


Patient Reported Traditional Chinese Medicine Spleen Deficiency Syndrome (TCM-SDS) Scale for Colorectal Cancer: Development and Validation in China

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Abstract

Introduction: Spleen Deficiency Syndrome (SDS) is recognized as one of the most common Traditional Chinese Medicine (TCM) syndromes in patients with colorectal cancer (CRC). However so far there is no existing patient-reported outcome (PRO) to evaluate SDS. Our study aimed to develop and validate a PRO TCM-SDS scale for CRC in China. **Methods:** We developed an initial 8-item TCM-SDS scale for CRC based on literature review and consultation with experts. We then pilot tested the scale ($n=40$) and performed item revision. We conducted a survey study among CRC patients from oncology clinics at a TCM Hospital to further determine the reliability and validity of the scale. **Results:** Among 100 patients finally enrolled and analyzed in the survey study, 46% were female with median age of 60 years old, 77% had left side tumors and 23% had stage IV disease. Factor loading indicated that there were three domains within TCM-SDS scale. The final TCM-SDS scale involves 5 items including “I feel loss of appetite,” “I feel abdomen fullness,” “I feel my arms and legs lack strength,” “I feel short of breath when talking,” and “My stool is formless” (Cronbach’s alpha coefficient 0.76). We calculated the total score of the scale by summing the 5 individual items and normalizing them to a value maximum of 10, with higher scores indicating greater burden of spleen deficiency syndrome. The average spleen deficiency score for all patients was 3.55 ± 1.54 . Among them, those who had stage IV disease had higher scores than stage I-III patients (4.30 vs 3.38, $P=.015$). Test-retest reliability after 2 weeks showed Pearson coefficient of 0.67 and all items were highly related ($P<.001$). Compared with healthy controls, CRC patients had significantly higher spleen deficiency scores (3.55 vs 3.23, $P=.045$). **Conclusion:** The patient-reported TCM-SDS scale for CRC showed adequate initial reliability and validity. The development of the scale provided an outcome measurement tool, which could facilitate future studies to better evaluate the role of TCM in treating CRC.

Keywords

traditional Chinese medicine, spleen deficiency syndrome, patient reported outcome, colorectal cancer, scale development, reliability, validity

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Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second cause of cancer-related death around the world.¹ With the advances of target therapy and immunotherapy, CRC patients have acquired better survival outcomes during the past decades.² However, many CRC survivors still suffer from certain symptom burdens which could impair their quality of life.³ Specifically, previous studies show that fatigue, insomnia and bowel function

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including constipation, diarrhea, and appetite loss had high prevalence in this population.⁴ To better control and relieve these symptoms, Traditional Chinese Medicine (TCM) including herbal medicine and acupuncture has usually been utilized not only in China and but also in many western countries.⁵

Treatment with syndrome differentiation is a fundamental basic TCM theory, which requires TCM physicians to prescribe the TCM treatment plan according to the patient's symptoms, pulse and tongue.⁶ Current clinical trials on TCM herbs or other interventions have been encouraged to add TCM syndrome differentiation to study design and make it closer to real clinical practice.^{7,8} A systematic review showed that prescription of herbal medicine according to TCM syndrome differentiation could promote survival benefits and reduce side effects of chemotherapy for patients with advanced non-small cell lung cancer (NSCLC), compared with TCM treatments without syndrome differentiation.⁹ In addition, researchers found that cancer patients with different TCM syndromes could have unique disease characters or special biomarkers. For example, an observational study showed that NSCLC patients who had Yin-cold syndrome were more likely to have epidermal growth factor receptor (EGFR) mutations compared to Yang-hot syndrome.¹⁰ Thus, it is necessary to apply and promote syndrome differentiation to TCM clinical practice and scientific research in cancer treatment.

