European Journal of Integrative Medicine 7 (2015) 358–364

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/eujim

Methodological challenges in mapping chinese medicine syndrome with conventional diagnosis: Implications for multi-centre trials in integrative medicine☆

Scott R. Shuldiner[a], Vincent CH Chung[a,b,*], Xinyin Wu[a,b], Jessica Ching[a,c], Robin ST Ho[b], Pui Kuan Cheong[a,c], Wendy Wong[a,d], Justin CY Wu[a,c]

[a] Hong Kong Institute of Integrative Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
[b] Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
[c] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
[d] School of Chinese Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

ARTICLE INFO

Article history:
Received 30 April 2015
Received in revised form 3 July 2015
Accepted 12 July 2015

Keywords:
Functional dyspepsia
Syndrome differentiation
Diagnosis
Randomized controlled trial

ABSTRACT

Introduction: Chinese medicine (CM) diagnostic instruments are increasingly developed to classify patients into different syndrome subtypes, potentially allowing for subgroup analyses in randomized trials. However, its external validity has been questioned. We illustrated this problem by evaluating a previously validated Functional Gastrointestinal Disorder CM Syndrome Differentiation Instrument (FDCMI) on a heterogeneous sample of functional dyspepsia (FD) patients.
Methods: A cross-sectional study was performed using two questionnaires to diagnose FD patients from both conventional and CM perspectives. CM diagnostic subtypes were classified into Spleen-Stomach Qi Deficiency (QD), Liver Qi Stagnation (LQS), Dampness Syndrome (DS), and Qi Stagnation (QS) by the FDCMI. Descriptive analyses were used to illustrate relationships between conventional and CM diagnostic criteria. Explanatory factor analysis (EFA) was performed to explore the underlying factor structure of FDCMI in the current sample.
Results: Data were successfully collected from 224 FD patients, with a response rate of 83.7%. Respectively 49 (21.9%) and 162 (72.3%) patients qualified for conventional FD diagnostic criteria under the Rome III (R-FD) criteria and modified Rome III (M-FD) criteria. Respectively 118 (52.7%), 116 (51.8%), 116 (51.8%) and 107 (47.8%) patients qualified for a diagnosis of QD, LQS, DS and QS under the FDCMI criteria using a 30% cutoff threshold of the total subscale score for each CM diagnostic subtype. Forty patients (17.9%) did not qualify for any single CM subtype under this threshold. Most patients belonged to more than one CM subtype. EFA results revealed an 8-factor structure that accounts for only 59.4% of the total variance.
Conclusions: Due to population heterogeneity, differences in disease phenotype, diagnostic performance of conventional tests, co-morbidity and cut-off threshold, CM diagnostic instruments may have limited external validity, potentially reducing their applicability in multicenter trials.

1. Introduction

Integrative medicine (IM) aspires to combine elements of conventional and complementary medicine to provide holistic healthcare based on inter-professional collaboration between clinicians from both paradigms [1]. However, the reconciliation of the two schools of medical thought has been relatively controversial, especially regarding the fundamental differences in diagnostic approaches. For instance, syndromes identified from Chinese medicine (CM) diagnosis may be highly heterogeneous, even for a single disease confirmed by conventional medicine standard [2]. Without a concordant diagnosis between conventional and Chinese medicine, designing pragmatic randomized clinical trials that incorporate CM syndrome types becomes difficult, if not impossible. Thus, many existing trials disregard

Abbreviations: FDCMI, functional gastrointestinal disorder CM syndrome differentiation instrument; QD, spleen–stomach Qi deficiency; LQS, liver Qi stagnation; DS, dampness syndrome; QS, Qi stagnation.

☆ This article belongs to the Special Issue on Diagnostic Techniques and Outcome Measures for Integrated Health.

* Corresponding author at: 4/F, School of Public Health Building, Prince of Wales Hospital, Shatin, Hong Kong.
E-mail address: vchung@cuhk.edu.hk (V.C. Chung).

http://dx.doi.org/10.1016/j.eujim.2015.07.027
1876-3820/

CM syndrome type, which limits the model and external validity of trial results [3].

One possible solution to this issue is the development of psychometrically sound, patient-reported CM syndrome differentiation instruments for a specific conventional diagnosis [4]. With good reliability, validity, responsiveness and clinical relevance [5], it is expected that such an instrument could be used as a prognostic factor for subgroup analysis of pragmatic trials [6]. However, whether these psychometric properties can be preserved across populations is unknown. For instance, a CM syndrome differentiation instrument developed in the United States has reported "excess", "deficiency" or "mixed excess—deficiency" CM subtypes among American patients with irritable bowel syndrome (IBS) [7], but its applicability in other populations (e.g., IBS patients in China) is unknown. External validation of CM syndrome differentiation instruments is required to confirm its psychometric stability among heterogeneous populations [8]. This is particularly important in the design of multi-center, pragmatic CM trials, which often involve heterogeneous samples of patients. For instance, if a US-China multi-center trial on Chinese herbal medicine for IBS were planned, it would be essential to know whether it is possible to classify IBS patients from both populations into the three subgroups of "excess", "deficiency" or "mixed excess—deficiency." Indeed, some other scheme may be needed to classify the Chinese sample.

