.84, 95% CI = 1.18–6.82) TCMBC were significantly associated with moderate-to-severe cancer-related fatigue.

Conclusion: TCMBC could be used as a clinical tool to identify cancer patients prone to experience moderate-to-severe cancer-related fatigue, and to provide Chinese medicine practitioners a basis for selecting an appropriate treatment approach based on TCMBC.

1. Introduction

Fatigue is one of the most prevalent adverse events reported by cancer patients, and cancer-related fatigue is defined as the feeling of extraordinary exhaustion associated with a high level of distress, disproportionate to patients' activity and unrelieved by sleep or rest.[1] Furthermore, according to the guidelines of the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as "a distressing, persistent, subjective sense of physical, emotional, and or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".[2]

The prevalence of cancer-related fatigue has been estimated to range from 59 to nearly 100%, depending on the clinical status and types of the cancer.[3] Cancer-related fatigue can lead to a poor quality of life [4] and the latter is associated with a poor prognosis and low survival rate in cancer patients.[5] Since there is currently no standard treatment for cancer-related fatigue,[6] cancer patients often turn to the use of complementary and alternative medicine to relieve their fatigue.[7–9] In Asia, cancer patients often use traditional Chinese Medicine (TCM) to relieve the side effects of chemotherapy.[10,11]

According to TCM theory, Yang and Qi are the driving forces of biological activities in the human body. Deficiencies in Yang and Qi are common in patients with "fatigue syndrome".[12] Cancer patients often suffer from vital Qi deficiency,[13] and those with cancer-related fatigue and Qi deficiency is associated with a poor quality of life.[14] Therefore, identifying patients with Qi deficiency is critical for predicting prognosis or disease progression and guide the corresponding treatment

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principles of Chinese Medicine.

Traditional Chinese Medicine body constitution (TCMBC) ("Tizhi" in Chinese) refers to an integrated, relatively stable, and natural system of classifying individuals according to developmental, physiological, and psychological characteristics, innate or acquired over time.[15] The TCMBC includes nine constitutions: Gentleness (Neutral, Balance), Qi-deficiency, Yang-deficiency, Qi-depression (Qi stagnation), Yin-deficiency, Phlegm-wetness (Phlegm-dampness), Blood-stasis, Wetness-heat (Dampness-heat), and Special diathesis (Inherited special constitution).[16] Based on the sign and symptoms presented, the type of TCMBC of a patient can be determined. The TCMBC not only relates to the susceptibility and predisposition to certain pathogens and diseases, but it can also influence the prognosis and treatment of diseases.[17] Therefore, the aim of the present study was to investigate the association between TCMBC and cancer-related fatigue in cancer patients.

2. Materials and methods

2.1. Study design and data collection

This was a cross-sectional design study with convenience sampling. Cancer patients were recruited from both inpatients and outpatients from the Department of Chinese Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation from January 2013 to July 2014. All participants completed a structured questionnaire to collect their demographic information and other relevant information, including cancer type, cancer stage, and cancer treatment. The questionnaires were administered using face-to face interviews by a research assistant either at the outpatient waiting room or in the ward of the study hospital. The study protocol was approved by the Ethical Committee for Human Research at Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (approval number: B10204015).

2.2. Study participants

Based on the results of a study on the correlation of Qi deficiency and cancer-related fatigue in patients with breast cancer,[18] we estimated a sample size of 150 would be required to able to use logistic regression analysis to detect a significant difference in cancer-related fatigue (a proportion of 0.24) between patients with (a proportion of 0.65) or without Qi deficiency (a proportion of 0.33) with an alpha level of 0.05 and a power of 90%.[19] We further increased the sample size by 25% from 150 to 190 patients to compensate for the possibility of nonresponse and differences in the types of cancer in our study sample.

A total of 190 patients of ages between 20 and 80 years with cancer diagnosed by pathology or imaging and receiving radiotherapy or chemotherapy were recruited in the study. Due to incomplete questionnaire responses, 20 patients were excluded from the study (Fig. 1).