Spleen Deficiency Syndrome (SDS), as shown in literature reviews, was one of the most highly reported TCM syndromes among CRC patients.¹¹ According to TCM theory, SDS indicates a cluster of symptoms including lack of appetite, fatigue and diarrhea.¹² Data mining study showed that spleen tonifying Chinese Medicine herbs including Bai-zhu, Fu-ling, Huang-qi and Gan-cao were most frequently used for TCM interventions in CRC.¹³ Meta-analysis indicated that TCM JianPi (tonifying spleen) and JieDu (eliminating toxins) herbs could improve CRC patients' quality of life and relieve symptom burden.¹⁴ Basic research revealed that CRC patients with SDS were associated with an immunosuppressive microenvironment, as well as metabolic changes mediated through gut microbiota.¹⁵⁻¹⁷ So far, diagnostic standards of SDS are still based on qualitative descriptions.^{18,19} Existing measurement instruments of SDS had not been widely utilized due to lack of patient-reported outcomes (PRO) and quantitative scales.²⁰ This study aimed to develop and validate a patient-reported TCM-SDS scale as an outcome measurement for TCM treatment of CRC in the future.

Methods

We initially developed an 8-item TCM-Spleen Deficiency Syndrome (TCM-SDS) Scale and then conducted a two-phase study among a convenience sample of 142 CRC

patients (phase I, $N=40$; phase II, $N=102$) including outpatients and inpatients from the Oncology Department of Xiyuan Hospital of China Academy of Chinese Medical Sciences in Beijing. In phase I, we conducted a pilot study and performed item-amendment. In phase II, we determined the reliability of the scale, performed item-reduction and tested validity by comparing TCM-SDS score between CRC patients and healthy controls (through a web based survey). We also conducted a second visit to evaluate the test-retest reliability of the scale. Informed consent including aim and content of the study had been printed on the top of the questionnaire and was presented for all individual participants included in both phase I and II study; because we did not collect any identifying information including name or medical record number, patients were orally consented to participate in the study and were not required to sign consent as part of this survey. The Institutional and Ethics Review Board of Xiyuan Hospital, China Academy of Chinese Medical Sciences (CACMS) approved the study protocol (2018XLA048-4).

Items Development

According to *Expert's Consensus on TCM Spleen Deficiency Syndrome Diagnosis and Treatments 2017*, spleen Qi deficiency syndrome was defined as following: Pale and/or teeth-printed tongue and weak pulse with at least 2 main and 2 secondary symptoms, or 1 main and 3 secondary symptoms (main symptoms including fatigue, loose stool, appetite loss; secondary symptoms including tired and lazy, abdomen fullness after meal, abdominal pain, tastelessness in mouth, sallow complexion, weak defecation).²¹ Based on this consensus and our clinical observational studies on SDS related symptoms among CRC patients, we finally generated the initial 8 items of the TCM-SDS scale (in Chinese) and obtained approval by TCM oncologists and physicians. In this scale, we asked patients whether they had experienced the following 8 symptoms within 7 days: "I feel loss of appetite," "I feel abdomen fullness," "I feel bowel gurgling sound after eating cold food," "I feel my arms and legs lack strength," "I feel short of breath when talking," "I feel sweating a lot after physical activity," "My stool is formless" "I need to stool more than twice a day." We scored the degree of each item on a 5-point Likert scale (1=never, 2=occasionally, 3=sometimes, 4=often, 5=always).

Pilot Study and Revision

In 2018 we conducted a pilot study on the initial version of TCM-SDS Scale among 40 CRC patients with advanced diseases in Xiyuan Hospital. We also asked patients whether all items were easy to understand or answer. Based on the pilot study, we revised the question "I don't have enough

energy to talk” to “I feel short of breath when talking” as the previous expression brought some difficulties for understanding and answering.

