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Somatic Symptom Scale-China (SSS-Ch) study: protocol for measurement and severity evaluation of a self-report version of a somatic symptom questionnaire in a general hospital in China

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Keywords:	Somatic Symptom Scale-China, somatic symptom disorder, mental disorders management

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Somatic Symptom Scale-China (SSS-Ch) study: protocol for measurement and severity evaluation of a self-report version of a somatic symptom questionnaire in a general hospital in China

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ABSTACT

Aim The current self-reporting questionnaires neither sufficiently consider accompanying anxiety and depression nor are validated for monitoring the treatment efficacy of the patients with somatic symptom disorder (SSD). The Somatic Symptom Scale-China (SSS-Ch) questionnaire was developed due to the urgent clinical demand in general hospitals. We attempt to determine if this self-administered SSS-Ch could serve as a timely and practical instrument to detect SSD and to assess the severity of this disorder.

Methods/Design A prospective diagnostic study conducted at 3 centres. Patients without organic disease but presenting with physical discomfort will be recruited and undertake the SSS-Ch, the Patient Health Questionnaire-15 (PHQ-15), the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder Scale-7 (GAD-7) checklists. An independent diagnosis will be made by a primary care physician using the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criterion standards. Patient with SSD will be selectively prescribed according to the severity category assessed by physician, selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors. Two-, 6-, and 10-week follow-ups will be scheduled for repeating the questionnaires in patient with SSD. The primary outcomes will be diagnosis and severity assessment accuracy of SSD. Secondary outcomes will be whether the SSS-Ch is effective in monitoring treatment efficacy of SSD in primary care patients, whether the current cut-off value needs to be optimized, and how often somatic disorder is accompanied by anxiety or depression.

Ethics and dissemination Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016. The findings of this study will be disseminated via peer-reviewed journals and presented at international conferences.

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Strengths and limitations of this study

1. A strength of this study is that solid validation is achieved. The SSS-Ch is designed to be double verified by both the DSM-5 and treatment efficacy.

2. It is suitable for Chinese national conditions.

3. 50% of the items in the SSS-Ch are designed for depression or anxiety since it is stated in the DSM-5 that SSD can be accompanied by depression or anxiety.

4. The current SSS-Ch study is further modified based on the DSM-5 and, for the first time, is applied for evaluating its clinical utility.

5. A potential limitation of this study is that our current study only represents the efficacy of SSS-Ch utility in patients without organic diseases, and the study was designed as a midterm investigation with four measurement points, so missing data are to be considered.

Keywords

Somatic Symptom Scale-China; somatic symptom disorder; mental disorders management.

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INTRODUCTION

One of the most common medical conditions seen in general hospitals is somatic symptom disorder (SSD)[1 2]. SSD refers to symptoms reported by patients that often difficult to explain after adequate evaluation[3], and even when significant medical disease is present, the patients' symptoms may nonetheless be unrelated to their disease[2]. Cardiac neurosis, irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome are related terms to describe these "functional diseases" in various clinical departments, while "SSD" is the term used in the field of psychiatry and psychology (ICD-10, DSM-5)[2 4]. The disorder has an estimated current prevalence in the general population of 1% to 19%[2] and in general medical practice of 16% to 30%[5-7]. Up to 70-80% of patients choose to visit a general hospital instead of a psychiatric clinic[2]. The recognition rate is unsatisfactory due to the diagnostic complexity; therefore, patients would sustain somatic symptoms without appropriate treatment due to the lack of awareness or effective screening instruments for SSD. Patients with somatization had approximately twice the outpatient and inpatient medical care utilization and twice the annual medical care costs as non-somatizing patients. An estimated $256 billion in annual medical care cost is attributable to the incremental effects of somatization alone[1]. Whereas depression and anxiety disorders are widely researched, SSD has been far less studied. Follow-up or treatment studies of this kind are even scarcer. Hence, it is of great importance for primary care physicians to be prepared to, in a timely manner, identify as well as grade symptom severity and treat SSD, which can result in high degrees of morbidity, lost productivity, and overutilization of medical resources[8 9].

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is currently the "gold standard" for the diagnosis of SSD[2], with the aim of avoiding the omission of patients and assessing the disorder severity. The DSM-5 criteria emphasized that it is important to evaluate patients in terms of psychology, behaviour and their body

conditions and then treat the patients according to the severity of the disorder. The DSM-5, however, is hard to follow clinically since it depends on qualified and experienced physicians with an interview longer than half an hour. It is more clinically practical to detect a disorder by self-administered questionnaires, where patients can score symptoms according to their own condition and severity in a short time. The most available questionnaires are the Patient Health Questionnaire-9 (PHQ-9)[10] and the Generalized Anxiety Disorder Scale-7 (GAD-7)[11]. The PHQ-9 is used for assessing depression, and the GAD-7 is focused on anxiety. Both are widely used in clinical practice and research, but it remains unknown whether they can be used for screening SSD. The Patient Health Questionnaire-15 (PHQ-15)[12] and its simplified version—the Somatic Symptom Scale-8 (SSS-8)[13]—were developed in recent years, aiming to provide a reference for physicians to detect suspected somatic burden quickly in health care visits. However, their efficacy for treatment evaluation is unclear. In addition, it is stated in the DSM-5 that SSD could be accompanied by depression or anxiety. Approximately 57.7% of SSD patients had comorbid anxiety or depressive disorder, as reported by Arthur et al.[1], but there are just 2 items related to depression on the PHQ-15 and SSS-8 scales. We developed a self-administered questionnaire, the SSS-Ch, that integrates somatic symptoms with depression and anxiety items. It is designed to aid in screening for SSD diagnosis, SSD burden assessment and follow-up monitoring.

The Somatic Symptom Scale-China (SSS-Ch) was developed based on the DSM-5 to investigate suspected SSD. It is an abbreviated 20-item version of somatic symptoms that can be entirely self-administered by the patient. The SSS-Ch is designed to assess the presence and severity of common somatic symptoms. Our previous study validated its reliability and validity[14]. Items in the scale include somatic symptoms (50%, 10/20 items), anxiety (20%, 4/20 items), depression (20%, 4/20 items), and anxiety and depression (10%, 2/20 items). Unlike the severity category from the DSM-5, the severity assessment of the SSS-Ch is based

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on both individual items and the general evaluation. In addition, it is specified in each item and avoids certain questions to accommodate Chinese culture. The SSS-Ch is designed to be administered to outpatients in internal medicine. It aims to establish a more accessible and affordable way to increase the health of patients.

Study objectives and research questions

Primary objectives

The primary objectives of this study are to test the clinical utility: (1) Diagnostic accuracy: we expect that with a DSM-5-referenced physician diagnosis as the gold standard, somatic symptom disorder assessed by the SSS-Ch will be as accurate as the current PHQ-15 evaluation. (2) Somatic burden assessment: we expect to use the SSS-Ch for measuring SSD severity.

Secondary objectives

Secondary objectives include the following: (1) We intend to observe the characteristics of the SSS-Ch for its efficacy in monitoring the treatment effect in primary care patients. In detail, we intend to explore whether the SSS-Ch is non-inferior compared to the PHQ-15, PHQ-9, or GAD-7 and to determine in which aspect the SSS-Ch has an advantage. (2) We intend to evaluate whether the current cut-off value needs to be optimized. (3) We aim to determine how often SSD is accompanied by anxiety or depression or in which circumstances SSD is accompanied by anxiety or depression.

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METHODS

Study overview

This study will use a prospective interventional diagnostic design and will be conducted in the internal medicine department at 3 sites of a tertiary general hospital in Shanghai, China. This study protocol was approved by the ethics committees of Renji Hospital, and written informed consent will be obtained from all study participants. Clinical trial registration can be found at https://register.clinicaltrials.gov/, and the registration number is NCT03513185.

Particular attention will be paid to ensure the appropriate storage of this study. Patient and reviewer confidentiality will be maintained, and no identifying features will be published. The protocol development is adhered to the EMA guideline for diagnosis study[15].

Description of the SSS-Ch and Assessment of Severity

The SSS-Ch is a somatic symptom scale (**Figure 1**) we derived from the DSM-5. It queries approximately 10 somatic clusters that account for 50% of the physical complaints (1 item per body system). Another 50% composes the anxiety and depression items (anxiety, 20% (4/20); depression, 20% (4/20); anxiety and depression, 10%). Subjects are asked the following: "Since you have felt unwell, how often have you been bothered by any of the following problems?" For scoring, subjects are asked to rate the severity of each symptom as 1 ("does not exist"), 2 ("bearable"), 3 ("influences daily work to some extent") or 4 ("unbearable"). Thus, in determining the SSS-Ch score, each individual symptom is coded as 1-4, and the total score ranges from 20 to 80. Severity categories are assessed in accordance with SSS-Ch percentile ranks. SSS-Ch scores within cut-off points of normal range-39, 40-59, and ≥60 represent mild, moderate, and severe SSD. The selection of these cut-off values takes into account the results of our previous study (a reliability and validity study of the early version of SSS-Ch) [4] and clinical experience.

Study Design

Consecutive outpatients complaining about physical discomfort will first undergo corresponding examinations. For patients with no systemic disease that can account for their discomfort, the patient will be considered to have a probability of somatic disorder. Patients will then be transferred to a specialist clinic for suspected SSD. Before seeing their physicians, patients will undertake the SSS-Ch, the PHQ-15, the PHQ-9 and the GAD-7 questionnaires, and non-clinical research assistants will collect the questionnaires and determine the scores. A physician who is blind to the results of the SSS-Ch will separately evaluate the patient and will give prescriptions according to the DSM-5 severity category. Two-, 6-, 10-week follow-ups will be scheduled for repeating the questionnaires for patient with medications. A 20-Item Short Form Health Survey (SF-20) will be conducted as the healthy reference during follow-up. A study flow chart is shown in **Figure 2**.

Participants and procedure

Inclusion criteria

(1) patients aged 18-80 years old; (2) patients who have no previous diagnosis of somatic disease; (3) patients without systemic disease that can account the physical discomfort; (4) patients who agree to complete the checklists and undergo assessment by a physician.

Exclusion criteria

(1) patients who have lost their self-assessed abilities or refuse to participate; (2) patients who have been previously confirmed to have serious mental disorders, mental retardation or dementia; (3) patients who are taking anti-anxiety agents or anti-depression agents; (4) patients who are unable to complete at least 1 follow-up.

Blinding

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After a patient with suspected SSD is transferred to the specialist clinic, the patient will first complete the questionnaires in a separate room; then, an initial consultation will be blindly conducted by a physician who has been qualified as a National Psychological counsellor. An independent diagnosis and severity category will be assigned by the physician using the DSM-5 criterion standard. The time of the self-report scale and the physician assessment will be separately recorded.

Intervention

Medications will be given according to the physician's evaluation. Anti-anxiety treatment or anti-depression treatment will be selectively administered according to the severity of somatic symptom burden. Generally, members of the thioxanthene class, such as Deanxit, that are used as mild, selective serotonin reuptake inhibitors (SSRIs) are applied for moderate symptoms, and serotonin-norepinephrine reuptake inhibitors (SNRIs) are applied for severe symptoms based on the DSM-5, with the serotonin antagonist and reuptake inhibitor (SARI) class prescribed if sleeping problems exist.

Follow-up

A face-to-face interview will be scheduled at 2, 6, and 10 weeks for patients taking medication in order to follow-up using the SSS-Ch, PHQ-15, PHQ-9 and GAD-7 questionnaires. An SF-20 survey will be conducted as the healthy reference to evaluate patient status.

Outcome measures

Reliability & Validity

Reliability will be measured by the Cronbach's alpha. A randomized sample of approximately 100 participants will be asked to complete the checklists 1 week after the initial completion to analyse the test-retest reliability.

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Criterion validity will be calculated by the correlations of the diagnostic results and severity assessments of somatic symptoms between the SSS-Ch and the gold standard.

Construct validity will be tested by confirmatory factorial analysis comparing corresponding factors with the PHQ-15, PHQ-9 and GAD-7. (The SSS-Ch consists of 10 questions for somatic symptom, 4 for depression, 4 for anxiety, and 2 for depression-anxiety.)

Diagnostic performance

Diagnostic accuracy of a questionnaire is measured by the AUC of an ROC curve, the sensitivity / specificity under given cut-off values, and the positive / negative predictive values in the study population, referring to the physician diagnosis as the gold standard.

Accuracy of severity assessment of a questionnaire is measured by the Spearman correlation between the questionnaire score and the physician's severity assessment.

Other Clinical utilities

Convenience in clinical practice is measured by the average time taken to complete each questionnaire or receive a diagnosis from a physician.

Clinical utility in monitoring treatment efficacy of SSD in primary care patients is measured by correlation with the reference SF-20 during follow-up visits.

Sample size calculation

The calculation considers the sample sizes for both the comparison of SSD diagnosis and the severity assessment, whichever one was larger. In the pilot study, the prevalence of SSD was 76.9% in the study population who were referred to the special clinics, the AUC of the ROC curve for PHQ15 was 0.88, and the correlation of the PHQ15 score with the physician's diagnosis was 0.77 (95%CI: 0.43, 0.92). The correlation of SSS-CH and PHQ15 scores was set to 0.6. With a non-inferiority margin of 0.05, α=0.025, and β=0.8, the sample size for SSD diagnosis was 852. With a non-inferiority margin of 0.1, α=0.025, and β=0.8, the sample size

for severity assessment was 579. Therefore, as the overall sample size of this study was N=852 with SSD-positive N+=655, and SSD-negative N-=197, both the positive and negative sample size requirements were met.

Statistical analysis

We will compute the mean (SD) questionnaire scores and the number of patients (%) in each diagnostic category as descriptive statistics.

Reliability will be measured using Cronbach's α. The criterion validity will be measured by the kappa coefficient of diagnosis and the Kendall tau-b of severity assessment. Construct validity will be tested using confirmatory factor analyses.

The primary analysis of the diagnostic performance will consist of two comparisons using Bonferroni correction: (1) the non-inferior comparison of SSS-Ch with PHQ-15 in the SSD diagnostic accuracy as measured by the AUC of ROC with Δ=0.05, α=0.025 in the whole study population; (2) the non-inferior comparison of SSS-Ch with PHQ-15 in the SSD severity assessment measured by Spearman's correlation with Δ=0.1, α=0.025 in the population with a confirmed SSD diagnosis. Both comparisons refer to the physician's diagnosis as the gold standard. If either non-inferior is met, the corresponding superior will be tested.

