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STUDY PROTOCOL

Protocol for a Prospective, Multicenter Cohort Study on the Treatment of Chronic Cardiorenal Syndrome with Qishen Yiqi Dropping Pills

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Background: Chronic Cardiorenal Syndrome (CRS types 2/4) involves the mutual exacerbation of heart failure and chronic kidney disease, with over half of heart failure patients affected by renal impairment that increases mortality and rehospitalization. Despite advances in management, prospective evidence for Traditional Chinese Medicine in chronic CRS is lacking. Qishen Yiqi Dropping Pills (QSYQ) have proven safe in cardiovascular care, but their concurrent renoprotective effects remain unconfirmed. Based on preliminary cardiorenal protective findings, this study evaluates QSYQ combined with standard therapy on symptoms, function, biomarkers, and outcomes in chronic CRS.

Methods: This is a prospective, multicenter, observational cohort study. Patients will be stratified into two groups based on whether or not they receive QSYQ treatment: an "Exposure Group" (standard background pharmacotherapy plus QSYQ; n=60) and a "Non-exposure Group" (standard background pharmacotherapy alone; n=60). The study duration is 270 days, with the exposure period set to the initial 90 days. Follow-up assessments will be conducted at baseline, and on days 90, 120, 180, and 270. The primary outcome measure is the 6-Minute Walk Test (6MWT). Secondary outcome measures include the New York Heart Association (NYHA) functional classification, N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine (Cr), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), trimethylamine N-oxide (TMAO), major adverse renal and cardiovascular events (MARCE), the Veterans Specific Activity Questionnaire (VSAQ), and the Kansas City Cardiomyopathy Questionnaire (KCCQ). Throughout the entire study period, adverse events will be recorded to facilitate safety assessments.

Discussion: This study will comprehensively assess QSYQ's clinical utility for chronic CRS, evaluating functional capacity, quality of life, biomarkers, and long-term outcomes to provide prospective evidence for integrating Traditional Chinese Medicine into chronic CRS management.

Keywords: Qishen Yiqi Dropping Pills, chronic cardiorenal syndrome, prospective cohort study, study protocol

Introduction

CRS is a complex clinical syndrome characterized by the mutual interaction and reciprocal exacerbation of structural or functional abnormalities within the heart and kidneys.[1] Based on the classic classification system, CRS is categorized into five types; specifically, Types 2 and 4 represent chronic cardiorenal injury and chronic renocardiac injury, respectively, and together they constitute the predominant clinical subtypes of chronic CRS.[2] Clinically, the syndrome typically manifests as symptoms associated with the coexistence of chronic heart failure and chronic kidney disease, such as dyspnea, orthopnea, reduced exercise tolerance, edema, and albuminuria.[3] A real-world study involving over 170,000 hospitalized heart failure patients revealed that 55.0% of these patients had concomitant chronic kidney disease (CKD), and that the presence of CKD was associated with a significantly increased risk of in-hospital mortality and readmission;[4] Another study, comprising approximately 22,000 heart failure patients, confirmed that among individuals with an eGFR of <30 mL/min/1.73 m^2, the

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4-year cumulative incidence of all-cause mortality reached as high as 72.2%. Furthermore, this patient subgroup demonstrated a notably elevated risk of renal outcome events; indeed, adverse renal outcomes frequently emerged as the initial adverse event occurring even more commonly than heart failure-related hospitalizations, suggesting that advanced renal dysfunction can profoundly alter the subsequent trajectory of clinical events in patients with heart failure.[5] Consequently, the implementation of early identification, risk stratification, and collaborative, interdisciplinary cardiorenal interventions represents a critical avenue for mitigating adverse outcomes and alleviating the healthcare burden associated with CRS.[6] CRS is not merely a simple comorbidity of heart and kidney disease; rather, it constitutes a complex, cross-organ pathological state driven by a confluence of mechanisms, including hemodynamic disturbances, neuroendocrine activation, and metabolic abnormalities.[7,8] Despite continuous advancements in therapeutic modalities such as diuretic therapy, neuroendocrine blockade, device-based interventions, and renal replacement support, the clinical management of CRS remains beset by challenges, including complex treatment decision-making, significant inter-individual heterogeneity, and suboptimal long-term prognoses.[9–11] These persistent challenges underscore the inadequacy of single-target or organ-centric intervention models for fully addressing the long-term management needs of patients with chronic CRS, underscoring an urgent imperative to identify stable, effective, and sustainable therapeutic strategies that enhance the overall clinical benefits of CRS management.