Validation Survey Study

Between November 2018 and November 2019, we conducted the phase II survey study with CRC patients from Xiyuan Hospital to further evaluate the reliability and validate the TCM-SDS scale. Inclusion criteria included colorectal cancer patients with pathology diagnosis at any stage and good understanding and expression of Mandarin Chinese. Exclusion criteria included all types of missed data of all the items and basic disease information. We collected patients' personal information including gender, age and Body Mass Index (BMI), disease information including tumor site, TNM stage, and time since diagnosis. We also re-contacted the patients to detect the repeated reliability of the scale two weeks after the first visit. To test whether the scale could detect the differences of SDS burden between CRC patients and healthy controls, we conducted another survey study among healthy volunteers through a web-based survey between March second and March seventh 2020. We asked volunteers to fill out the TCM-SDS scale and score their overall health condition, as well as other comorbidities if they had them.

Sample Size Calculation

For the phase I pilot study, we defined sample size as 40 to explore the feasibility of the scale. For the phase II study, we defined sample size as 10 to 15 times beyond the total number of items in the scale, which was 80, to examine its reliability and validity. By taking 20% as the missing data and no response rate into consideration, the final sample size for phase II study was calculated as 100.

Statistical Analysis

We presented descriptive data of participants' gender, age, tumor site and BMI. We also performed descriptive statistics for each scale item and examined whether ceiling or floor effects existed in any item. Factor analysis was done to evaluate correlations between items and a main factor was defined if eigenvalue was higher than 1. In addition, we performed principal components analysis to explore the potential number and characteristics of the domains. Interpretation of the results of the principal components analysis was guided by identifying eigenvalues greater than 1 and the rotated loadings of variables on the identified components. We then divided the 8 items into different domains based on factor analysis as well as clinical judgement. Cronbach's alpha coefficient was calculated for each domain. We chose the domain of items which achieved

Cronbach's alpha coefficient above 0.70, a value that is considered optimum for measuring attitude.²² We then calculated the score of the scale by summing the final items and normalizing them to a value maximum of 10. For categorical data, we presented the numbers and proportion of each group. We calculated the mean and standard deviation for continuous data such as age, BMI and TCM-SDS score. We evaluated the construct validity by correlating scores on the TCM-SDS Scale and patients' disease information by 2-sample *t*-test. We hypothesized that patients' TCM-SDS score related to their disease burden and spleen deficiency related to disease characteristics. In addition, repeated reliability was evaluated by correlation analysis. All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). All statistics were two-sided with an alpha of 0.05.

Results

Patients' Characteristics

In the phase II survey study, we finally enrolled 102 CRC patients, 2 of whom failed to finish the scale. Among 100 patients who had finally been analyzed, 46% were female with a median age of 60 years old (± 9 , Table 1). 77% of CRC patients had left sided tumors and 23% had stage IV disease. The average BMI was 23 (± 3.5).

Factor Analysis and Reliability

Factor loading indicated that there are 3 domains within TCM-SDS scale (Table 2, eigenvalues 2.74, 1.19, 1.01 respectively, explained 61.7% of the scale). We chose the first 2 domains indicating “Spleen Qi deficiency” and “Spleen Yang Deficiency” respectively. The “Spleen Qi deficiency” domain includes items 1, 2, 4, 5, and 7 (Cronbach's alpha coefficient 0.76). The “Spleen Yang Deficiency” domain includes items 3, 6, and 8 (Cronbach's alpha coefficient 0.34). Since the first domain showed good reliability, we chose these 5 items to form the final 5-item brief TCM-SDS Scale. None of the items in each domain showed ceiling or floor effects.

TCM-SDS Scale Score and Impact Factors

Among 8 items in the initial TCM-SDS scale, “I need to stool more than twice a day” had the highest score (2.67 ± 0.92), followed by “My stool is formless” (2.22 ± 0.94 , Figure 1). We calculated the total score of the scale by summing the 5 individual items (items 1, 2, 4, 5, and 7 in Table 2) and normalizing them to a value between 0 and 10. Higher scores indicated greater burden of spleen deficiency syndrome. The average TCM-SDS scale score of all patients was 3.55 ± 1.54 . Among them, those who had

Table 1. Patients' Information and TCM-SDS Scale Score.