As a secondary analysis, the sensitivity, specificity, and positive and negative predictive values will also be reported. We will further optimize and validate the cut-off values of the SSS-Ch. In addition, we will compare the time to complete each questionnaire and be diagnosed by a physician and will compare the correlation between questionnaire scores and the quality of life (SF-20) in the follow-up data.

Sensitivity analysis will be conducted by comparing the analysis results with and without sex and age adjustment. Missing values will be imputed with a state-of-the-art technique[16].

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Patient and public involvement statement

Development of the research question

Up to 70-80% of patients with SSD visit a general hospital instead of a psychiatric clinic. The current self-reporting questionnaires neither sufficiently consider accompanying anxiety and depression nor are validated for monitoring the treatment efficacy of such groups. The SSS-Ch questionnaire was developed due to the urgent clinical demand in general hospitals.

Outcome measures informed by patients' priorities, experience, and preferences.

Research assistant will be dedicated to help patient understand the questions. We also take care of the patients' comfort in completing the questionnaires including the set of questionnaires needed, special clinic prepared, patient privacy protection.

Patients involvement in the design of this study

Patients were got involved in the following aspects in the design of this study: the understandability, acceptability of the language of the questionnaires, the number of questionnaires, the acceptable time to complete the questionnaires, the follow-up method, the manner of notification of the disease condition, the manner of feedback during the research process.

Patient involvement in the recruitment and conduct of the study

Patient are allowed to recommend other potential study candidates. We also encourage patients to give feedback on issues in the early and mid-term phase of the study.

Study dissemination to study participants

Patients will be informed of the results immediately after the physician consultant and the questionnaire are completed. Patients will communicate with the doctor throughout the

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diagnosis and treatment. The study results will be written and submitted for publication in peer-reviewed journals. Patients can get the published article for personal use.

Current status

The first study participant was enrolled in November 2017. In May 2018, patient recruitment was not completed.

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DISCUSSION

In this study protocol, we describe a diagnostic study design that evaluates the efficacy of a newly developed somatic symptom scale from China for patients with suspected somatic diseases, which might be applied as a first-line instrument for screening and monitoring the treatment efficacy in individual outpatient consultations. We expect that a study physician will benefit from the SSS-Ch on a clinically significant level in a timely manner and that the participants will benefit from improving their awareness and self-monitoring of the disease. Moreover, we will examine the characteristics of the SSS-Ch compared with other somatic symptom questionnaires.

Our SSS-Ch is designed as a "one-stop shop" tool that combines somatic items with mental disorder items. This is consistent with the suggestion in the DSM-5 that somatic symptoms are likely accompanied by depression and anxiety[1]. Somatic symptoms may interleave with mental items, and the mental symptoms may be triggered differently from conventional mental diseases in this group. Clinically, it is not easy to clearly separate body from mental status, and each item's significance is unknown. We caution that 50% of mental items have the possibility of increasing the incidence of SSD, and a subgroup score with somatic symptom items alone is used for this appraisal.

This trial had some limitations. First, SSD can be accompanied by diagnosed medical disorders. Our current study, however, only represents the efficacy of SSS-Ch utility in patients without organic diseases. With this in mind, further application of the SSS-Ch in specific diseases should be separately investigated. Second, the study was designed as a mid-term investigation with four measurement points, so missing data are to be considered. Referring to the fact that only 16% of patients in the PRIME-MD study (primary care evaluation of mental disorders study) were involved in follow-up [17], we estimate that a high rate of missing data will occur in patients with SSD. Fortunately, each subject in our study

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will undergo the same set of questionnaires for the entire scale, so the missing samples who are lost to follow-up will not differ among the groups and therefore will not produce significant bias and will not affect our assessment.

The study had several strengths. First, solid validation is achieved. The SSS-Ch is designed to be double verified by both the DSM-5 and treatment efficacy. Second, it is suitable for national conditions. Considering Chinese culture, we modified some items such as sexual discomfort into "discomfort at the below region", and each item was detailed for subjects to choose in order not to miss a patient's ailment or promote sensitivity. Third, 50% of the items in the SSS-Ch are designed for depression or anxiety since it is stated in the DSM-5 that SSD can be accompanied by depression or anxiety. Finally, our previous study has shown the reliability and factorial validity of the SSS-Ch by utilizing an early version of SSS-Ch [14]. The current study is further modified based on the DSM-5 and, for the first time, is applied for evaluating its clinical utility.

This study will help to clarify whether the developed SSS-Ch score is an effective tool for rapid screening and assessment of severity in patients with suspected SSD in a general hospital clinic and for convenient follow-up. If the SSS-Ch turns out to be effective, it can be implemented as a first-line screen and follow-up option for outpatient use to provide personalized information to consulting physician in a timely manner. The study results will contribute to better outpatient care for SSD.

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Conflict of interests: The authors declare that they have no competing interests.

Ethics approval: Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016.

Consent for publication: All participants provided written informed consent.

Authors' contributions: XS: design and conduction of study, acquisition of data, analysis and interpretation of data, drafting the manuscript. WTZ: analysis, statistics and interpretation of data, drafting the manuscript. CG: analysis, statistics and interpretation of data. JLM: made substantial contributions to conception, design and interpretation of data. Revising it critically for important intellectual content. MJ: made substantial contributions to conception, design and interpretation of data. Revising it critically for important intellectual content. JP: made substantial contributions to conception, design and interpretation of data.

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Figure Legends

Figure 1 The Somatic Symptom Scale-China (SSS-Ch).

Figure 2 Study flow. SSS-Ch the Somatic Symptom Scale-China; PHQ-15 the Patient Health Questionnaire-15; PHQ-9 the Patient Health Questionnaire-9; GAD-7 the Generalized Anxiety Disorder Scale-7; SF-20 the 20-Item Short Form Health Survey; SSD Somatic Symptom Disorder.

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Figure 1

Somatic Symptoms Scale-China

1. Basic Information

Name_____Sex_____Age_____Date_____Tel_____

Education_____Occupation_____Duration of symptoms_____

2. Instructions:

This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding programs that you may have. It may play a key role of your course of treatment.

Not at all (NAA): not exist
Mild: bearable, do not influent daily work
Moderate: influent daily work to some extent
Severe: unbearable

	Symptoms	NAA	Mild	Moderate	Severe
1	Do you feel dizzy, vertigo, have head heaviness, headache or faint?	1	2	3	4
2	Do you have difficult to fall asleep, easily dreamful or woke up by panic, nightmare, early-wake up, sleeplessness?	1	2	3	4
3	Do you feel tired or low energy?	1	2	3	4
4	Do you have less interest and feel moody, or don't want to be bothered?	1	2	3	4
5	Do you have chest discomfort like palpitation, chest tightness, chest pain or shortness of breath?	1	2	3	4
6	Are you easily anxious, nervous, worried, afraid or panic, even feel like going to die?	1	2	3	4
7	Do you feel worried, thinking too much or easily having negative idea?	1	2	3	4
8	Do you have poor concentration, attention or memory decreased?	1	2	3	4
9	Do you feel tummy bloated and painful, burping, poor appetite, constipation or frequent bowel open, nausea or bad breath?	1	2	3	4
10	Do you have muscle pain at neck, shoulder, upper or lower back and legs?	1	2	3	4
11	Are you easily sad or crying?	1	2	3	4
12	Do you have numbness, stiffness, twitching, shivering or chills in the joints of hands /legs or other parts of body?	1	2	3	4
13	Do you have vision blurry, eye dryness or eye vision decreased during a short period?	1	2	3	4
14	Are you easily irritated and restless, sensitive to voice or easily terrified?	1	2	3	4
15	Do you feel you have certain thoughts and behaviors out of control?	1	2	3	4
16	Do you have sensitive skin, macula rash, itching, skin redness, hot flashes or sweating easily?	1	2	3	4
17	Are you excessively worries about your own or family's health issues, and often having attention on health status?	1	2	3	4
18	Do you feel breath difficultly, have chest tightness easily, often have big sigh, cough or have pain at rib cages or flanks?	1	2	3	4
19	Do you have throat discomfort or feel choking, get stuffy nose and ringing sound around ears?	1	2	3	4
20	Are you easily having pain when urinating, urinary frequency or urgency, discomfort at below side?	1	2	3	4

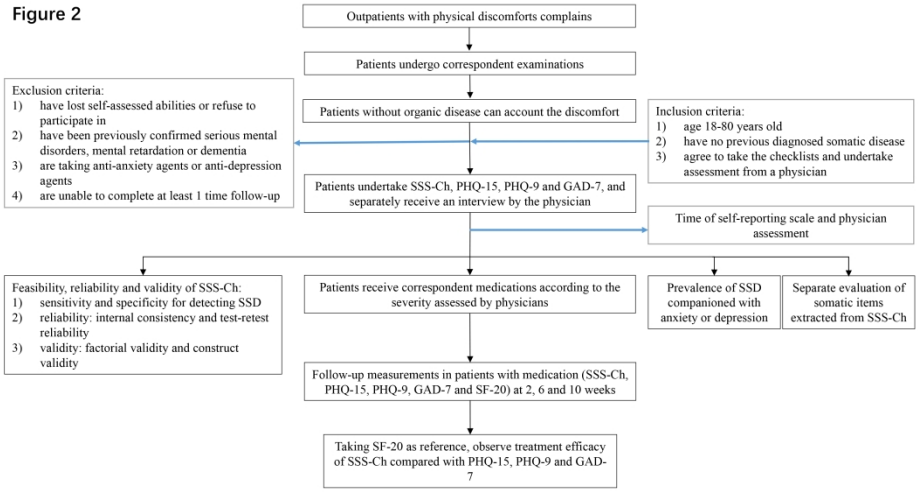
Total score =

If you checked off any problems on this questionnaire so for, how difficult have these problems made it for you to do your work, take care of thing at home, or get along with other people?

☐ Not at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

The Somatic Symptom Scale-China (SSS-Ch).

215x279mm (300 x 300 DPI)



Study flow. SSS-Ch the Somatic Symptom Scale-China; PHQ-15 the Patient Health Questionnaire-15; PHQ-9 the Patient Health Questionnaire-9; GAD-7 the Generalized Anxiety Disorder Scale-7; SF-20 the 20-Item Short Form Health Survey; SSD Somatic Symptom Disorder.

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Research Protocol for a Diagnostic Study: Identifying and Measuring the Severity of Somatic Symptom Disorder Using the Self-reported Somatic Symptom Scale-China (SSS-Ch)

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ABSTRACT

Aim The recognition rate of somatic symptom disorder (SSD) in general hospitals is unsatisfactory. The current self-reported questionnaires do not sufficiently consider both physical and psychological symptoms and are not validated for monitoring treatment efficacy in patients with SSD. The Somatic Symptom Scale-China (SSS-Ch) questionnaire was developed due to the urgent clinical demand. The aim of this research is to validate the self-reported SSS-Ch as a timely and practical instrument to identify SSD and to assess the severity of this disorder.

Methods and Analysis At least 852 patients without organic disease but presenting with physical discomfort will be recruited at a general hospital. Each patient will undergo a DSM-5-guided physician diagnosis, including disease identification and severity assessment, as a reference standard. This research will utilize the SSS-Ch to evaluate its diagnostic performance in SSD compared to that of the Patient Health Questionnaire-15 (PHQ-15) and other SSD-related questionnaires. Statistical tests for the area under the curve (AUC) of the receiver operating curve (ROC) and Spearman's correlation will be used to compare the accuracy of the SSD identification and severity assessment respectively. In addition to this standard diagnostic study, we will conduct follow-up investigations to explore the characteristics of the SSS-Ch in monitoring treatment effects.

Ethics and Dissemination Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016. The findings of this study will be disseminated via peer-reviewed journals and presented at international conferences.

Trial registration number: NCT03513185

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Strengths and limitations of this study

1. First, we introduce a tool to facilitate daily clinical work. The tool provides clinicians with an easy-to-use questionnaire that can be completed quickly and combines both somatic and psychological features to improve physicians' comfort level in screening suspected SSD patients and referring them to specific doctors.
2. Second, our previous study has shown the reliability and factorial validity of the SSS-Ch by utilizing an early version of the scale. The current study further modifies the SSS-Ch based on the DSM-5 and, for the first time, is applied to evaluate its clinical utility.
3. Third, patients will benefit by improving their awareness of the disease and their ability to self-monitor their symptoms.
4. A potential limitation of this study is that it represents the efficacy of the SSS-Ch only in patients without organic disease. Therefore, further application of the SSS-Ch in patients with specific diseases should be separately investigated.
5. Since only patients without a positive physical examination will be referred to the special clinic, a referral bias exists due to the nature of our clinic. Moreover, the epidemiology of health care facilities is different from that of general hospitals; therefore, the diagnostic accuracy in a health care sample needs additional investigation.
6. The potential of monitoring the treatment effect will be affected by loss to follow-up bias due to the unpredictable pattern of loss to follow-up.

Keywords

Somatic Symptom Scale-China; somatic symptom disorder; mental disorders management

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INTRODUCTION

One of the common medical conditions observed in general hospitals is somatic symptom disorder (SSD) and related disorders[1 2]. SSD refers to symptoms that are often difficult to explain after adequate evaluation[3]; even when significant medical disease is present, the patients' symptoms may nonetheless be unrelated to their disease[2]. Diagnosis of SSD emphasizes the existence of positive symptoms and signs (one or multiple somatic symptoms plus abnormal thoughts, feelings, and behaviours in response to these symptoms)[2]. The disorder has an estimated current prevalence in the general population of 5-7%[2]. Individuals with somatic symptoms are commonly encountered in general hospitals and primary care as well as in psychiatric and other mental health settings[2]. The recognition rate of SSD is unsatisfactory due to the diagnostic complexity, and some physicians may not feel sufficiently trained to evaluate patients with suspected SSD; thus, SSD could be underdiagnosed in routine care. Therefore, patients may sustain somatic symptoms without appropriate treatment due to the lack of awareness of SSD. Patients with somatization had approximately twice as much outpatient and inpatient medical care utilization and annual medical care costs as patients without somatization. An estimated $256 billion in annual medical care costs is attributable to the incremental effects of somatization alone[1]. Whereas depression and anxiety disorders are widely researched, SSD has been far less studied. Follow-up or treatment studies of this disorder are even scarcer. Hence, it is highly important that physicians be prepared to identify SSD, grade the symptom severity and treat it in a timely manner; failure to do so can result in high degrees of morbidity, lost productivity, and overutilization of medical resources[4 5].