As research continues to deepen, the conceptual framework for understanding cardiorenal diseases is evolving. In 2023, the American Heart Association introduced the concept of Cardiovascular-Kidney-Metabolic (CKM) health, emphasizing that cardiovascular diseases, kidney diseases, dysmetabolism (of glucose and lipids), and obesity are not isolated entities but rather intertwined, continuously progressing systemic processes. Consequently, clinical management should shift from a single-organ therapeutic approach toward staged, patient-centered, and comprehensive interventions. These developments suggest that the therapeutic assessment of chronic CRS should not be confined solely to cardiorenal function itself.[12,13] Rather, it must simultaneously address multidimensional benefits—including symptom burden, inflammatory responses, metabolic abnormalities, and long-term clinical outcomes. TCM with its emphasis on a holistic perspective and syndrome differentiation-based treatment, is characterized by the synergistic regulation of multiple components across multiple biological pathways. This approach aligns closely with the integrative philosophy advocated for the comprehensive management of chronic CRS, suggesting that TCM holds promise as a complementary therapeutic modality for such complex, chronic, and multi-organ diseases. Against this backdrop, the identification of proprietary Chinese medicines with potential for bidirectional cardiorenal protection, followed by their prospective clinical evaluation, holds significant practical relevance.

QSYQ is composed of four traditional Chinese medicinal ingredients: *Astragalus membranaceus, Salvia miltiorrhiza, Panax notoginseng, and Dalbergia odorifera oil*, and has been approved for the treatment of cardiovascular diseases such as coronary heart disease and chronic heart failure, thereby possessing a well-established foundation for clinical application.[14–16] As an adjunctive therapy, QSYQ has demonstrated the ability to improve certain clinical outcomes in patients with ischemic heart failure,[17] furthermore, systematic reviews suggest that QSYQ can enhance cardiac function and improve specific biochemical markers within the heart failure population.[18] Moreover, existing evidence indicates that its overall safety profile is reliable, with no observed increase in the risk of significant adverse events.[19] Our team's previous studies have confirmed that, within pressure-overload models, QSYQ exerts protective effects on both the myocardium and the kidneys; specifically, it ameliorates pathological myocardial changes while simultaneously delaying the progression of renal interstitial fibrosis, thereby suggesting its potential for bidirectional cardio-renal intervention.[20,21,] However, prospective clinical evidence regarding the use of QSYQ for the treatment of chronic CRS remains insufficient, and its efficacy and safety in this specific patient population require further evaluation. Consequently, there is a compelling need to conduct a rigorously designed, prospective, multicenter cohort study to assess the efficacy and safety of QSYQ in treating chronic CRS within a real-world clinical setting, thereby providing clinical evidence to support the integration of Traditional Chinese Medicine into the comprehensive management of CRS.

Materials and Methods

Study Design

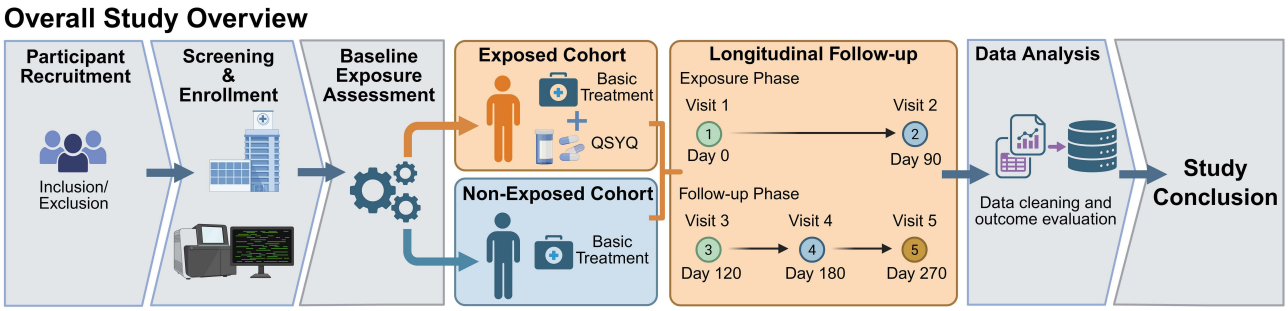
This study is a prospective, multicenter, observational cohort study to be conducted at the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, the Affiliated Hospital of the Tianjin Academy of Traditional Chinese Medicine,