Characteristics	N (%)	TCM-SDS score (SD) [†]	P-value (95% C.I.) [§]
Gender (n=98)			
Male	53 (54)	3.32 (1.31)	.09 (-1.17, 0.09)
Female	45 (46)	3.86 (1.76)	
Age (n=94)			
≤60	49 (52)	3.62 (1.67)	.5 (-0.44, 0.84)
>60	45 (48)	3.43 (1.34)	
Tumor site (n=92)			
Right colon	22 (24)	3.98 (1.89)	.19 (-0.26, 1.26)
Left colon	40 (44)	3.48 [‡] (1.43)	
Rectum	30 (33)		
TNM stage (n=94)			
I	8 (9)		.015 (-1.67, -0.18)
II	25 (27)	3.38 [‡] (1.35)	
III	39 (42)		
IV	22 (23)	4.30 S (1.92)	
BMI (n=95)			
≤23	42 (44)	4.03 (1.80)	.022 (0.11, 1.39)
>23	53 (56)	3.28 (1.27)	

Abbreviations: SD, standard deviation; 95% C.I., confidential interval; BMI, body max index.

[†]TCM-SDS score was described as mean (standard deviation), we used a t test to compare the mean differences between groups.

[‡]For tumor site, TCM-SDS score was compared between right side and left side (including left colon and rectum); For TNM stage, TCM-SDS score was compared between stage I-III and stage IV.

[§]Statistical significance was set at $P = .05$.

Table 2. Factor Analysis of TCM-SDS Scale.

Items	Factor 1 [†]	Factor 2 [‡]	Factor 3
No. 1 I feel loss of appetite	0.808	-0.209	0.058
No. 2 I feel abdomen fullness	0.573	-0.230	0.441
No. 3 I feel bowel gurgling sound after eating cold food	0.424	0.497	-0.029
No. 4 I feel my arms and legs lack strength	0.730	-0.195	-0.278
No. 5 I feel short of breath when talking	0.746	-0.344	-0.136
No. 6 I feel sweating a lot after physical activity	0.197	0.550	-0.440
No. 7 My stool is formless	0.583	0.374	-0.208
No. 8 I need to stool more than twice a day	0.325	0.499	0.694
Eigenvalue	2.74	1.19	1.01
Cronbach's alpha coefficient	.76	.34	—

[†]Factor 1 indicating "Spleen Qi deficiency" domain, which includes items 1, 2, 4, 5, and 7 (items appeared in bold).

[‡]Factor 2 indicating "Spleen Yang Deficiency" domain includes items 3, 6 and 8 (items appeared in bold).

stage IV disease had higher TCM-SDS scores than stage I-III patients (4.30 vs 3.38, $P = .015$). Patients with BMI lower than 23 had higher TCM-SDS burden (4.03 vs 3.08, $P = .022$).

Test-Retest Reliability

There were 69 patients who accepted our second visit. The score between the first and second-time measure

(3.06 ± 1.18) is highly correlated (Pearson coefficient of 0.73, $P < .001$).

Validity

We enrolled 222 healthy controls and excluded those who perceived their overall healthy conditions were lower than 5 (0-10), as well as those who had hypertension, diabetes, heart diseases and gastro-dysfunctional diseases. Among