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is currently widely used for the diagnosis of SSD[2] (see Supplementary Figure 1 for detailed criteria) with the aim of identifying patients and assessing the severity of the disorder. The

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DSM-5 criteria replace the DSM-IV criteria for somatization disorder, undifferentiated somatoform disorder and pain disorder[6], and they emphasize that it is important to evaluate patients in terms of their psychology, behaviour and physical condition altogether and then treat the patients according to the severity of the disorder. They also incorporate illness anxiety disorder. Differences in medical care across cultures affect the management of these somatic symptoms. Individuals in China usually refuse to receive psychological counselling. Thus, in general medical hospitals, non-psychiatric physicians must face more patients with psychological symptoms. The DSM-5, however, is difficult to follow clinically since it depends on qualified and experienced physicians conducting an interview[6]. Moreover, the fact that anxiety and depressive disorder are often associated with SSD in medical settings (in approximately 57.7% of SSD patients)[1] adds severity and complexity to the somatic components, which makes clinicians feel less confident in dealing with such individuals. It is more clinically practical to detect a disorder by self-administered questionnaires, where patients can score the symptoms related to their own condition and severity in a short time. A series of studies has focused on this issue, using various self-reported questionnaires asking about either physical or psychological symptoms to screen for SSD[7-12]. Laferton et al. used the Patient Health Questionnaire 15-item somatic scale (PHQ-15), the Whiteley Index-7 and the Scale for the Assessment of Illness Behavior questionnaires to identify SSD[7]. The Somatic Symptom Scale-8 and Somatic Symptom Scale-12 have been used to assess the validity and reliability of somatic symptoms and the psychological symptoms of SSD, respectively[8-11]. Tu et al. have reported using the Whiteley Index-7 to screen for SSD[12].

Based on the published studies, we aim to develop a self-administered questionnaire to provide a more comprehensive reflection of the true clinical picture than can be achieved by assessing the somatic complaints alone. Our Somatic Symptom Scale-China (SSS-Ch) integrates somatic symptoms with depression and anxiety items. It incorporates affective,

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cognitive, and behavioural components. It is designed to be used in general medical facilities and to provide a tool for clinicians to quickly detect suspected somatic burden. It aims to establish a more accessible and time-saving way to assess the status of subjects.

The SSS-Ch questionnaire was developed based on the DSM-5. Additionally, it simultaneously evaluates depression and anxiety. It introduces illness anxiety disorder, which was previously not included in the DSM-IV. For the first time, an organ-based evaluation is used. The questionnaire is an abbreviated 20-item version that can be entirely self-administered by the patient. The SSS-Ch is designed to assess the presence and severity of the symptoms. Our previous study validated its reliability and validity[13]. Briefly, in that study, the SSS-Ch was composed of 4 dimensions: physical disorder, anxiety disorder, depression disorder, and anxiety and depression disorder. The test-retest reliability was 0.9. The correlation coefficient between each dimension and the total was between 0.76 and 0.88, and the correlation coefficient within dimensions was 0.56-0.70. Items in the scale assess somatic symptoms (50%, 10/20 items), anxiety (20%, 4/20 items), depression (20%, 4/20 items), and anxiety and depression (10%, 2/20 items).

Study objectives and research questions

Primary objective

The primary objective of this study is to test two types of diagnostic accuracy with a DSM-5-guided physician diagnosis as the reference standard: (1) the accuracy of the SSS-Ch compared to the PHQ-15 for identifying SSD and (2) the accuracy of the SSS-Ch compared to the PHQ-15 for assessing severity.

Secondary objective

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The secondary objective is to explore the potential utility of the SSS-Ch in monitoring treatment effect. We intend to observe the trends in how the score of the SSS-Ch and other questionnaires after treatment changes over time.

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METHODS

Study overview

This study will use a prospective diagnostic design and will be conducted at a tertiary general hospital in Shanghai, China. The study protocol was approved by the ethics committees of Renji Hospital, and written informed consent will be obtained from all study participants. The clinical trial registration can be found at https://register.clinicaltrials.gov/, and the registration number is NCT03513185.

Particular attention will be paid to the appropriate storage of this study. Patient confidentiality will be maintained, and no identifying features of the patients will be published. The protocol development will adhere to the EMA guidelines for diagnosis study[14].

Description of the SSS-Ch and Assessment of Severity

The SSS-Ch is a somatic symptom scale (**Figure 1**) derived from the DSM-5. It queries approximately 10 somatic clusters that account for 50% of the physical complaints (1 item per body system, items 1, 5, 9, 10, 12, 13, 16, and 18-20). Anxiety and depression items compose another 50% (anxiety, 20% (4/20), items 6, 14, 15, and 17; depression, 20% (4/20), items 3, 4, 7, and 11; and anxiety and depression, 10%, items 2 and 8). Subjects answer the following question: “Since you have felt unwell, how often have you been bothered in the previous 6 months by any of the following problems?” For scoring, the subjects rate the frequency of each symptom as 1 (“does not exist”), 2 (“the problem occurred occasionally for a couple of days per month and/or is endurable”), 3 (“the problem occurred almost half of the days per month and/or I hope it will ease up”) or 4 (“the problem occurred almost every day and/or is unendurable”). Thus, in determining the SSS-Ch score, each question has a score ranging from 1 to 4, corresponding to the frequency of the problem occurrence, and the total score ranges from 20 to 80. The severity categories are assessed according to the sum of the

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scores. The SSS-Ch scores range from 20 to 29, 30 to 39, 40 to 59, and ≥60 and represent normal, mild, moderate, and severe SSD, respectively. The selection of these cut-off values takes into account the results of our previous study[15] (a cut-off score of 30 was obtained from the receiver operating curve (ROC), reaching a sensitivity of 0.97 and a specificity of 0.96) and clinical experience.

Study Design

The study is composed of 2 stages (Figure 2) corresponding to the primary and secondary research objectives. The first stage is a prospective diagnostic study to test the diagnostic performance of the SSS-Ch questionnaire. The second stage is an exploratory follow-up stage that uses the SSS-Ch questionnaire as a tool to monitor treatment effects.

Briefly, consecutive outpatients with physical discomfort presenting to internal medicine departments in a tertiary hospital in China will first undergo the corresponding examination. Patients with no organic disease that can account for their discomfort will be considered to have a probability of somatic disorder. Those patients will then be transferred to a specialist clinic for the treatment of suspected SSD. They will successively fill out the SSS-Ch questionnaire (and other self-reported instruments for the sake of validity estimation), and non-clinical research assistants will collect the questionnaires and determine the scores. A physician or a psychologist who is blind to the results of the SSS-Ch will separately interview the patient to diagnose SSD according to the corresponding DSM-5 criteria. Prescriptions will be given if the patient is diagnosed with SSD. Two-, 6-, and 10-week follow-ups will be scheduled to repeat the questionnaires for patients receiving medications. Since health-related quality of life is often impaired in patients with SSD, the 20-item Short Form Health Survey (SF-20) will be administered as an indicator of therapeutic effects during follow-up.

Participants and Procedure

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Inclusion criteria

(1) Patients aged 18-80 years old; (2) patients who have no previous diagnosis of somatic disease; (3) patients without systemic disease that can account for their physical discomfort; and (4) patients enrolled as outpatients after they agree to complete the questionnaires and undergo assessment by a physician will meet the inclusion criteria.

Exclusion criteria

(1) Patients who have lost their self-assessment ability or refuse to participate; (2) patients who have been previously confirmed to have serious mental disorders, mental retardation or dementia; (3) patients who are taking anti-anxiety agents or anti-depression agents; and (4) patients who are deemed unable to complete face-to-face follow-up after at least 1 month (such as those who live abroad) will be excluded from the study.

Reference standard

As in Axelsson et al[6], judgement by a physician is set as the reference standard to test consistency. The physician team is composed of both general hospital "specified physicians" (that is, physicians qualified as national psychological counsellors) and psychologists. The status of the subject will be assessed by the physician or psychologist using the DSM-5 SSD criteria (SSD, 300.82 (F45.1) and unspecified somatic symptom and related disorder, 300.82 (F45.9)) (Supplementary Figure 1), anxiety disorder criteria and depression disorder criteria. When there is diagnostic uncertainty, the senior physician will be consulted with.

Assessing capacity and obtaining informed consent

Informed consent will be sought by a trained researcher who will provide all necessary information about this study to the potential participants. It will be made clear to participants that they are under no obligation to take part, their usual care will not be affected by their decision, and they can withdraw consent without giving a reason. Participants will be given a

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sheet with contact details for the research team and instructions on what to do if they wish to withdraw or require further information.

Blinding

After a patient with suspected SSD is transferred to the specialist clinic, the patient will first complete the questionnaires in a separate room, and the research assistant will help the patient understand the questions. We will also ensure that the patients are comfortable. Then, an initial consultation will be blindly conducted by a physician who has been qualified as a national psychological counsellor. An independent diagnosis and severity category will be assigned by the physician using the DSM-5 criteria. The duration of the self-reported scale and the physician assessment will be separately recorded.

Medication

The patients will be informed of the results immediately after the physician consultation and the questionnaire completion. The patients will communicate with the doctor throughout the diagnosis and treatment. Since patients in China usually refuse to accept psychotherapy, medications will be prescribed according to the physician's evaluation. Anti-anxiety treatment or anti-depression treatment will be selectively administered according to the severity of the somatic symptom burden. Generally, members of the thioxanthene class, such as Deanxit, are used for mild symptoms; selective serotonin reuptake inhibitors (SSRIs) are applied for moderate symptoms; and serotonin-norepinephrine reuptake inhibitors (SNRIs) are applied for severe symptoms, with the serotonin antagonist and reuptake inhibitor (SARI) class prescribed if sleeping problems exist.

Follow-up

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A face-to-face interview will be scheduled at 2, 6, and 10 weeks to follow up using the SSS-Ch, PHQ-15, PHQ-9 and GAD-7 questionnaires for patients taking medication. An SF-20 survey will be conducted to evaluate quality of life.

Outcome measures

Reliability and validity

Reliability will be measured by Cronbach's alpha. A randomized sample of approximately 100 participants will be asked to complete the questionnaires 1 week after the initial completion to analyse the test-retest reliability.

The criterion validity will be calculated by the correlations of the diagnostic results and the severity assessments of somatic symptoms between the SSS-Ch and the reference standard.

The SSS-Ch consists of 10 questions for somatic symptoms, 4 for depression, 4 for anxiety, and 2 for depression and anxiety. The construct validity will be tested by confirmatory factor analysis, comparing the corresponding factors with the PHQ-15, Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder Scale-7 (GAD-7).

Diagnostic performance

The diagnostic accuracy of a questionnaire for SSD identification is measured by the area under the curve (AUC) of an ROC, the sensitivity/specificity under a prespecified cut-off value, and the positive/negative predictive values in the study population, referring to the physician diagnosis as the reference standard. The accuracy of the severity assessment of a questionnaire is measured by the Spearman correlation between the questionnaire score and the physician's severity assessment.

Other Clinical utilities

Convenience in clinical practice is measured by the average time taken to complete each questionnaire or receive a diagnosis from a physician.

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Clinical utility in monitoring treatment efficacy in patients is measured by correlation with the SF-20 during follow-up visits.

Sample size calculation

The sample size calculation considers the comparison of diagnostic accuracy for both SSD identification and severity assessment, whichever is larger. In the pilot study, the prevalence of SSD was 76.9% in the study population who were referred to the special clinics, the AUC of the ROC for PHQ-15 was 0.88, and Spearman's correlation of the PHQ-15 score with the physician's diagnosis was 0.77 (95% CI: 0.43, 0.92). The correlation of the SSS-Ch and PHQ-15 scores was set to 0.6. With a non-inferiority margin of 0.05, α=0.025, and β=0.8, the sample size for SSD diagnosis was 852. With a non-inferiority margin of 0.1, α=0.025, and β=0.8, the sample size for severity assessment was 579. Therefore, as the overall sample size of this study was N=852 with SSD-positive N+=655 and SSD-negative N-=197, both the positive and negative sample size requirements were met.

Statistical analysis

We will report our results according to STARD. We will compute the median (P25, P75) scores for each questionnaire and the number and percentage of patients (%) in each diagnostic category as descriptive statistics.

Reliability will be measured using Cronbach's α. The criterion validity will be measured by the kappa coefficient of diagnosis and the Kendall tau-b of severity assessment. Construct validity will be tested using confirmatory factor analyses.

The primary analysis of the diagnostic performance will consist of two comparisons using Bonferroni correction: (1) the non-inferior comparison of the SSS-Ch with the PHQ-15 in SSD diagnostic accuracy as measured by the AUC of the ROC with Δ=0.05, α=0.025 in the whole study population using Delong's method[16] and (2) the non-inferior comparison of the

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SSS-Ch with the PHQ-15 in SSD severity assessment measured by Spearman's correlation with Δ=0.1, α=0.025 in the population with a confirmed SSD diagnosis using Fisher's Z test. Both comparisons refer to the physician's diagnosis as the reference standard. If either non-inferiority criterion is met, the corresponding superiority will be tested.

As a secondary analysis, the sensitivity, specificity, and positive and negative predictive values will also be reported. Prespecified cut-off values will be validated. In addition, we will compare the time needed to complete each questionnaire and be diagnosed by a physician.

In the follow-up data, questionnaire scores by time will be demonstrated in a line chart with error bars.

Missing values will be imputed with multiple imputation[17]. Subgroup analysis according to gender and age will also be conducted. All statistical analyses will be performed with R (version 3.5.1)

Patient and public involvement statement

Patients were involved at the design stage of the trial, including clarifying the understandability of the SSS-Ch questionnaire and discussing the length of the consultation time, the manner of notification of the disease condition, the follow-up method, and the dissemination of the results. Before the formal recruitment started, we received feedback from patients who had SSD during a pretest of the case report form (CRF) and used it to improve the final design of the CRF. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate the main results to the trial participants via email. The study outcomes will be disseminated in conference reports and academic publications.

Current status

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The first study participant was enrolled in November 2017. In November 2018, patient recruitment was not completed.

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DISCUSSION

In this study protocol, we describe a diagnostic study design that evaluates the efficacy of a newly developed somatic symptom scale adapted to China for patients with suspected somatic diseases that might be applied as a first-line instrument for screening and monitoring treatment efficacy in individual outpatient consultations. We expect that a physician will benefit from the SSS-Ch on a clinically significant level through improved self-confidence and timeliness and that the participants will benefit through improving their awareness of the disease and ability to self-monitor their symptoms. Moreover, we will examine the characteristics of the SSS-Ch compared with other somatic symptom questionnaires.