1.1. Chinese medicine diagnostic instruments: does one size fits all?

The ideal of stratifying patients with a certain conventional diagnoses by a fixed CM diagnostic subtype may not be feasible, especially when a CM diagnostic instrument developed in one sample is being applied in another. Limitations on external validity can vary according to the following [9]:

(i) differences in population heterogeneity (e.g., patients' severity and duration of symptoms);
(ii) differences in the target condition itself (e.g., presence of co-morbidities and variations in disease symptomology);
(iii) diagnostic performance of different conventional tests (e.g., variations in sensitivity and specificity among different diagnostic tests); and
(iv) co-morbidity and cutoff threshold of the CM diagnostic instrument (e.g., presence of overlapping CM syndrome and arbitrary choice of cutoff score)

In this study, we aim to demonstrate how these four factors may interact to impact CM diagnostic classification, using a case study of mapping CM and conventional diagnoses of functional dyspepsia (FD) as an example.

1.2. Diagnosis of functional dyspepsia: perspectives from conventional and chinese medicine

From a conventional medicine perspective, FD is characterized by a variety of painful and non-painful symptoms including upper abdominal fullness, bloating, early satiety, nausea, epigastric burning, vomiting and belching. FD and its associated dyspeptic symptoms are extremely common in the general population with an estimated prevalence of 30% in industrialized nations [10]. In Asia, the prevalence has been estimated at 8–23% [11]. Conventional medicine characterizes FD as a heterogeneous condition lacking easily identifiable physiological markers and pathology. According to the most recent Rome III criteria [12,13] FD manifests as four cardinal symptoms believed to originate from the gastroduodenal region: (i) postpradial fullness, (ii) early satiety, (iii) epigastric pain and (iv) epigastric burning [14]. The symptomology of FD is made more complex by the presence of a common co-morbidity, irritable bowel syndrome (IBS) [15]. These variations in disease characteristics have made FD a good candidate to demonstrate how such variation may impact the concordance of conventional and CM diagnoses (Point (ii) of Section 1.1).

From the CM perspective, the Functional Gastrointestinal Disorder CM Syndrome Differentiation Instrument (FDCMI) has been published as a patient-reported CM diagnostic instrument for FD. The 24-item FDCMI has been developed using structural equation modelling and item response theory, and it has been validated in a sample of 301 FD patients in Guangzhou, China. The instrument claims to classify FD patients into four major CM diagnostic subgroups by the following subscales: (i) liver-Qi stagnation (LQS, 3 items), (ii) dampness syndrome (DS, 3 items), (iii) spleen–stomach Qi deficiency (QD, 11 items) and (iv) Qi stagnation (QS, 7 items) [16]. For each item, patients provided a rating on a Likert scale, with 11 items on major symptoms (主證) scored from 1 to 5 and the remaining 13 items on supplementary symptoms scored from 0.5 to 2.5 (次證). Classification is based on patients' total scoring on each of these four subscales, but there is no established threshold to determine when a patient should belong to a particular subgroup. With varying thresholds (e.g., 30–50% of total subscale score), a patient can often have more than one CM subtype diagnosis. If a high degree of overlapping exists, then the original goal of using CM diagnostic groups for subgroup analysis in trials is unlikely to be feasible due to lack of clear distinctions between patient subgroups. Overlapping CM diagnoses and lack of established diagnostic cutoff scores are common limitations among CM diagnostic instruments like FDCMI. Thus, the FDCMI represents an ideal candidate for demonstrating how these problems may hinder the application of CM subgrouping in pragmatic trials (Point (iv) of Section 1.1).

Table 1
Conventional FD and IBS diagnoses for the two samples.

	FD diagnostic criteria		Rome III-based IBS diagnosis						
	M-FD	R-FD	IBS	IBS-C	IBS-D	IBS-M	IBS-U	R-FD + IBS	M-FD + IBS
Sample 1 [n (%)]	95 (74.2)	28 (21.9)	9 (7.0)	2 (1.6%)	2 (1.6)	2 (1.6)	3 (2.3)	5 (3.9)	8 (6.3)
Sample 2 [n (%)]	67 (69.8)	21 (21.9)	8 (8.3)	0 (0.0)	3 (4.5)	5 (3.1)	0 (0.0)	4 (4.2)	8 (8.3)
TOTAL [n (%)]	**162 (72.3)**	**49 (21.9)**	**17(7.6)**	**2 (0.9)**	**5 (2.2)**	**7 (3.3)**	**3 (1.3)**	**9 (4.0)**	**16 (7.1)**

Keys: FD, functional dyspepsia; M-FD, modified diagnostic criteria for functional dyspepsia; R-FD, Rome III diagnostic criteria for functional dyspepsia; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, IBS with mixed constipation and diarrhea; IBS-U, unsubtyped IBS.