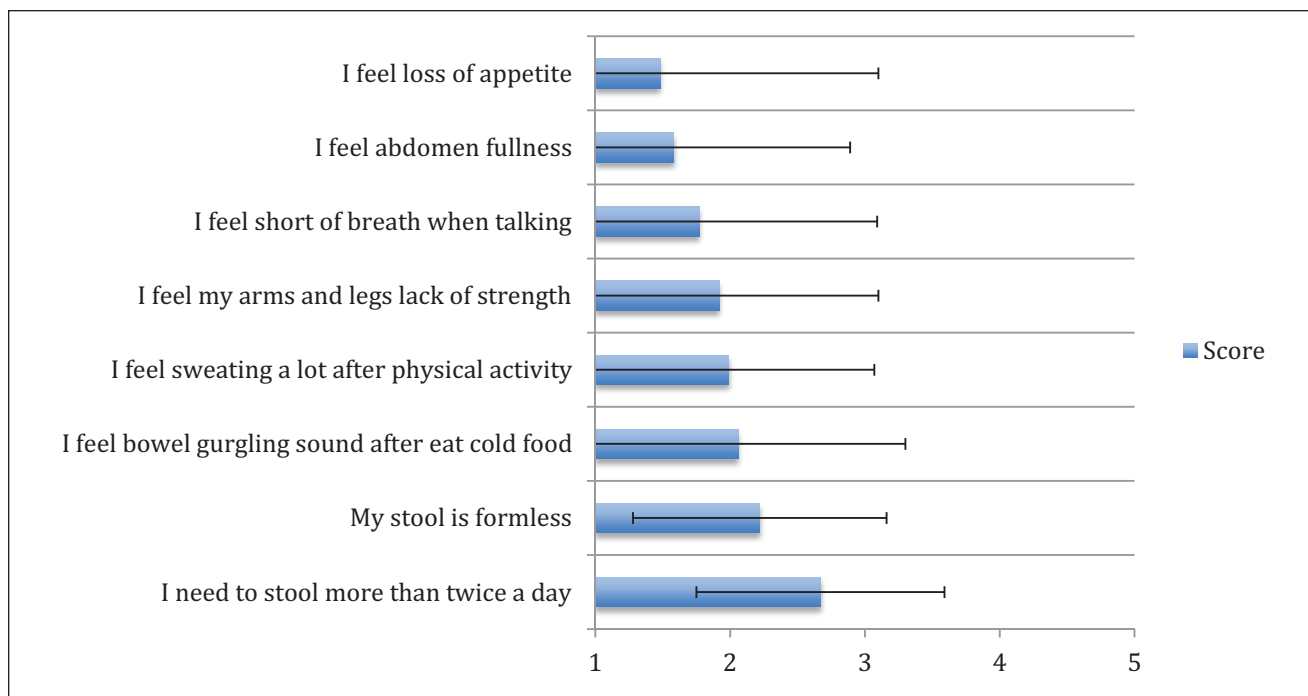


Figure 1. Score for each item in TCM-SDS scale.

176 healthy controls, the average score for TCM-SDS was 3.23 ± 1.15 , which was significantly lower than that for CRC patients (3.55 ± 1.54 , $P = .045$).

Discussion

In this study, we developed a patient-reported TCM-SDS scale (5 brief item) for CRC patients to measure spleen deficiency syndrome related symptom burden. All items and scoring methods could be easily understood and answered by patients. The scale had reliable consistency with a Cronbach's alpha coefficient reaching 0.76, as well as repeated reliability. Measurement of TCM-SDS is sensitive when comparing the scores between CRC patients and healthy controls, which indicated a good validity. In addition, we found that TCM-SDS score was significantly correlated with CRC patients' TNM stage and BMI. We believed that TCM-SDS scale could provide a reliable and quantitative tool for study outcome measurement on TCM interventions for CRC.