Our SSS-Ch is designed as a "one-stop shop" tool that combines somatic items with mental disorder items. This design is consistent with the suggestion in the DSM-5 that somatic symptoms are likely accompanied by depression and anxiety[1]. Somatic symptoms may interact with mental items, and mental symptoms may be triggered differently than conventional mental diseases in this group. Clinically, it is not easy to clearly separate body from mental status, and the significance of each item is unknown. We caution that 50% of mental items have the possibility of increasing the incidence of SSD, and a subgroup score with somatic symptom items alone is used for this appraisal.

The study has several strengths. First, we will introduce a tool to facilitate daily clinical work. The tool provides clinicians with an easy-to-use questionnaire that can be completed quickly to improve physicians' comfort level in screening suspected SSD patients and to refer them to specific doctors. Second, our previous study has shown the reliability and factorial validity of the SSS-Ch by utilizing an early version of it[13]. The current study further modifies the SSS-Ch based on the DSM-5 and, for the first time, evaluates its clinical utility. Third, patients will benefit by improving their awareness of the disease and their ability to self-monitor their symptoms.

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This trial has some limitations. First, SSD can be accompanied by diagnosed medical disorders. The current study, however, represents the efficacy of the SSS-Ch only in patients without organic diseases. Therefore, the further application of the SSS-Ch to patients with specific diseases should be separately investigated. Moreover, the epidemiology of health care facilities is different from that of general hospitals; therefore, the diagnostic accuracy in a health care sample needs additional investigation. Second, there is no gold standard for SSD diagnosis. Similar to Axelsson et al., our study uses an appraisal by an "experienced" physician team as the reference standard. In this way, we measure only the consistency between the physician assessment and questionnaire score. Third, the study was designed as a mid-term investigation with four measurement time points, and thus missing data must be considered. Referring to the fact that only 16% of patients in the primary care evaluation of mental disorders (PRIME-MD) study were involved in the follow-up[18], we estimate that a high rate of missing data will also occur in our patients. Fortunately, each subject in our study will undergo the same set of questionnaires for the entire scale, and thus the missing samples lost to follow-up will not differ among the groups; therefore, they will not produce significant bias and will not affect our assessment.

This study will help to clarify whether the developed SSS-Ch score is an effective tool for rapid screening and assessment of severity in patients with suspected SSD in a general hospital clinic and for convenient follow-up. If the SSS-Ch is found to be effective, it can be implemented as a first-line screening and follow-up option. Additionally, we expect that the SSS-Ch could provide personalized information to consulting physicians in a timely manner. The study results will contribute to better outpatient care for patients with SSD.

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Conflict of interests: The authors declare that they have no competing interests.

Ethical approval: Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016.

Consent for publication: All participants to date have provided written informed consent.

Authors' contributions: JLM: substantial contributions to the conception, design and interpretation of data, drafting and critical revisions for important intellectual content. WTZ: analysis, statistics and interpretation of data, drafting the manuscript. XS: design and implementation of study, acquisition of data, analysis and interpretation of data, drafting the manuscript. CG: analysis, statistics and interpretation of data. BXC: acquisition of data, analysis and interpretation of data, drafting the manuscript. ZHF: acquisition of data, analysis and interpretation of data, drafting the manuscript. MJ: substantial contributions to the conception, design and interpretation of data, critical revisions for important intellectual content. JP: substantial contributions to the conception, design and interpretation of data.

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Registration name: The validation and utility of the somatic symptom scale China (SSS-Ch) for assessing somatic symptom disorder in general hospital outpatients.

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Figure Legends

Figure 1 The Somatic Symptom Scale-China (SSS-Ch).

Figure 2 Study flow. SSS-Ch, Somatic Symptom Scale-China; PHQ-15: Patient Health Questionnaire-15; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder Scale-7; SF-20: 20-Item Short Form Health Survey; SSD: Somatic Symptom Disorder.

Supplementary Figure 1 Criteria of somatic symptom disorder, unspecified somatic symptoms and related disorders from the DSM-5 (adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)).

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Self-rating Somatic Symptoms Scale

1. Basic information

Name _____Mobile phone_____ Gender ___Age___ Education level _____Occupation_____
Date___ Course of symptoms ____Number of Self-rating ____Historical diagnosis_____
Medications administered_____

2. Instruction:

To better understand the degree to which you're bothered by the problems, please read carefully the following 20 items and CIRCLE the corresponding points at the right column that best describe your health. You MUST circle all the items listed in this questionnaire.

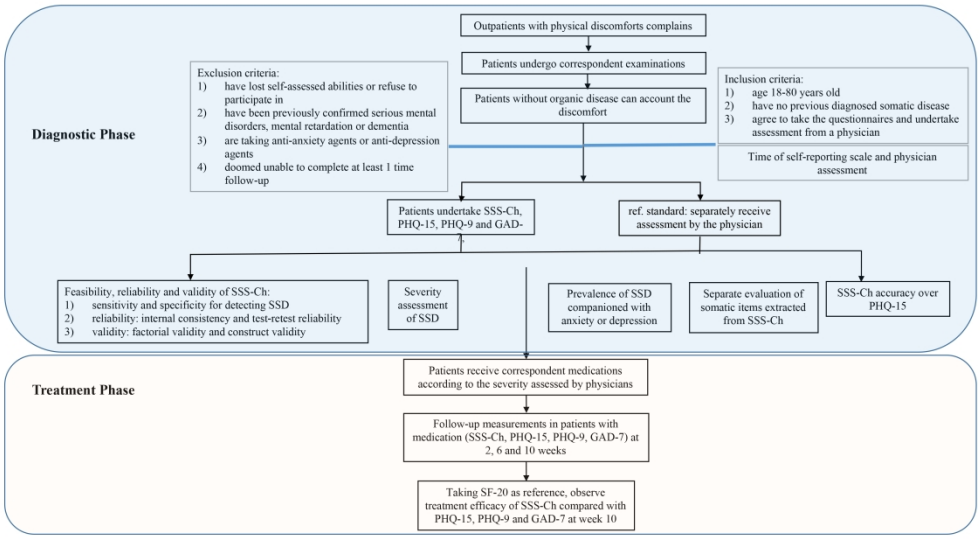
1: not existent
2: the problem occurred occasionally for a couple of days per-month and/or is endurable
3: the problem occurred almost half days per-month and/or hoping to ease up
4: the problem occurred almost every day and/or unendurable

In the past 6 month, do you have the following symptoms:

1)	Dizziness, swelling in the head, heavy head, headache, spinning head, faint, buzzing in head	1	2	3	4
2)	Trouble sleeping (difficulty falling asleep/staying asleep, waking up too early, oversleeping, easily drear nightmare, awakened for no reason)	1	2	3	4
3)	Feeling tired or having low energy	1	2	3	4
4)	Losing interest, moody, don't want to be bothered, lacking patience	1	2	3	4
5)	Chest pain, shortness of breath, racing/pounding/fluttering heart, chest tightness	1	2	3	4
6)	Easily anxious, nervous, feeling scared, panicky, feeling I'm going to die, out of control	1	2	3	4
7)	Worried, apprehensive, negative ideation	1	2	3	4
8)	Reduced attention & thinking abilities, forgetful, absentminded	1	2	3	4
9)	Bloating, stomach pain, gas, loss of appetite, constipation, loose bowels, nausea, becoming thin, dry o bitter mouth	1	2	3	4
10)	Pain in the neck, back, shoulders, waist, arm, legs	1	2	3	4
11)	Sensitive, easily sad and crying	1	2	3	4
12)	Unusual sensations in the joints of hands or legs (numb, rigid, twitching, shivering, pricking, chilly)	1	2	3	4
13)	Blurry vision, eye dryness, eye pain or swelling, decreased eye vision over a short period of time	1	2	3	4
14)	Easily agitated or irritable, sensitive to voice, susceptible to startle	1	2	3	4
15)	Obsessive-compulsive thoughts or behaviors	1	2	3	4
16)	Skin allergies, itching, rash, skin flushing, hot flash, sweating	1	2	3	4
17)	Excess concerns about health issues, excessive worry that you or family members are ill	1	2	3	4
18)	Difficulty breathing, feeling oppressed or suffocated, frequent long sigh, coughing, intercostal pain	1	2	3	4
19)	Choking feeling in the throat, nasal dryness and obstruction, ringing in the ears or ear blockage	1	2	3	4
20)	Frequent urination, urgent need to urinate, painful urination, or discomfort in perineum	1	2	3	4

Functional impairment in work, study, family life, and interpersonal relationship: Not at all, A little bit, Quite a bit, or Very much/Severe

Figure 2



345x199mm (300 x 300 DPI)

Somatic Symptom Disorder

Diagnostic Criteria **300.82 (F45.1)**

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.

B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:

1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
2. Persistently high level of anxiety about health or symptoms.
3. Excessive time and energy devoted to these symptoms or health concerns.

C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months).

Specify if:

With predominant pain (previously pain disorder): This specifier is for individuals whose somatic symptoms predominantly involve pain.

Specify if:

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 months).

Specify current severity:

Mild: Only one of the symptoms specified in Criterion B is fulfilled.

Moderate: Two or more of the symptoms specified in Criterion B are fulfilled.

Severe: Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom).

Unspecified Somatic Symptom and Related Disorder

300.82 (F45.9)

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the somatic symptom and related disorders diagnostic class. The unspecified somatic symptom and related disorder category should not be used unless there are decidedly unusual situations where there is insufficient information to make a more specific diagnosis.

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TITLE OR		
Page 1, line 1-2	**1**	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
Page 2, line 2-18 for protocol article	**2**	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
Page 4-5, line 2-21	**3**	Scientific and clinical background, including the intended use and clinical role of the index test
Page 5, line 22-page 6, line3; Page 6,line 17-page 7, line 3	**4**	Study objectives and hypotheses
METHODS		
Study design Page 8, line 3; Page 14,line 13-22	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants Page 10,line 1-11	**6**	Eligibility criteria
Page 9,line 12-16	**7**	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
Page 9, line 12-21	**8**	Where and when potentially eligible participants were identified (setting, location and dates)
Page 9, line 12	**9**	Whether participants formed a consecutive, random or convenience series
Test methods Page 8,line 12-page 9, line 6; Figure 1	**10a**	Index test, in sufficient detail to allow replication
Page 10,line 12-19;Suppl Fig1	**10b**	Reference standard, in sufficient detail to allow replication
Page 4,line 23-page 5, line 5	**11**	Rationale for choosing the reference standard (if alternatives exist)
Page 8,line 19-page 9,line 6	**12a**	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing
Suppl Fig1	**12b**	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
Page 9, line 18-21	**13a**	Whether clinical information and reference standard results were available
Page 9, line 16-18; Page 12, line 1-3	**13b**	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis Page12，line 15-21	**14**	Methods for estimating or comparing measures of diagnostic accuracy
Page10，line 19	**15**	How indeterminate index test or reference standard results were handled
Page 14,line 10-12	**16**	How missing data on the index test and reference standard were handled
Page12，line 15-21	**17**	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
Page 13, line 3-13	**18**	Intended sample size and how it was determined
RESULTS		
Participants	**19**	Flow of participants, using a diagram
NA	**20**	Baseline demographic and clinical characteristics of participants
NA	**21a**	Distribution of severity of disease in those with the target condition
NA	**21b**	Distribution of alternative diagnoses in those without the target condition
NA	**22**	Time interval and any clinical interventions between index test and reference standard
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard

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NA	**24**	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
NA	**25**	Any adverse events from performing the index test or the reference standard
DISCUSSION		
Page 17,line 1-16	**26**	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
Page 16,line 2-9;line 18-25; Page 17,line 17-22	**27**	Implications for practice, including the intended use and clinical role of the index test
OTHER		
Page 2,line 24;Page 18,line 23-24；	**28**	Registration number and name of registry
NA	**29**	Where the full study protocol can be accessed
Page 18,line 15-22	**30**	Sources of funding and other support; role of funders

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Research Protocol for a Diagnostic Study: Identifying and Measuring the Severity of Somatic Symptom Disorder Using the Self-reported Somatic Symptom Scale-China (SSS-CN)

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Research Protocol for a Diagnostic Study: Identifying and Measuring the Severity of Somatic Symptom Disorder Using the Self-reported Somatic Symptom Scale-China (SSS-CN)

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ABSTRACT

Aim The recognition rate of somatic symptom disorder (SSD) in general hospitals is unsatisfactory. Self-report questionnaires that combine both somatic symptoms and psychological characteristics are useful in screening for SSD. The Somatic Symptom Scale-China (SSS-CN) questionnaire was developed due to urgent clinical demand. The aim of this research is to validate the self-reported SSS-CN as a timely and practical instrument to identify SSD and to assess the severity of this disorder.

Methods and Analysis At least 852 patients without organic disease but presenting with physical discomfort will be recruited at a general hospital. Each patient will undergo a DSM-5-guided physician diagnosis, including disease identification and severity assessment, as a reference standard. This research will utilize the SSS-CN to evaluate its diagnostic performance in SSD compared to that of the Patient Health Questionnaire-15 (PHQ-15) and other SSD-related questionnaires. Statistical tests for the area under the curve (AUC) and volume under the surface (VUS) of the receiver operating curve (ROC) will be used to compare the accuracy of the SSD identification and severity assessment, respectively. In addition to this standard diagnostic study, we will conduct follow-up investigations to explore the characteristics of the SSS-CN in monitoring treatment effects.

Ethics and Dissemination Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016. The findings of this study will be disseminated via peer-reviewed journals and presented at international conferences.

Trial registration number: NCT03513185

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Strengths and Limitations of this Study

1. First, we introduce a tool to benefit patients and to facilitate daily clinical work. The primary goal is to screen suspected somatic symptom disorder (SSD) patients via accurate and brief diagnostic tools. Patients will benefit by improving their awareness of the disease and their ability to self-monitor their symptoms. Additionally, the tool provides clinicians with an easy-to-use questionnaire that can be completed quickly and combines both somatic and psychological features.
2. Second, our previous study has shown the reliability and factorial validity of the Somatic Symptom Scale-China (SSS-CN) by utilizing an early version of the scale. The current study further modifies the SSS-CN based on the DSM-5 and, for the first time, is applied to evaluate its clinical utility.
3. A potential limitation of this study is that it represents the efficacy of the SSS-CN only in patients without organic disease. Further research on the application of SSS-CN in patients with both SSD and diagnosed medical disorders is required.
4. Because only patients without a positive physical examination will be referred to the special clinic, a referral bias exists due to the nature of our clinic. Moreover, the epidemiology of health care facilities is different from that of general hospitals; therefore, the diagnostic accuracy in a health care sample needs additional investigation.
5. The potential of monitoring the treatment effect will be affected by loss to follow-up bias due to the unpredictable pattern of loss to follow-up.