2.3. Measurement of traditional Chinese medicine body constitution

All of the participants completed a Constitution in Chinese Medicine Questionnaire (CCMQ) developed by Qi Wang for measuring the type of TCMBC.[15,20] The scale consisted of 60 items with nine sub-scales scored on a 5-point Likert scale for classifying a person into one or more of the nine types of TCMBC, namely, Gentleness (8 items), Qi-deficiency (8 items), Yang-deficiency (7 items), Yin-deficiency (8 items), Phlegm-wetness (8 items), Wetness-heat (6 items), Blood-stasis (7 items), Qi-depression (7 items), and Special diathesis (7 items). The coexistence of multiple TCMBC types is possible and is consistent with the traditional Chinese medicine theory. A score of 30 or higher on each of the nine sub-scales of the CCMQ was set as the threshold for the respective TCMBC, following original CCMQ scoring algorithm.[21] In this study, we selected CCMQ over other TCMBC scales such as the Body Constitution Questionnaire (BCQ) [22,23] because we believe that it is necessary to use a scale with more body constitution types in order to differentiate the conditions in cancer patients.

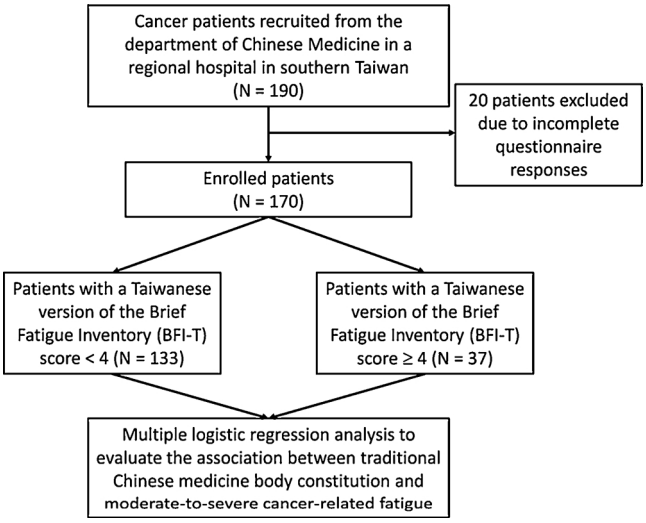

Fig. 1. Study flow chart.

The reliability and validity were previously evaluated on 2500 participants recruited from five different geographical districts in China. Good internal consistency with Cronbach's α ranged from 0.76 to 0.90 and good test-retest reliability ranged from 0.76 to 0.90 for the nine sub-scales were reported. In addition, good criterion validity was demonstrated by the correlations between CCMQ and health-related quality of life scores.[24]

Furthermore, the psychometric properties of the CCMQ were evaluated in 1084 adult patients attending a Western medicine outpatient clinic and two Chinese medicine outpatient clinics in Hong Kong. Satisfactory internal reliability with a Cronbach's $\alpha > 0.6$ and good test-retest reliability with intraclass correlation coefficients ranged from 0.71 to 0.88 was obtained. In addition, content validity of the CCMQ was confirmed using convenience samples of 10 patients and 10 Chinese medicine practitioners. Construct validity was supported by moderate correlations between CCMQ and health-related quality of life scores. Moreover, confirmatory factor analysis showed a reproducible structure as hypothesized.[21]

2.4. Measurement of cancer-related fatigue

Cancer-related fatigue was measured using the Taiwanese version of the Brief Fatigue Inventory (BFI-T). The original scale was developed at the University of Texas MD Anderson Cancer Center to rapidly assess fatigue severity in cancer patients.[25] The scale consists of 9 items based on an 11-point (0–10) rating scale. The first three items assess fatigue severity of the current level, usual level during the past 24 h, and the worst level during the past 24 h. The other six items assess fatigue interference with daily activities during the past 24 h, including general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life. Factor analysis revealed that the original scale was uni-dimensional with an excellent internal consistency (Cronbach's $\alpha = 0.96$). The severity of cancer-related fatigue for each patient was calculated by dividing the total BFI-T score by 9. A mean score of < 4 points indicated mild fatigue, 4–6 points indicated moderate fatigue, and > 7 points indicated severe fatigue. Moderate or severe fatigue suggests that quality of life might have been adversely affected by cancer-related fatigue, and therefore, we dichotomized our data into patients with mild fatigue or with moderate-to-severe cancer-related fatigue in subsequent analyses.[25,26] A validation study of the BFI-T based on 439 Taiwanese patients with multiple cancer diagnoses revealed that it is a reliable, valid, sensitive, and clinically easy-to-use

scale for measuring cancer-related fatigue. The study also found that the BFI-T measured a single construct, with high factor loadings ranged from 0.80 to 0.94 for the nine items, and therefore the mean of the nine items could be used as an overall score for fatigue. Internal consistency was indicated by Cronbach's α of 0.97, and convergent validity was established by correlating the BFI-T worst fatigue and fatigue severity composite scores with the vigor and fatigue subscales scores of the Profile of Mood States (POMS).[27]