Compared with existing TCM-SDS measuring methods, ours has shown consistency with previous findings and certain advantages. Similar to the final 5 items in our scale, Hou et al²⁰ had also found that fatigue, tiredness, loose stool and poor appetite were related with TCM-SDS among CRC patients and developed a quantified diagnostic standard of SDS for CRC. However, the description of the symptoms in Hou's study utilized traditional TCM terminology, for

example "Shen Pi" and "Na Dai," which were difficult for patients and researchers without TCM educational background to understand. In our scale, we interpreted all symptoms in a more comprehensible way and used a 5-point Likert score to evaluate symptom levels instead of the two-category options in Hou's scale. Other methods, for example artificial intelligence (AI) tongue diagnosis, still have barriers for clinical utilization.²³

In our study, we found that CRC patients with metastatic disease had higher TCM-SDS score than those in early stage. Although patients with advanced disease usually had higher symptom burden, whether TCM-SDS score could predict survival outcomes still needs further evaluation. According to our results, patients with lower BMI had higher TCM-SDS score, which might be related to impaired digestive function. A previous cross-sectional study showed that among 1390 healthy, sub-healthy participants and chronic disease patients, the severity of SDS was significantly associated with age.¹⁹ However, we did not find such difference in our study. During test-retest, the TCM-SDS score had been significantly decreased after 2 weeks because most participants in our study were undergoing TCM treatments at the time of survey. A randomized controlled trial showed that TCM herbal medicine LiuJunZi decoction could significantly improve dyspepsia symptoms among patients with SDS.²⁴ The TCM-SDS scale could be used as a reliable measurement tool for evaluating TCM's

effectiveness on relieving symptom burden and promoting quality of life among CRC patients.

The mechanism of TCM-SDS and its relationship with CRC is still not fully clear. In 2016, Yang et al²⁵ observed that the serum microRNA of patients with SDS were significantly enriched in 18 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and 7 Gene Ontology (GO) molecular functions including metabolism, signaling pathways of insulin and chemokines, invasion of bacterium and so on. Lin et al¹⁷ found that the abundance of *Firmicutes* in SDS patients' stool samples was largely increased while *Bacteroidetes* were significantly decreased. Yang et al¹⁵ hold the view that immunosuppressive cytokines from chronic inflammation, tumor-derived immunosuppressive factors and surrendered immune cells-regulatory T cells constituted the tumor microenvironment of CRC patients with SDS. By analyzing 80 CRC patients' tissues and blood samples, Sui et al¹⁶ found that there were significant differences on protein expression levels (especially for mutant TP53, PCNA, PD-L1, and Ki-67) between SDS and dampness-heat syndrome. Based on these findings, the interaction between the microbiome and immune regulation is one of the future directions to better understand the role of SDS in colorectal cancer's development and treatment.

We have certain limitations in this study. First, the current survey study was conducted among patients who had been receiving treatments at a TCM hospital. The scale needs to be tested in a more diverse population, for example CRC survivors who are not under active cancer treatments or TCM treatments. In addition, the reliability and validity of the English version of the current scale still needs further evaluation to adapt cultural differences. We also need to point out that the current TCM-SDS scale could not provide diagnostic threshold value for whether patient had or did not have SDS. Receiver operator characteristic curve (ROC) analysis is necessary to further investigate the potential diagnostic function of TCM-SDS scale. In the future, we will keep on updating the TCM-SDS scale to make it fit for patients with other cancer types and gastrointestinal benign tumors.

In conclusion, the development of this quantitative and patient-reported TCM-SDS scale could facilitate future studies to better evaluate TCM's role in treating CRC, especially those related with SDS. The brief 5-item TCM-SDS Scale for CRC has good reliability and validity which could be applicable to clinical practice and research as an outcome measurement instrument. Future study will be dedicated to validating the scale in other language outside China and to carrying out more prospective studies to expand its application.

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Authors' Contributions

Lingyun Sun, study design, analysis and manuscript drafting; Jun J Mao, study design and manuscript drafting; Yunzi Yan, data collection; Yun Xu, study design; Yufei Yang, study design and administration support.



Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The Institutional and Ethics Review Board of Xiyuan Hospital, China Academy of Chinese Medical Sciences (CACMS) approved the study protocol (2018XLA048-4). All patients were orally consented before completed the scale survey. The authors report no conflicts of interest. All authors of this research paper have directly participated in the drafting of the manuscript. All authors of this paper have read and approved the final version submitted.

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