Keywords

Somatic Symptom Scale-China; somatic symptom disorder; mental disorders management

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INTRODUCTION

One of the common medical conditions observed in general hospitals is somatic symptom disorder (SSD) and related disorders[1 2]. SSD refers to symptoms that are often difficult to explain after adequate evaluation[3]; even when a significant medical disease is present, the patients' symptoms may nonetheless be unrelated to their disease[2]. The diagnosis of SSD emphasizes the existence of symptoms and signs (one or multiple somatic symptoms plus abnormal thoughts, feelings, and behaviours in response to these symptoms)[2]. The disorder has an estimated current prevalence in the general population of 5-7%[2]. The prevalence is estimated to be higher in China[4]. Individuals with somatic symptoms are commonly encountered in general hospitals and primary care as well as in psychiatric and other mental health settings[2]. The recognition rate of SSD is unsatisfactory due to the diagnostic complexity, and some physicians may not feel sufficiently trained to evaluate patients with suspected SSD; thus, SSD could be underdiagnosed in routine care. Therefore, patients may sustain somatic symptoms without appropriate treatment due to the lack of awareness of SSD. Patients with somatization had approximately twice as much cost as patients without somatization on medical care utilization and annual medical care. An estimated $256 billion in annual medical care costs is attributable to the incremental effects of somatization alone[1]. Whereas depression and anxiety disorders are widely researched, SSD has been far less studied. Follow-up or treatment studies of this disorder are even scarcer. Hence, it is highly important that physicians are prepared to identify SSD, assess the symptom severity and treat it in a timely manner; failure to do so can result in high degrees of morbidity, lost productivity, and overutilization of medical resources[5 6].

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) aims to identify SSD patients and assessing the severity of the disorder[2]. It agreed that the SSD companioned anxiety and depressive disorder (in approximately 57.7% of SSD patients)[1] adds severity and complexity to the somatic components. It emphasizes that it is important to evaluate patients in terms of their psychological situation, behaviour and physical condition altogether

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and then treat the patients according to the severity of the disorder. It also emphasizes the evaluation in subjects who have excessive concerns about health issues. Recent studies, including one by Laferton et al., have also indicated that the combination of self-report measures could increase diagnostic quality in clinical practice[7]. The DSM-5, however, is clinically difficult to follow because it depends on qualified and experienced physicians conducting an interview[8], which makes clinicians in the general hospital feel less confident in dealing with such individuals. On the other hand, individuals in China usually refuse to receive psychological counselling. Thus, in general medical hospitals, non-psychiatric physicians must face more patients with psychological symptoms. It is more favourable to have a tool to screen suspected SSD patients via accurate and brief diagnostic questionnaires and to facilitate daily clinical work. A series of studies has focused on this issue; the Patient Health Questionnaire-15 (PHQ-15) and the Somatic Symptom Scale-8 are screening tools for SSD[9 10]; however, these types of self-report questionnaires do not incorporate psychological features. The Whiteley Index-7 focuses on health anxiety[11], the Scale for the Assessment of Illness Behavior questionnaires focuses on excessive illness behaviour, and the Somatic Symptom Scale-12 assesses psychological features[12 13]. The latter three questionnaires focus less on physical features.

Based on published studies, we aim to develop a self-administered questionnaire to provide a comprehensive reflection of both somatic and psychological features. The Somatic Symptom Scale-China (SSS-CN) questionnaire was developed based on the DSM-5. Psychology and behaviour items are interleaved with somatic symptoms. It incorporates affective, cognitive, and behavioural components. It is designed to be used in general medical facilities and to provide clinicians with an easy-to-use questionnaire to detect both somatic and psychological features in a time-saving way.

Study Objectives and Research Questions

Primary objective

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The primary objective of this study is to test two types of diagnostic accuracy with a DSM-5-guided physician diagnosis as the reference standard: (1) the accuracy of the SSS-CN compared to the PHQ-15 for identifying SSD and (2) the accuracy of the SSS-CN compared to the PHQ-15 for assessing severity.

Secondary objective

The secondary objective is to explore the potential utility of the SSS-CN in monitoring the treatment effect. We intend to observe the trends in how the score of the SSS-CN and other questionnaires after treatment changes over time.

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METHODS

Study Overview

This study will use a prospective diagnostic design and will be conducted at a tertiary general hospital in Shanghai, China. The study protocol was approved by the ethics committees of Renji Hospital, and written informed consent will be obtained from all study participants. The clinical trial registration can be found at https://register.clinicaltrials.gov/, and the registration number is NCT03513185.

Particular attention will be paid to the appropriate storage of the data. Patient confidentiality will be maintained, and no identifying features of the patients will be published. The protocol development will adhere to the European Medicines Agency guidelines for diagnosis study[14].

Description of the SSS-CN and Assessment of Severity

The SSS-CN is a somatic and psychological symptom scale (**Figure 1**) derived from the DSM-5. It is designed to assess the presence and severity of the symptoms. Our previous study validated its reliability and validity[15]. The test-retest reliability was 0.9. The correlation coefficient between each dimension and the total was between 0.76 and 0.88, and the correlation coefficient within dimensions was 0.56-0.70.

The questionnaire is self-administered with an abbreviated 20-item measure. Briefly, in that study, the SSS-CN was composed of 4 dimensions: physical disorder, anxiety disorder, depression disorder, and anxiety and depression disorder. The SSS-CN assesses 10 somatic clusters that account for 50% of the physical complaints (1 item per body system, items 1, 5, 9, 10, 12, 13, 16, and 18-20). Anxiety and depression items account for the remaining 50% (anxiety, 20% (4/20), items 6, 14, 15, and 17; depression, 20% (4/20), items 3, 4, 7, and 11; and anxiety and depression, 10%, items 2 and 8). Subjects answer the following question: "Since you have felt unwell, how often have you been bothered in the previous 6 months by any of the following problems?" For scoring, the subjects rate the frequency of each symptom as 1 ("does not exist"), 2 ("the problem

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occurred occasionally for a couple of days per month and/or is endurable"), 3 ("the problem occurred almost half of the days per month and/or I hope it will ease up") or 4 ("the problem occurred almost every day and/or is unendurable"). Thus, in determining the SSS-CN score, each question has a score ranging from 1 to 4, corresponding to the frequency of the problem occurrence, and the total score ranges from 20 to 80. The severity categories are assessed according to the sum of the scores. The SSS-CN scores range from 20 to 29, 30 to 39, 40 to 59, and ≥60 and represent normal, mild, moderate, and severe SSD, respectively. The selection of these cut-off values takes into account the results of our previous study[16] (a cut-off score of 30 was obtained from the receiver operating curve (ROC), reaching a sensitivity of 0.97 and a specificity of 0.96) and clinical experience.

Study Design

The study is composed of 2 stages (Figure 2) corresponding to the primary and secondary research objectives. The first stage is a prospective diagnostic stage to test the diagnostic performance of the SSS-CN questionnaire. The second stage is an exploratory follow-up stage that uses the SSS-CN questionnaire as a tool to monitor treatment effects.

Briefly, consecutive outpatients with physical discomfort presenting to internal medicine departments in a tertiary hospital in China will first undergo the corresponding examination to exclude organic disease. For example, a patient with chest pain would be recommended by a physician to receive an EKG, echocardiography, a treadmill test or coronary angiography to exclude cardiovascular disease. Patients with no organic disease that can account for their discomfort will be considered to have a probable psychosomatic disorder. These patients will then be transferred to a specialist clinic for the diagnosis and treatment of suspected SSD (the initial consultation). They will fill out the SSS-CN questionnaire, we use other self-reported instruments including PHQ15, Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder Scale-7 (GAD-7) and SF-20, to verify the structural validity of SSS-CN. Non-clinical research assistants

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will collect the questionnaires and determine the scores. A physician or a psychologist who is blind to the results of the SSS-CN will separately interview the patient to diagnose SSD base on the standard interview according to the corresponding DSM-5 criterion. Prescriptions will be given if the patient is diagnosed with SSD. Follow ups will be scheduled at 2, 6, and 10 weeks to repeat the questionnaires for patients receiving medications (the follow-up consultation). Because health-related quality of life is often impaired in patients with SSD, the 20-item Short Form Health Survey (SF-20) will be administered as an indicator of therapeutic effects during follow-up.

Participants and Procedure

Inclusion criteria

(1) Patients aged 18-80 years old; (2) patients who have no previous diagnosis of somatic disease; (3) patients without systemic disease that can account for their physical discomfort; and (4) patients enrolled as outpatients after they agree to complete the questionnaires and undergo assessment by a physician will meet the inclusion criteria.

Exclusion criteria

(1) Patients who have lost their self-assessment ability or refuse to participate; (2) patients who have been previously confirmed to have mental disorders, mental retardation or dementia; (3) patients who are taking anti-anxiety agents or anti-depression agents; and (4) patients who are deemed unable to complete face-to-face follow-up after at least 1 month (such as those who live abroad) will be excluded from the study.

Reference standard

Patients were interviewed by a standard procedure. A structured clinical interview (SCID-5-CV) according to the corresponding DSM-5 criterion was used by the physician. The interview questions include modules from somatic symptom and related disorder to depression disorder, anxiety disorder, obsessive-compulsive related disorder and sleep-wake disorders. The test time is approximately 30-45 minutes. The physician further assesses the severity based on the number of

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symptoms specified in excessive thoughts, feeling, or behaviours related to the somatic symptoms or associated health concerns (mild-1 symptom; moderate-two or more of the symptoms; severe-two or more of the symptoms plus multiple somatic complaints). The physician assessment is set as the reference standard. The physician team is composed of both general hospital "specified physicians" (that is, physicians qualified as national psychological counsellors) and psychologists. When there is diagnostic uncertainty, the patient will be referred to the senior physician to obtain a diagnosis.

Obtaining informed consent

The trained researched will give the patients informed consent and provide all necessary information about this study to the potential participants. It will be made clear to participants that they are under no obligation to take part, their usual care will not be affected by their decision, and they can withdraw consent without giving a reason. Participants will be given a sheet with contact details for the research team and instructions on what to do if they wish to withdraw or require further information.

Blinding

After a patient with suspected SSD is transferred to the specialist clinic, the patient will first complete the questionnaires in a separate room, and the research assistant will help the patient understand the questions. Then, an initial consultation will be blindly conducted by a physician who has been qualified as a national psychological counsellor. An independent diagnosis and severity category will be assigned by the physician. The duration of the self-reported scale and the physician assessment will be separately recorded.

Medication

The patients will be informed of the results immediately after the physician consultation and the questionnaire completion. During the follow-up consultations, the patients will be allowed to communicate with the doctor throughout the diagnosis and treatment. Because patients in China

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usually refuse to accept psychotherapy[4 17], medications will be prescribed according to the physician's evaluation. Anti-anxiety treatment or anti-depression treatment will be selectively administered according to the severity of the somatic symptom burden. Generally, members of the thioxanthene class, such as Deanxit, are used for mild symptoms; selective serotonin reuptake inhibitors (SSRIs) are applied for moderate symptoms; and serotonin-norepinephrine reuptake inhibitors (SNRIs) are applied for severe symptoms, with the serotonin antagonist and reuptake inhibitor (SARI) class prescribed if sleeping problems exist.

Follow-up

A face-to-face interview will be scheduled at 2, 6, and 10 weeks for patients taking medication. The subject will complete 5 questionnaires (SSS-CN, PHQ15, PHQ-9, GAD-7 and SF-20) both at the initial consultation and at the week 10 follow-up. The SF-20 survey aimed to evaluate quality of life. At the week 2 and week 6 follow ups, 4 questionnaires will be completed (SSS-CN, PHQ15, PHQ-9, GAD-7).

Outcome Measures

Reliability and validity

Reliability will be measured by Cronbach's alpha. A randomized sample of approximately 100 participants will be asked to complete the questionnaires 1 week after the initial completion to analyse the test-retest reliability.

The criterion validity will be determined by assessment of the presence and severity of SSD between the reference standard (physician assessment based on structure interview) and the SSS-CN questionnaire.

The SSS-CN consists of 10 questions for somatic symptoms, 4 for depression, 4 for anxiety, and 2 for depression and anxiety. The construct validity will be tested by confirmatory factor analysis, comparing the corresponding factors with the PHQ-15, PHQ-9 and GAD-7.

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Diagnostic performance

The diagnostic accuracy of a questionnaire for SSD identification is measured by the area under the curve (AUC) of an ROC, the sensitivity/specificity under a prespecified cut-off value, and the positive/negative predictive values in the study population, referring to the physician diagnosis as the reference standard. The accuracy of the severity assessment of a questionnaire is measured by the VUS (volume under the surface), which is a multi-class generalization of AUC of ROC between the questionnaire score and the physician's severity assessment[18].

Other Clinical utilities

Convenience in clinical practice is measured by the average time taken to complete each questionnaire or receive a diagnosis from a physician.

Clinical utility in monitoring treatment efficacy in patients is measured by correlation with the SF-20 during follow-up visits.

Sample Size Calculation

The sample size calculation considers the comparison of diagnostic accuracy for both SSD identification and severity assessment, whichever is larger. In the pilot study, the prevalence of SSD was 76.9% in the study population who were referred to the special clinics (where physicians qualified as national psychological counsellors and psychologists practice medicine), the AUC of the ROC for PHQ-15 was 0.88, and the VUS of multi-class ROC for PHQ-15 score with respect to the severity assessment was 0.7. The correlation between the SSS-CN and PHQ-15 scores was set to 0.6. With a non-inferiority margin of 0.05, α=0.025, and β=0.8, the sample size for SSD diagnosis was 852. With a non-inferiority margin of 0.1, α=0.025, and β=0.8, the sample size for severity assessment was 517. Therefore, as the overall sample size of this study was N=852 with SSD-positive N+=655 and SSD-negative N-=197, both the positive and negative sample size requirements were met.

Statistical Analysis

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We will report our results according to STARD. We will compute the median (P25, P75) scores for each questionnaire and the number and percentage of patients (%) in each diagnostic category as descriptive statistics.

Reliability will be measured using Cronbach's α. The criterion validity will be measured by the kappa coefficient between the questionnaire score and the physician assessment. Construct validity will be tested using confirmatory factor analyses.

The primary analysis of the diagnostic performance will consist of two comparisons using Bonferroni's correction: (1) the non-inferior comparison of the SSS-CN with the PHQ-15 in SSD diagnostic accuracy as measured by the AUC of the ROC with $\Delta=0.05$, $\alpha=0.025$ in the whole study population using Delong's method[19] and (2) Severity of PHQ-15 were based on scores, normal (score 0–4), low (score 5–9), medium (score 10–14), and high (score 15–30). SSS-CN scores range from 20 to 29, 30 to 39, 40 to 59, and ≥60 and represent normal, mild, moderate, and severe SSD, respectively. The non-inferior comparison of the SSS-Ch with the PHQ-15 in SSD severity assessment measured by VUS with $\Delta=0.1$, $\alpha=0.025$ in the population with a confirmed SSD diagnosis using Z test [18]. Both comparisons refer to the physician's diagnosis as the reference standard. If either non-inferiority criterion is met, the corresponding superiority will be tested.