2.5. Statistical analysis

Data are presented as means and standard deviations (SD) or frequencies and percentages. Differences between groups were compared using the Chi-square test or Fisher's exact test for categorical variables and Student *t*-test for continuous variables. The association between moderate-to-severe cancer-related fatigue and TCMBC was assessed using multiple logistic regression analysis with a backward selection procedure based on the likelihood ratio test. Potential confounding variables evaluated during model development included age, sex, body mass index, systolic blood pressure, diastolic blood pressure, cancer treatment, and cancer stage. The existence of multicollinearity in the independent variables was evaluated using variance inflation factor. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp. Armonk, NY). The significance level was set at 0.05 and all P values were two-tailed.

3. Results

Table 1 compares demographic and clinical characteristics between the two groups of patients with BFI-T < 4 or ≥ 4. The mean age of the 170 patients was 58 years and 58% of them were females. Slightly over a half of the patients (51%) received inpatient chemotherapy treatment, and 66% were at cancer stage III–IV. The most common types of cancer, in a descending order of frequency were breast (31.8%), head and neck (20.0%), colorectal (18.8%), other (15.3%), liver (7.6%), and lung (6.5%). In addition, no significant differences were observed between patients with or without moderate-to-severe cancer-related fatigue for all the variables in Table 1.

Table 1
Demographic and clinical characteristics of the study participants (N = 170).

Variable	n (%) or mean (SD)			P value
	All patients	Patients with BFI-T score < 4 133 (72.8)	Patients with BFI-T score ≥ 4 37 (21.8)	
Age (years)	58.0 (11.0)	57.7 (10.8)	59.1 (11.6)	0.485
Height (m)	161.0 (7.8)	160.6 (7.8)	162.3 (7.5)	0.225
Weight (kg)	60.0 (11.0)	60.2 (10.4)	59.1 (3.2)	0.571
Body mass index (kg/m^2)	23.1 (3.8)	23.4 (3.7)	22.3 (4.2)	0.152
Systolic blood pressure (mmHg)	121 (15)	121 (14)	122 (17)	0.821
Diastolic blood pressure (mmHg)	73 (5)	73 (5)	73 (6)	0.793
Sex				0.901
male	72 (42.4)	56 (42.1)	16 (43.2)	
female	98 (57.6)	77 (57.9)	21 (56.8)	
Cancer treatment				0.275
inpatient chemotherapy	87 (51.2)	71 (53.4)	16 (43.2)	
outpatient	83 (48.8)	62 (46.6)	21 (56.8)	
Cancer stage				0.873
I–II	57 (33.5)	45 (33.8)	12 (32.4)	
III–IV	113 (66.5)	88 (66.2)	25 (67.6)	
Cancer type				0.502
breast	54 (31.8)	44 (33.1)	10 (27.0)	
head and neck	34 (20.0)	28 (21.0)	6 (16.2)	
colorectal	32 (18.8)	25 (18.8)	7 (18.9)	
other	26 (15.3)	20 (15.0)	6 (16.2)	
liver	13 (7.6)	10 (7.5)	3 (8.1)	
lung	11 (6.5)	6 (4.5)	5 (13.5)	

BFI-T: Taiwanese version of the Brief Fatigue Inventory.

Table 2
Comparisons of nine types of traditional Chinese medicine body constitution between patients with mild and moderate-to-severe cancer-related fatigue.