As a secondary analysis, the sensitivity, specificity, and positive and negative predictive values will also be reported. Prespecified cut-off values will be validated. In addition, we will compare the time needed to complete each questionnaire and be diagnosed by a physician. In the follow-up data, questionnaire scores by time will be demonstrated in a line chart with error bars.

Missing values will be imputed with multiple imputation under the assumption of MAR[17]. Subgroup analysis according to gender and age will also be conducted. All statistical analyses will be performed with R (version 3.5.1)

Patient and Public Involvement Statement

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Patients were involved at the design stage of the trial, including ensuring that the content of the SSS-CN questionnaire can be understood, the length of the consultation time, the manner of notification of the disease condition, the follow-up method, and the dissemination of the results are acceptable. Before the formal recruitment started, we received feedback from patients who had SSD during a pretest of the case report form (CRF) and used it to improve the final design of the CRF. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate the main results to the trial participants via email. The study outcomes will be disseminated in conference reports and academic publications.

Current Status

The first study participant was enrolled in November 2017. As of Mar 2019, patient recruitment has not been completed.

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DISCUSSION

In this study protocol, we describe a diagnostic study design that evaluates the efficacy of a newly developed somatic and psychological symptom scale adapted to China for patients with suspected somatic diseases that might be applied as a first-line instrument for screening and monitoring treatment efficacy in individual outpatient consultations. We expect that a physician will benefit from the SSS-CN on a clinically significant level through improved self-confidence and timeliness and that the participants will benefit by improving their awareness of the disease and ability to self-monitor their symptoms. Moreover, we will examine the characteristics of the SSS-CN compared with another somatic symptom questionnaire (PHQ15).

Our SSS-CN is designed as a "one-stop shop" tool that combines somatic items with mental disorder items. This design is consistent with the suggestion in the DSM-5 that somatic symptoms are likely accompanied by depression and anxiety[1]. Somatic and mental symptoms may interact, and mental symptoms may be triggered differently than conventional mental diseases in this group. Clinically, it is not easy to clearly separate the body from mental status, and the significance of each item is unknown. We caution that 50% of mental items have the possibility of increasing the incidence of SSD, and a subgroup score with somatic symptom items alone is used for this appraisal.

The study has several strengths. First, we will introduce a tool to facilitate daily clinical work. The tool provides clinicians with an easy-to-use questionnaire in screening suspected SSD patients and to refer the patients to specific doctors. Second, our previous study has shown the reliability and factorial validity of the SSS-CN by utilizing an early version of it[15]. The current study further modifies the SSS-CN based on the DSM-5 and, for the first time, evaluates its clinical utility. Third, patients will benefit by improving their awareness of the disease and their ability to self-monitor their symptoms.

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This trial has some limitations. First, SSD can be accompanied by diagnosed medical disorders. The current study, however, represents the efficacy of the SSS-CN only in patients without organic diseases. Therefore, further research on the application of SSS-CN in patients with both SSD and diagnosed medical disorders is required. Moreover, the epidemiology of primary health care facilities is different from the epidemiology of general hospitals; therefore, the diagnostic accuracy in a health care sample needs additional investigation. Second, the study was designed as a mid-term investigation with four measurement time points, and thus missing data must be considered. Referring to the fact that only 16% of patients in the primary care evaluation of mental disorders (PRIME-MD) study were involved in the follow-up[18], we estimate that a high rate of missing data will also occur in our patients. Because of the difficulty of compliance, only a small fraction (16% by estimation) of patients in study would be involved in the follow-up, and the result of monitoring the treatment effect may be affected by loss to follow-up bias.

This study will help to clarify whether the developed SSS-CN score is an effective tool for rapid screening and assessment of severity in patients with suspected SSD in a general hospital clinic and for convenient follow-up. If the SSS-CN is found to be effective, it can be implemented as a first-line screening and follow-up option. Additionally, we expect that the SSS-CN could provide personalized information to consulting physicians in a timely manner. The study results will contribute to better outpatient care for patients with SSD.

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Ethical approval: Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016.

Consent for publication: All participants to date have provided written informed consent.

Authors' contributions: MJ: substantial contributions to the conception, design and interpretation of data, drafting and critical revisions for important intellectual content. WTZ: analysis, statistics and interpretation of data, drafting the manuscript. XS: design and implementation of study, acquisition of data, analysis and interpretation of data, drafting the manuscript. CG: analysis, statistics and interpretation of data. BXC: acquisition of data, analysis and interpretation of data, drafting the manuscript. ZHF: acquisition of data, analysis and interpretation of data, drafting the manuscript. JLM: substantial contributions to the conception, design and interpretation of data, critical revisions for important intellectual content. JP: substantial contributions to the conception, design and interpretation of data.

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Registration name: The validation and utility of the Somatic Symptom Scale-China (SSS-CN) for assessing somatic symptom disorder in general hospital outpatients.

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Figure Legends

Figure 1 The Somatic Symptom Scale-China (SSS-CN).

Figure 2 Study flow. SSS-CN, Somatic Symptom Scale-China; PHQ-15: Patient Health Questionnaire-15; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder Scale-7; SF-20: 20-Item Short Form Health Survey; SSD: Somatic Symptom Disorder.

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Self-rating Somatic Symptoms Scale

1. Basic information

Name _____Mobile phone_____ Gender ___Age___ Education level _____Occupation_____
Date___ Course of symptoms ____Number of Self-rating ____Historical diagnosis_____
Medications administered_____

2. Instruction:

To better understand the degree to which you're bothered by the problems, please read carefully the following 20 items and CIRCLE the corresponding points at the right column that best describe your health. All the items listed in this questionnaire are REQUIRED.
1: not existent
2: the problem occurred occasionally for a couple of days per-month and/or is endurable
3: the problem occurred almost half days per-month and/or hoping to ease up
4: the problem occurred almost every day and/or unendurable

In the past 6 month, do you have the following symptoms:

1)	Dizziness, swelling in the head, heavy head, headache, spinning head, faint, buzzing in head	1	2	3	4
2)	Trouble sleeping (difficulty falling asleep/staying asleep, waking up too early, oversleeping, easily drea nightmare, awakened for no reason)	1	2	3	4
3)	Feeling tired or having low energy	1	2	3	4
4)	Losing interest, moody, don't want to be bothered, lacking patience	1	2	3	4
5)	Chest pain, shortness of breath, racing/pounding/fluttering heart, chest tightness	1	2	3	4
6)	Easily anxious, nervous, feeling scared, panicky, feeling I'm going to die, out of control	1	2	3	4
7)	Worried, apprehensive, negative ideation	1	2	3	4
8)	Reduced attention & thinking abilities, forgetful, absentminded	1	2	3	4
9)	Bloating, stomach pain, gas, loss of appetite, constipation, loose bowels, nausea, becoming thin, dry o bitter mouth	1	2	3	4
10)	Pain in the neck, back, shoulders, waist, arm, legs	1	2	3	4
11)	Sensitive, easily sad and crying	1	2	3	4
12)	Unusual sensations in the joints of hands or legs (numb, rigid, twitching, shivering, pricking, chilly)	1	2	3	4
13)	Blurry vision, eye dryness, eye pain or swelling, decreased eye vision over a short period of time	1	2	3	4
14)	Easily agitated or irritable, sensitive to voice, susceptible to startle	1	2	3	4
15)	Obsessive-compulsive thoughts or behaviors	1	2	3	4
16)	Skin allergies, itching, rash, skin flushing, hot flash, sweating	1	2	3	4
17)	Excess concerns about health issues, excessive worry that you or family members are ill	1	2	3	4
18)	Difficulty breathing, feeling oppressed or suffocated, frequent long sigh, coughing, intercostal pain	1	2	3	4
19)	Choking feeling in the throat, nasal dryness and obstruction, ringing in the ears or ear blockage	1	2	3	4
20)	Frequent urination, urgent need to urinate, painful urination, or discomfort in perineum	1	2	3	4

Functional impairment in work, study, family life, and interpersonal relationship: Not at all, A little bit, Quite a bit, or Very much/Severe

Figure 1

210x297mm (300 x 300 DPI)

Figure 2

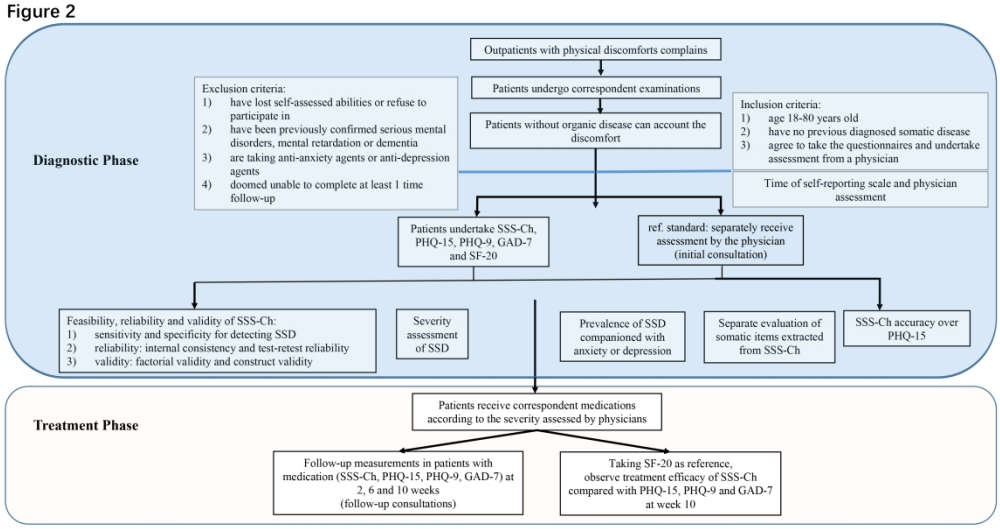

Figure 2

338x190mm (300 x 300 DPI)

TITLE OR		
Page 1, line 1-2	**1**	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
Page 2, line 2-18 for protocol article	**2**	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
Page 4-5, line 2-21	**3**	Scientific and clinical background, including the intended use and clinical role of the index test
Page 5, line 22-page 6, line3; Page 6,line 17-page 7, line 3	**4**	Study objectives and hypotheses
METHODS		
Study design Page 8, line 3; Page 14,line 13-22	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants Page 10,line 1-11	**6**	Eligibility criteria
Page 9,line 12-16	**7**	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
Page 9, line 12-21	**8**	Where and when potentially eligible participants were identified (setting, location and dates)
Page 9, line 12	**9**	Whether participants formed a consecutive, random or convenience series
Test methods Page 8,line 12-page 9, line 6; Figure 1	**10a**	Index test, in sufficient detail to allow replication
Page 10,line 12-19;Suppl Fig1	**10b**	Reference standard, in sufficient detail to allow replication
Page 4,line 23-page 5, line 5	**11**	Rationale for choosing the reference standard (if alternatives exist)
Page 8,line 19-page 9,line 6	**12a**	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing
Suppl Fig1	**12b**	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
Page 9, line 18-21	**13a**	Whether clinical information and reference standard results were available
Page 9, line 16-18; Page 12, line 1-3	**13b**	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis Page12，line 15-21	**14**	Methods for estimating or comparing measures of diagnostic accuracy
Page10，line 19	**15**	How indeterminate index test or reference standard results were handled
Page 14,line 10-12	**16**	How missing data on the index test and reference standard were handled
Page12，line 15-21	**17**	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
Page 13, line 3-13	**18**	Intended sample size and how it was determined
RESULTS		
Participants	**19**	Flow of participants, using a diagram
NA	**20**	Baseline demographic and clinical characteristics of participants
NA	**21a**	Distribution of severity of disease in those with the target condition
NA	**21b**	Distribution of alternative diagnoses in those without the target condition
NA	**22**	Time interval and any clinical interventions between index test and reference standard
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard

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NA	**24**	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
NA	**25**	Any adverse events from performing the index test or the reference standard
DISCUSSION		
Page 17,line 1-16	**26**	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
Page 16,line 2-9;line 18-25; Page 17,line 17-22	**27**	Implications for practice, including the intended use and clinical role of the index test
OTHER		
Page 2,line 24;Page 18,line 23-24；	**28**	Registration number and name of registry
NA	**29**	Where the full study protocol can be accessed
Page 18,line 15-22	**30**	Sources of funding and other support; role of funders

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Research Protocol for a Diagnostic Study: Identifying and Measuring the Severity of Somatic Symptom Disorder Using the Self-reported Somatic Symptom Scale-China (SSS-CN)

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Keywords:	Somatic Symptom Scale-China, somatic symptom disorder, mental disorders management

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Research Protocol for a Diagnostic Study: Identifying and Measuring the Severity of Somatic Symptom Disorder Using the Self-reported Somatic Symptom Scale-China (SSS-CN)

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ABSTRACT

Introduction The detection rate of somatic symptom disorder (SSD) in general hospitals is unsatisfactory. Self-report questionnaires that assess both somatic symptoms and psychological characteristics will improve the process of screening for SSD. The Somatic Symptom Scale-China (SSS-CN) questionnaire has been developed to meet this urgent clinical demand. The aim of this research is to validate the self-reported SSS-CN as a timely and practical instrument that can be used to identify SSD and to assess the severity of this disorder.

Methods and Analysis At least 852 patients without organic disease but presenting physical discomfort will be recruited at a general hospital. Each patient will undergo a DSM-5-guided physician diagnosis, including disease identification and severity assessment, as the reference standard. This research will compare the diagnostic performance of the SSS-CN for SSD, the Patient Health Questionnaire-15 (PHQ-15) and other SSD-related questionnaires. Statistical tests to measure the area under the curve (AUC) and volume under the surface (VUS) of the receiver operating curve (ROC) will be used to assess the accuracy of the SSD identification and the severity assessment, respectively. In addition to this standard diagnostic study, we will conduct follow-up investigations to explore the effectiveness of the SSS-CN in monitoring treatment effects.

Ethics and Dissemination Ethical approval was obtained from the Renji Hospital Human Research Ethics Committee, approval number 2015016. The findings of this study will be disseminated via peer-reviewed journals and presented at international conferences.

Trial registration number: NCT03513185

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Strengths and Limitations of this Study

1. The Somatic Symptom Scale-China (SSS-CN) questionnaire is developed according to the DSM-5, and its clinical utility is evaluated herein for the first time.
2. The SSS-CN will benefit patients by improving their awareness of SSD and their ability to self-monitor their symptoms.
3. The SSS-CN will provide clinicians with an easy-to-use tool that can be completed quickly and assess both somatic and psychological components.
4. Referral bias may be present in this study, as only patients without organic disease will be referred to our special clinic.
5. Treatment effect monitoring will be affected by the bias due to non-random loss to follow-up.

Keywords

Somatic Symptom Scale-China; somatic symptom disorder; mental disorders management

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INTRODUCTION

Somatic symptom disorder (SSD) [1 2] is a common medical condition observed in general hospitals. SSD is characterized by symptoms that are often difficult to explain after adequate evaluation[3]; even when a significant medical disease is present, the patients' symptoms may nonetheless be unrelated to their disease[2]. The diagnosis of SSD emphasizes the existence of symptoms and signs (one or multiple somatic symptoms, and abnormal thoughts, feelings, and behaviours in response to these symptoms)[2]. The current prevalence of this disorder is estimated to be 5-7%[2] in the general population, and it may be even higher in Asian individuals[4].

In general hospitals, the detection rate of SSD is unsatisfactory due to the diagnostic complexity of the disease and the lack of adequate training for physicians to evaluate patients with suspected SSD. Therefore, patients may sustain somatic symptoms without appropriate treatment due to the unawareness of SSD. The yearly cost of medical care among patients with somatization is nearly twice as high as the yearly cost among patients without somatization. An estimated $256 billion in annual medical care costs is attributable to the incremental effects of somatization alone[1]. Hence, it is highly important that physicians are trained to identify SSD, assess the symptom severity and treat it in a timely manner; failure to do so can result in high morbidity, lost productivity, and overutilization of medical resources[5 6]. However, compared to widely researched disorders such as depression and anxiety, SSD has been far less studied. Follow-up or treatment studies of this disorder are even scarcer.

It is more favourable to have a tool for screening patients suspected of having SSD via accurate and brief diagnostic questionnaires and to facilitate daily clinical work. One of the aims of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is to identify SSD patients and to assess the severity of the disorder[2]. The DSM-5 states that SSD comorbid with anxiety and depressive disorder (a combination present in approximately 57.7% of SSD patients)[1] adds severity and complexity to the somatic components. The DSM-5 emphasizes that it is important to evaluate patients in terms of their psychological situation, behaviour and

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physical condition altogether and then treat the patients according to the severity of the disorder. Furthermore, the DSM-5 emphasizes the evaluation of subjects who have excessive concerns about health issues. However, the DSM-5 is clinically difficult to follow because it requires qualified and experienced physicians to conduct an interview[7], which makes clinicians in general hospitals feel less confident when treating patients who are suspected to have SSD. In particular, individuals in China and other Asian countries tend to refuse psychological counselling [4 8]; thus, many patients with psychological symptoms have been treated by non-psychiatric physicians in general medical hospitals. A series of studies has focused on this issue; the Patient Health Questionnaire-15 (PHQ-15) and the Somatic Symptom Scale-8 are screening tools for SSD[9 10]; however, these self-report questionnaires do not assess psychological features. The Whiteley Index-7 focuses on health anxiety[11]; the Scale for the Assessment of Illness Behavior questionnaires focuses on excessive illness behaviour; and the Somatic Symptom Scale-12 assesses psychological features[12 13]. The latter three questionnaires focus less on physical features. Recent studies, including one by Laferton et al., have indicated that self-report measures that focus on different aspects could increase diagnostic quality in clinical practice[14].

Based on published studies, we aim to develop a comprehensive questionnaire to assess somatic symptoms of SSD comorbid with anxiety and depression symptoms. The Somatic Symptom Scale-China (SSS-CN) questionnaire was developed based on the DSM-5. The questionnaire assesses a combination of psychological, behavioural, and somatic symptoms. The questionnaire was designed for use in general medical facilities and to provide clinicians with an easy-to-use questionnaire for detecting both somatic and psychological features in a timely manner.

Study Objectives and Research Questions

Primary objective

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The primary objective of this study is to test two aspects of the diagnostic accuracy of the SSS-CN compared with the PHQ-15, with a DSM-5-guided physician diagnosis as the reference standard: (1) the accuracy for identifying SSD and (2) the accuracy for assessing SSD severity.

Secondary objective

The secondary objective is to explore the potential utility of the SSS-CN in monitoring the treatment effect. We aim to examine how the scores of the SSS-CN and other questionnaires change over time after treatment.

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METHODS

Study Overview

This study will use a prospective diagnostic design and will be conducted at a tertiary general hospital in Shanghai, China. The study protocol was approved by the ethics committees of Renji Hospital, and written informed consent will be obtained from all study participants. The clinical trial registration can be found at https://register.clinicaltrials.gov/, and the registration number is NCT03513185.

Particular attention will be paid to the appropriate storage of the data. Patient confidentiality will be maintained, and no identifying characteristics of the patients will be published. The protocol development will adhere to the European Medicines Agency guidelines for diagnosis study[15].

Description of the SSS-CN and Assessment of Severity

The SSS-CN is a somatic and psychological symptom scale (**Figure 1**) derived from the DSM-5. It is designed to assess the presence and severity of the symptoms. We validated its reliability and validity in a previous study[16]. The test-retest reliability was 0.9. The correlation coefficients between each dimension and the total ranged from 0.76-0.88, and the correlation coefficients within dimensions ranged from 0.56-0.70.

The questionnaire is self-administered with an abbreviated 20-item measure. Briefly, in the previous study, the SSS-CN was composed of 4 dimensions: physical disorder, anxiety disorder, depression disorder, and anxiety and depression disorder. Half of the items ask about physical complaints (1 item per body system, items 1, 5, 9, 10, 12, 13, 16, and 18-20). The remaining items ask about anxiety and depression (anxiety items 6, 14, 15, and 17; depression items 3, 4, 7, and 11; and anxiety and depression items 2 and 8). Subjects answer the following question: "Since you have felt unwell, how often have you been bothered in the previous 6 months by any of the following problems?" For scoring, the subjects rate the frequency of each symptom using the following response options: 1 ("does not exist"), 2 ("the problem occurred occasionally for a

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couple of days per month and/or is endurable"), 3 ("the problem occurred almost half of the days per month and/or I hope it will ease up") or 4 ("the problem occurred almost every day and/or is unendurable"). Thus, in determining the SSS-CN score, each question has a score ranging from 1 to 4, corresponding to the frequency of the problem occurrence, and the total score ranges from 20 to 80. The severity of SSD is determined based on the sum of the scores. SSS-CN scores ranging from 20-29, 30-39, 40-59, and ≥60 correspond to normal, mild, moderate, and severe SSD, respectively. The selection of the cutoff value of 30 is based on the results of our previous study (It was obtained from the receiver operating curve (ROC), reaching a sensitivity of 0.97 and a specificity of 0.96)[16]. Other cut-offs (40,60) are chosen based on clinical experience rather than previous research.

Study Design

The study is composed of 2 stages (Figure 2) corresponding to the primary and secondary research objectives. The first stage is a prospective diagnostic stage to assess the diagnostic performance of the SSS-CN questionnaire. The second stage is an exploratory follow-up stage that uses the SSS-CN questionnaire as a tool to monitor treatment effects.

Briefly, consecutive outpatients with physical discomfort presenting to internal medicine departments in a tertiary hospital in China will first undergo the corresponding examination to exclude organic disease. For example, a patient with chest pain will be recommended by a physician to receive an EKG, echocardiography, a treadmill test or coronary angiography to exclude cardiovascular disease. Patients with no organic disease that can account for their discomfort will be considered to have a probable psychosomatic disorder. These patients will then be transferred to a specialist clinic for the diagnosis and treatment of suspected SSD (the initial consultation). They will fill out the SSS-CN questionnaire; they will also complete other self-reported instruments, including the PHQ15, the Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder Scale-7 (GAD-7) and the SF-20, to verify the structural validity of SSS-CN. Non-

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clinical research assistants will collect the questionnaires and calculate the scores. A physician or a psychologist who is blind to the results of the SSS-CN will separately interview the patient to diagnose SSD using the standard interview criteria put forth in the DSM-5. Prescriptions will be given if the patient is diagnosed with SSD. For patients receiving medications, follow-up visits will be scheduled at 2, 6, and 10 weeks to repeat the questionnaires (the follow-up consultation). Because health-related quality of life is often impaired in patients with SSD, the 20-item Short Form Health Survey (SF-20) will be administered as an indicator of therapeutic effects during follow-up.

Participants and Procedure

Inclusion criteria

(1) Patients aged 18-80 years old; (2) patients who have no previous diagnosis of somatic disease; (3) patients without systemic disease that can account for their physical discomfort; and (4) patients enrolled as outpatients after they agree to complete the questionnaires and undergo assessment by a physician.

Exclusion criteria

(1) Patients who have lost their self-assessment ability or refuse to participate; (2) patients who have been confirmed to have mental disorders, mental retardation or dementia; (3)patients who currently take anti-anxiety agents or anti-depression agents; and (4) patients who are unable to complete face-to-face follow-up visits after at least 1 month.

Reference standard

Patients will be interviewed using the standard procedure. The physician will conduct a structured clinical interview (SCID-5-CV) in accordance with the corresponding DSM-5 criterion. The interview questions include modules from somatic symptom and related disorder to depression disorder, anxiety disorder, obsessive-compulsive related disorder and sleep-wake disorders. The interview will last approximately 30-45 minutes. The physician will assess the severity based on the

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number of symptoms, i.e., excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns (mild: one symptom; moderate: two or more of the symptoms; severe: two or more of the symptoms plus multiple somatic complaints). The physician assessment will be used as the reference standard. The physician team will be composed of both general hospital "specified physicians" (that is, physicians qualified as national psychological counsellors) and psychologists. When there is diagnostic uncertainty, the patient will be referred to the senior physician to obtain a diagnosis.

Obtaining informed consent

A trained researcher will obtain informed consent and provide all necessary information about this study to the potential participants. It will be made clear to participants that they are under no obligation to take part, their usual care will not be affected by their decision, and they can withdraw consent without giving a reason. Participants will be given a sheet with contact details for the research team and instructions on what to do if they wish to withdraw or require further information.

Blinding

After a patient with suspected SSD is transferred to the specialist clinic, the patient will first complete the questionnaires in a separate room, and the research assistant will help the patient understand the questions. Then, an initial consultation will be conducted by a physician who has been qualified as a national psychological counsellor and who has been blinded to the patient's responses to the SSS-CN. An independent diagnosis and severity assessment will be made by the physician. The durations of the self-reported scale and the physician assessment will be recorded separately.

Medication

The patients will be informed of the results immediately after the physician consultation and the questionnaire. During the follow-up consultations, the patients will be allowed to communicate

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with the doctor throughout the diagnosis and treatment. Because patients in China usually refuse to accept psychotherapy[4 8], medications will be prescribed according to the physician's evaluation. Anti-anxiety treatment or anti-depression treatment will be selectively administered according to the severity of the somatic symptoms. Generally, drugs that are classified as thioxanthenes, such as Deanxit, are prescribed for mild symptoms; selective serotonin reuptake inhibitors (SSRIs) are prescribed for moderate symptoms; and serotonin-norepinephrine reuptake inhibitors (SNRIs) are prescribed for severe symptoms. Serotonin antagonist and reuptake inhibitors (SARIs) are prescribed for sleeping problems.

Follow-up

A face-to-face interview will be scheduled at 2, 6, and 10 weeks for patients taking medication. The patient will complete 5 questionnaires (SSS-CN, PHQ15, PHQ-9, GAD-7 and SF-20) both at the initial consultation and at the week 10 follow-up. The SF-20 aims to evaluate the respondent's quality of life. At week 2 and week 6, the patient will complete 4 questionnaires (SSS-CN, PHQ15, PHQ-9, GAD-7).

Outcome Measures

Reliability and validity

Reliability will be measured by Cronbach's alpha. A randomized sample of approximately 100 participants will be asked to complete the questionnaires 1 week after the initial completion to analyse the test-retest reliability.

The criterion validity will be determined by comparing the presence and severity of SSD between the reference standard (physician assessment based on structure interview) and the SSS-CN questionnaire.

The SSS-CN consists of 10 items assessing somatic symptoms, 4 items assessing depression, 4 items assessing anxiety, and 2 items assessing depression and anxiety. The construct validity will

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be tested by confirmatory factor analysis, comparing the corresponding factors with the PHQ-15, PHQ-9 and GAD-7.

Diagnostic performance

The diagnostic accuracy of a questionnaire for SSD identification is measured by the area under the curve (AUC) of an ROC, the sensitivity/specificity under a prespecified cutoff value, and the positive/negative predictive values in the study population, using the physician diagnosis as the reference standard. The accuracy of the severity assessment of a questionnaire is measured by the volume under the surface (VUS), which is a multiclass generalization of AUC of a ROC between the questionnaire score and the physician's severity assessment[17].

Other Clinical utilities

Convenience in clinical practice is measured by the average time taken to complete each questionnaire or receive a diagnosis from a physician.

Clinical utility in monitoring treatment efficacy in patients is measured by assessing the correlation with the SF-20 during follow-up visits.

Sample Size Calculation

The sample size calculation considers the comparison of diagnostic accuracy for both SSD identification and severity assessment, whichever is larger. In the pilot study, the prevalence of SSD was 76.9% among patients who were referred to the special clinics (where physicians qualified as national psychological counsellors and psychologists practice medicine); the AUC of the ROC for the PHQ-15 was 0.88; and the VUS of the multiclass ROC for the PHQ-15 with respect to the severity assessment was 0.7. The correlation between the SSS-CN and PHQ-15 scores was 0.6. With a non-inferiority margin of 0.05, α=0.025, and β=0.8, the sample size for SSD diagnosis was 852. With a non-inferiority margin of 0.1, α=0.025, and β=0.8, the sample size for severity assessment was 517. Therefore, as the overall sample size of this study was N=852 with SSD-

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positive N+=655 and SSD-negative N-=197, both the positive and negative sample size requirements were met.

Statistical Analysis

We will report our results according to STARD. We will compute the median (P25, P75) scores for each questionnaire and the number and percentage of patients (%) in each diagnostic category as descriptive statistics.

Reliability will be measured using Cronbach's α. The criterion validity will be measured by the kappa coefficient between the questionnaire score and the physician assessment. Construct validity will be tested using confirmatory factor analyses.