TCMBC	n (%)			P value
	Total 170 (100)	BFI-T < 4 133 (72.8)	BFI-T ≥ 4 37 (21.8)	
Gentleness				< 0.001
yes	64 (37.6)	63 (47.4)	1 (2.7)	
no	106 (62.4)	70 (52.6)	36 (97.3)	
Qi-deficiency				< 0.001
yes	44 (25.9)	24 (18.0)	20 (54.1)	
no	126 (74.1)	109 (82.0)	17 (45.9)	
Yang-deficiency				< 0.001
yes	50 (29.4)	28 (21.1)	22 (59.5)	
no	120 (70.6)	105 (78.9)	15 (40.5)	
Qi-depression				0.005
yes	29 (17.1)	17 (12.8)	12 (32.4)	
no	141 (82.9)	116 (87.2)	25 (67.6)	
Yin-deficiency				0.646
yes	32 (18.8)	26 (19.5)	6 (16.2)	
no	138 (81.2)	107 (80.5)	31 (83.8)	
Phlegm-wetness				0.768
yes	19 (11.2)	16 (12.0)	3 (8.1)	
no	151 (88.8)	117 (88.0)	34 (91.9)	
Blood-stasis				> 0.999
yes	19 (11.2)	15 (11.3)	4 (10.8)	
no	151 (88.8)	118 (88.7)	33 (89.2)	
Wetness-heat				> 0.999
yes	8 (4.7)	7 (5.3)	1 (2.7)	
no	162 (95.3)	126 (94.7)	36 (97.3)	
Special diathesis				> 0.999
yes	2 (1.2)	2 (1.5)	0 (0)	
no	168 (98.8)	131 (98.5)	37 (100)	

BFI-T: Taiwanese version of the Brief Fatigue Inventory; TCMBC: traditional Chinese medicine body constitution.
P-values obtained from Chi-square or Fisher's exact test, as appropriate.

Table 2 shows the results comparing the proportions of patients with or without moderate-to-severe fatigue for each of the nine types of TCMBC. The proportion of patients with Gentleness TCMBC was significantly higher in those without moderate-to-severe cancer-related fatigue (P < 0.001). Conversely, the proportions of patients with Qi-deficiency (P < 0.001), Yang-deficiency (P < 0.001), and Qi-depression (P = 0.005) TCMBC were significantly higher in those with moderate-to-severe cancer-related fatigue. No significant differences were observed between the two groups in the remaining four types of TCMBC.

Of the 170 patients, 78 were classified as having only one type of TCMBC, whereas 87 and 5 were classified as having two or three types of TCMBC, respectively. Moreover, of those with two types of TCMBC, the most common combination was Qi-deficiency and Yang-deficiency (15, 8.8%), followed by Qi-deficiency and Qi-depression (8 patients, 4.7%) and Yang-deficiency and Qi-depression (6 patients, 3.5%).

Results from the multiple logistic regression analysis are shown in Table 3. Moderate-to-severe cancer-related fatigue was independently and significantly associated with Qi-deficiency TCMBC (adjusted odds ratio [aOR] = 2.84, 95% Cl = 1.18–6.82) and Yang-deficiency-depression TCMBC (aOR = 3.55, 95% Cl = 1.50–8.40), but inversely associated with Gentleness TCMBC (aOR = 0.08, 95% Cl = 0.01–0.60).

Other independent variables included during the evaluation of the multiple logistic regression model included age, sex, body mass index, systolic blood pressure, diastolic blood pressure, cancer treatment, cancer stage, Qi-depression TCMBC, Yin-deficiency TCMBC, Phlegm-

Table 3
Multiple logistic regression analysis of moderate-to-severe cancer-related fatigue.

Variable	Odds ratio (95% confidence interval)	P value
Gentleness	0.08 (0.01–0.60)	0.015
Qi-deficiency	2.84 (1.18–6.82)	0.020
Yang-deficiency	3.55 (1.50–8.40)	0.004

Nagelkerke $R^2 = 0.378$. Hosmer and Lemeshow goodness-of-fit test, $P = 0.190$.

wetness TCMBC, Blood-stasis TCMBC, Wetness-heat TCMBC, and Special diathesis TCMBC.

4. Discussion

This study is the first to show a significant association between TCMBC and moderate-to-severe cancer-related fatigue in cancer patients. Specifically, patients with Qi-deficiency TCMBC and Yang-deficiency TCMBC were independently associated with a higher risk of moderate-to-severe cancer-related fatigue, whereas those with a Gentleness TCMBC were independently associated with a lower risk of moderate-to-severe cancer-related fatigue. The larger magnitude in the adjusted odds ratio for Yang-deficiency (aOR = 3.55) compared with that for Qi-deficiency (aOR = 2.84) was consistent with the TCM theory that Yang-deficiency generally represents a more severe condition than Qi-deficiency. Conversely, the significant inverse association between a Gentleness TCMBC was also in line with the TCM theory. Individuals with a Gentleness TCMBC mean that their bodily condition is in a state of relative balance of Yin and Yang. These individuals are therefore, less prone to suffer from moderate-to-severe cancer-related fatigue.

According to TCM theory, the TCMBC of individuals is formed by Yin and Yang, and an imbalance between Yin and Yang in the body can render them more prone to certain diseases.[28–30] Several abnormalities underlie the pathogenesis of cancer-related fatigue, including the promotion of inflammatory cytokines imbalance, hypothalamus-pituitary-adrenal axis dysfunction, anemia, and cachexia have been postulated.[31,32] In addition, Yang-deficiency may not only be related to hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-thyroid axis dysfunction, but also to functional disorders of the cyclic nucleotide and immune systems.[33]

The present study found that patients with Yang-deficiency TCMBC were strongly associated with a higher risk of moderate-to-severe cancer-related fatigue. Yang is the energy needed for maintaining proper body function, and Yang deficiency can be defined as the decline of energy level. Symptoms of Yang deficiency typically include cool extremities, weak pulse, and aversion to cold temperatures.[15] It should be noted that the CCMQ should not be used as a diagnostic tool, but rather as a way to assist syndrome differentiation in TCM practice. The CCMQ is a well-validated instrument that can be used for guiding the treatment approach by Chinese medicine practitioners during disease consultation.

Fatigue is a highly common and often treatable problem that affects a cancer patient's quality of life. Therefore, all cancer patients should routinely be screened for fatigue using patient-reported outcome measures.[34] Patients with moderate or severe fatigue may benefit from pharmacologic and nonpharmacologic interventions.[35] Increasing evidence showed that TCM can safely be used as a helpful adjunct to conventional care in the treatment of cancer-related fatigue.[10,36] Clinical studies have also shown that Yang-deficiency TCMBC could be improved by acupuncture and moxibustion.[37,38] Chen et al.[39] reviewed the evidence for using TCM in the treatment of chronic fatigue syndrome. The authors indicated that ginseng root has been the most widely studied herb for fatigue because of its effect of invigorating Qi and Yang. A recent systematic review of *Panax ginseng* concluded that it is a viable and promising treatment for fatigue in people with chronic illness.[40] Moreover, Leong et al. proposed that Yang- and Qi-invigorating tonic herbs, such as *Cistanches Herba* and *Schisandrae Fructus*, might be beneficial in the treatment of chronic fatigue syndrome through their enhancement in mitochondrial function and regulation.[41]

It should be noted that while a question on "Do you get tired easily?" was included in the calculation of both the Qi-deficiency TCMBC and Gentleness TCMBC, it measured a different aspect of fatigue compared with the BFI-T. The former is an overall subjective feeling of fatigue over a long period of time (in the past year) whereas the BFI-T reflects the short-term (in the past 24 h) symptoms of fatigue. In other words, the one question on fatigue in the TCMBC and the BFI-T are not merely overlapped items on fatigue-related issues.

Some limitations of the current study should be mentioned. First, the sample size is relatively small and thus precluded further subgroup analyses to examine the association of TCMBC with different types of cancer. Second, the study participants were recruited based on convenience sampling from one regional hospital and therefore, the possibility of selection bias cannot be ruled out.

5. Conclusions

The findings of this study indicated that patients with Qi-deficiency TCMBC and Yang-deficiency TCMBC were more susceptible to moderate-to-severe cancer-related fatigue. The CCMQ could be served as a clinical tool to identify and cancer patients who are prone to experience moderate-to-severe cancer-related fatigue, and to provide Chinese medicine practitioners a basis for selecting an appropriate treatment approach based on TCMBC. Further studies on effects of prescriptions for balancing Yang and Qi on alleviating moderate-to-severe cancer-related fatigue in cancer patients are warranted.

Authorship

All authors made significant contributions to the study design, acquisition of data, drafting of the article, and final approval of the article.

Conflicts of interest statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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