The primary analysis of the diagnostic performance will consist of two comparisons using Bonferroni's correction: (1) the non-inferior comparison of the SSS-CN with the PHQ-15 with respect to SSD diagnostic accuracy, as measured by the AUC of the ROC with Δ=0.05, α=0.025 in the whole study population using Delong's method[18]; and (2) severity of PHQ-15 based on scores (normal: 0–4; low: 5–9; medium: 10–14; high: 15–30). SSS-CN scores ranging from 20 to 29, 30 to 39, 40 to 59, and ≥60 correspond to normal, mild, moderate, and severe SSD, respectively. The non-inferior comparison will also be conducted between the SSS-Ch and the PHQ-15 with respect to SSD severity, as measured by the VUS with Δ=0.1, α=0.025 in the population with a confirmed SSD diagnosis using a Z-test[17]. Both comparisons will use the physician's diagnosis as the reference standard. If neither non-inferiority criterion is met, the corresponding superiority will be tested.

As a secondary analysis, the sensitivity, specificity, and positive and negative predictive values will also be determined. Prespecified cutoff values will be validated. In the follow-up data, questionnaire scores by time will be demonstrated in a line chart with error bars.

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Missing values will be imputed with multiple imputation under the assumption of MAR[17]. Subgroup analysis according to gender and age will also be conducted. All statistical analyses will be performed with R (version 3.5.1)

Patient and Public Involvement Statement

Patients were involved at the design stage of the trial, including ensuring that the content of the SSS-CN questionnaire can be understood and that the length of the consultation time, the manner of notification of the disease condition, the follow-up method, and the dissemination of the results are acceptable. Before the formal recruitment started, we received feedback from patients who had SSD during a pretest of the case report form (CRF), and this feedback was used to improve the final design of the CRF. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate the main results to the trial participants via email. The study outcomes will be disseminated in conference reports and academic publications.

Ethics and Dissemination Ethical approval was obtained from the Renji Hospital Human Research Ethics Committee, approval number 2015016. The findings of this study will be disseminated via peer-reviewed journals and presented at international conferences.

Current Status

The first study participant was enrolled in November 2017. As of June 2019, patient recruitment has not been completed.

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DISCUSSION

In this study protocol, we describe a diagnostic study design that evaluates the efficacy of a newly developed somatic and psychological symptom scale adapted to China for patients with suspected somatic diseases. This scale might be applied as a first-line instrument for screening and monitoring treatment efficacy in individual outpatient consultations. We expect that physicians will benefit from the SSS-CN on a clinically significant level in the form of improved self-confidence and timeliness; participants will benefit from this scale in the form of improved awareness of the disease and improved ability to self-monitor their symptoms. Moreover, we will compare the characteristics of the SSS-CN with another somatic symptom questionnaire, namely, the PHQ15.

The SSS-CN is designed as a "one-stop shop" tool that combines somatic items with mental disorder items. This design is consistent with the suggestion in the DSM-5 that somatic symptoms are likely accompanied by depression and anxiety[1]. Somatic and mental symptoms may interact, and mental symptoms may be triggered differently from conventional mental diseases among SSD patients. Clinically, it is not easy to clearly separate the body from mental status, and the significance of each item is unknown. We caution that 50% of mental items may increase the incidence of SSD, and a subgroup score with only somatic symptom items is used for this appraisal.

In our study, there is no plan to supplement medication treatment of psychotherapy. This is because there are societal and cultural culture differences in response to psychotherapy between Asian and non-Asian patients. The Chinese World Mental Health Survey (2001–02) conducted in Beijing and Shanghai found that only 3.4% of respondents with a psychiatric disorder sought professional help during the previous 12 months[19]. Similarly, in a large epidemiologic study conducted in four provinces of China[63004 participants aged 18 years or older in 96 urban neighbourhoods and 267 rural villages], only 8% of individuals with mental disorders sought professional help within the general healthcare setting, and only 5% sought help from mental health professionals (mainly hospital-based psychiatrists)[20]. Second, Chinese and Asian Americans

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are likely to drop out and prematurely terminate psychotherapy services[8]. Third, there is a shortage of psychiatrists, psychiatric nurses, and counselling and clinical psychologists to provide psychotherapy[21]. In particular, China had only 1.49 psychiatrists per 100 000 people, while, on average, middle- and high-income countries worldwide have 2.03 psychiatrists per 100 000. Finally, insurance currently pays for treatment with medication but typically does not support psychotherapy, community recovery services, or preventive care.

The study has several strengths. First, we introduce a tool to facilitate daily clinical work. The tool provides clinicians with an easy-to-use questionnaire for screening suspected SSD patients and referring the patients to specific doctors. Second, our previous study showed the reliability and factorial validity of the SSS-CN by utilizing an early version of it[16]. The current study further modifies the SSS-CN based on the DSM-5 and, for the first time, evaluates its clinical utility. Third, patients will benefit from the SSS-CN in the form of improved awareness of the disease and improved ability to self-monitor their symptoms.

This trial has some limitations. First, SSD can be accompanied by diagnosed medical disorders. The current study, however, represents the efficacy of the SSS-CN only in patients without organic diseases. Therefore, further research on the application of SSS-CN in patients with both SSD and diagnosed medical disorders is required. Moreover, the epidemiology of primary healthcare facilities is different from the epidemiology of general hospitals; therefore, the diagnostic accuracy in a health care sample requires additional investigation. Second, the study was designed as a mid-term investigation with four measurement time points; thus, missing data must be considered. Because only 16% of patients in the primary care evaluation of mental disorders (PRIME-MD) study were involved in the follow-up[22], we estimate that there will be a high rate of missing data in our study. Because of the difficulty with compliance, only a small fraction (approximately 16%) of patients in study would be involved in the follow-up, and the result of monitoring the treatment effect may be affected by loss to follow-up.

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This study will help to clarify whether the SSS-CN is an effective tool for rapidly screening and assessing the severity of symptoms in patients with suspected SSD in a general hospital clinic and during follow-up. If the SSS-CN is found to be effective, it can be implemented as a first-line screening and follow-up option. Additionally, we expect that the SSS-CN could provide personalized information to consulting physicians in a timely manner. The study results will contribute to better outpatient care for patients with SSD.

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Conflict of interests: The authors declare that they have no competing interests.

Ethical approval: Ethical approval was provided by the Renji Hospital Human Research Ethics Committee, approval number 2015016.

Consent for publication: All participants to date have provided written informed consent.

Authors' contributions: MJ: substantial contributions to the conception, design and interpretation of data, drafting and critical revisions for important intellectual content. WTZ: analysis, statistics and interpretation of data, drafting the manuscript. XS: design and implementation of study, acquisition of data, analysis and interpretation of data, drafting the manuscript. CG: analysis, statistics and interpretation of data. BXC: acquisition of data, analysis and interpretation of data, drafting the manuscript. ZHF: acquisition of data, analysis and interpretation of data, drafting the manuscript. JLM: substantial contributions to the conception, design and interpretation of data, critical revisions for important intellectual content. JP: substantial contributions to the conception, design and interpretation of data.

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Registration name: The validation and utility of the Somatic Symptom Scale-China (SSS-CN) for assessing somatic symptom disorder in general hospital outpatients.

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Figure Legends

Figure 1 The Somatic Symptom Scale-China (SSS-CN).

Figure 2 Study flow. SSS-CN, Somatic Symptom Scale-China; PHQ-15: Patient Health Questionnaire-15; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder Scale-7; SF-20: 20-Item Short Form Health Survey; SSD: Somatic Symptom Disorder.

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Self-rating Somatic Symptoms Scale

1. Basic information

Name _____Mobile phone_____ Gender ___Age___ Education level _____Occupation_____
Date___ Course of symptoms ____Number of Self-rating ____Historical diagnosis_____
Medications administered_____

2. Instruction:

To better understand the degree to which you're bothered by the problems, please read carefully the following 20 items and CIRCLE the corresponding points at the right column that best describe your health. All the items listed in this questionnaire are REQUIRED.

1: not existent
2: the problem occurred occasionally for a couple of days per-month and/or is endurable
3: the problem occurred almost half days per-month and/or hoping to ease up
4: the problem occurred almost every day and/or unendurable

In the past 6 month, do you have the following symptoms:

1)	Dizziness, swelling in the head, heavy head, headache, spinning head, faint, buzzing in head	1	2	3	4
2)	Trouble sleeping (difficulty falling asleep/staying asleep, waking up too early, oversleeping, easily drea nightmare, awakened for no reason)	1	2	3	4
3)	Feeling tired or having low energy	1	2	3	4
4)	Losing interest, moody, don't want to be bothered, lacking patience	1	2	3	4
5)	Chest pain, shortness of breath, racing/pounding/fluttering heart, chest tightness	1	2	3	4
6)	Easily anxious, nervous, feeling scared, panicky, feeling I'm going to die, out of control	1	2	3	4
7)	Worried, apprehensive, negative ideation	1	2	3	4
8)	Reduced attention & thinking abilities, forgetful, absentminded	1	2	3	4
9)	Bloating, stomach pain, gas, loss of appetite, constipation, loose bowels, nausea, becoming thin, dry o bitter mouth	1	2	3	4
10)	Pain in the neck, back, shoulders, waist, arm, legs	1	2	3	4
11)	Sensitive, easily sad and crying	1	2	3	4
12)	Unusual sensations in the joints of hands or legs (numb, rigid, twitching, shivering, pricking, chilly)	1	2	3	4
13)	Blurry vision, eye dryness, eye pain or swelling, decreased eye vision over a short period of time	1	2	3	4
14)	Easily agitated or irritable, sensitive to voice, susceptible to startle	1	2	3	4
15)	Obsessive-compulsive thoughts or behaviors	1	2	3	4
16)	Skin allergies, itching, rash, skin flushing, hot flash, sweating	1	2	3	4
17)	Excess concerns about health issues, excessive worry that you or family members are ill	1	2	3	4
18)	Difficulty breathing, feeling oppressed or suffocated, frequent long sigh, coughing, intercostal pain	1	2	3	4
19)	Choking feeling in the throat, nasal dryness and obstruction, ringing in the ears or ear blockage	1	2	3	4
20)	Frequent urination, urgent need to urinate, painful urination, or discomfort in perineum	1	2	3	4

Functional impairment in work, study, family life, and interpersonal relationship: Not at all, A little bit, Quite a bit, or Very much/Severe

Figure 1

210x297mm (300 x 300 DPI)

Figure 2

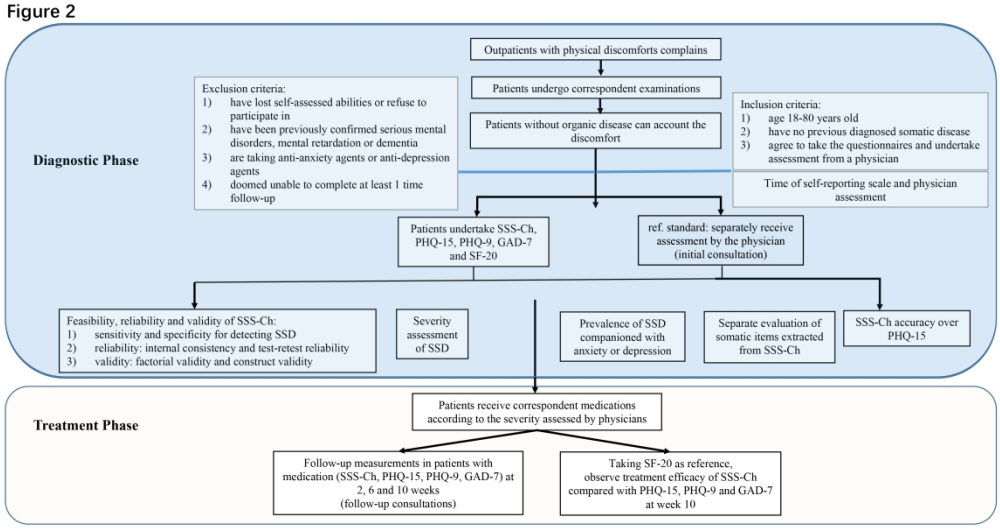

Figure 2

338x190mm (300 x 300 DPI)

Section & Topic	No	Item
TITLE OR ABSTRACT		
Page 2, line 12-15	**1**	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
Page 2	**2**	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
Page 4,line 2-page 5, line 21	**3**	Scientific and clinical background, including the intended use and clinical role of the index test
Page 5,line 22-Page 6,line7	**4**	Study objectives and hypotheses
METHODS		
Study design Page 8,line 13-14,pros	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants Page 9,line 10-14	**6**	Eligibility criteria
Page 8,line 16-21	**7**	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
Page 8,line 21-22	**8**	Where and when potentially eligible participants were identified (setting, location and dates)
Page 8,line 16,consecutive	**9**	Whether participants formed a consecutive, random or convenience series
Test methods Page 7,line 11-Page 8,line 10	**10a**	Index test, in sufficient detail to allow replication
Page 9,line 20-Page 10,line7	**10b**	Reference standard, in sufficient detail to allow replication
Page 9,line 21-24	**11**	Rationale for choosing the reference standard (if alternatives exist)
Page 8,line 7-10	**12a**	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from
Page 10, line1-3	**12b**	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
Page 8,line 25-Page 9,line1	**13a**	Whether clinical information and reference standard results were available to the performers/readers of the index test
Page 9,line 1-3	**13b**	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis Page12，line 3-9 Page13，line 10-20	**14**	Methods for estimating or comparing measures of diagnostic accuracy
Page 10,line 6-7	**15**	How indeterminate index test or reference standard results were handled
Page 14,line 1	**16**	How missing data on the index test and reference standard were handled
Page14，line 2	**17**	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
Page 12,line 15-Page 13,line2	**18**	Intended sample size and how it was determined
RESULTS		
Participants	**19**	Flow of participants, using a diagram
NA	**20**	Baseline demographic and clinical characteristics of participants
NA	**21a**	Distribution of severity of disease in those with the target condition
NA	**21b**	Distribution of alternative diagnoses in those without the target condition
NA	**22**	Time interval and any clinical interventions between index test and reference standard
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
NA	**24**	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
NA	**25**	Any adverse events from performing the index test or the reference standard
DISCUSSION		
Page 16,line 15-Page 17,line 2	**26**	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
Page 17,line 3-8	**27**	Implications for practice, including the intended use and clinical role of the index test
OTHER INFORMATION		
Page 2,line 23;Page 18,last 2 lines	**28**	Registration number and name of registry

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Page 7,line 5-7	**29**	Where the full study protocol can be accessed
Page 18	**30**	Sources of funding and other support; role of funders

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STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

For peer review only