the Dongguan Hospital of Guangzhou University of Traditional Chinese Medicine, and the Qian'an Hospital of Traditional Chinese Medicine. Its aim is to evaluate differences in functional status, symptom burden, heart- and kidney-related laboratory parameters, and adverse clinical outcomes between CRS patients receiving QSYQ treatment and those not receiving it, in a real-world clinical setting. All patients will receive standard baseline therapy as recommended by clinical guidelines; the use of QSYQ will be determined by the treating physician based on clinical practice and patient preference, with the investigators playing no role in prescribing decisions or treatment allocation. Once patients meet the inclusion and exclusion criteria and have signed the informed consent form, the research team will determine their exposure status based on their baseline medication use. Th e 120 patients scheduled for enrollment will be divided into a non-exposure group (receiving only baseline pharmacotherapy; n=60) and an exposure group (receiving both baseline pharmacotherapy and QSYQ treatment; n=60). The primary outcome measure of the study is 6MWT. Secondary outcome measures include the NYHA functional classification, cardiac function markers (NT-proBNP), renal function markers (Cr, BUN, eGFR), inflammatory markers (CRP, TMAO), and the VSAQ, KCCQ, and MARCE scales. Safety will be evaluated by recording adverse events occurring throughout the study period. As this is a prospective, observational cohort study in which investigators do not assign interventions, blinding will not be employed. The flowchart for this study is presented in Figure 1.

Inclusion and Exclusion Criteria

Inclusion Criteria

Referencing the *2024 Guidelines for the Diagnosis and Treatment of Heart Failure in China*[22] and the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*.[23]



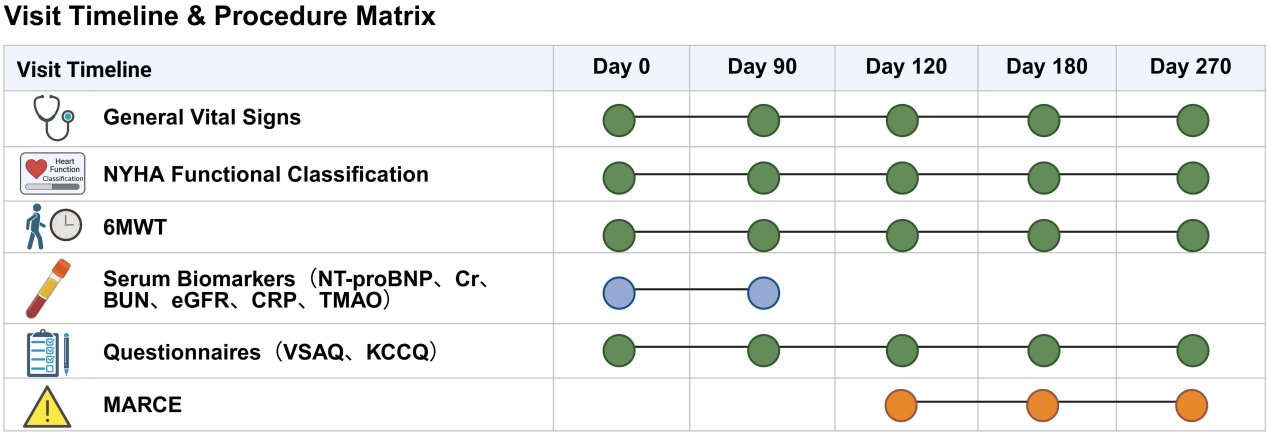


Figure 1 Overall study design and visit schedule of the prospective multicenter cohort study. This figure illustrates the overall workflow of the present prospective, multicenter, observational cohort study. After screening and enrollment, eligible patients are assigned to the Exposure Cohort (standard background therapy plus QSYQ) or the Non-Exposure Cohort (standard background therapy alone) according to real-world treatment exposure. The total study duration is 270 days, including a 90-day exposure phase and a subsequent follow-up phase. Study visits are scheduled at Day 0, Day 90, Day 120, Day 180, and Day 270. The lower visit matrix summarizes the timing of key assessments, including general vital signs, NYHA functional classification, 6MWT, serum biomarkers, patient-reported questionnaires and MARCE. Green circles indicate assessments performed at all five visits, blue circles indicate assessments performed only at Day 0 and Day 90, and Orange circles indicate assessments performed at Day 120, Day 180, and Day 270. This figure provides an integrated overview of participant flow, exposure allocation, follow-up timeline, and outcome assessment schedule. Created with BioRender.com.

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(1) Presence of symptoms of heart failure, such as exertional dyspnea, paroxysmal nocturnal dyspnea or orthopnea, cough, sputum production and/or hemoptysis, reduced physical capacity, and fatigue/weakness, and/or signs of heart failure, including edema, pleural and/or abdominal effusions, bilateral basal fine crackles, jugular venous distension, and hepatomegaly; BNP > 35 ng/L and/or NT-proBNP > 125 ng/L; and echocardiographic evidence indicating objective structural and/or functional cardiac abnormalities;
(2) Presence of the following renal structural or functional abnormalities persisting for more than 3 months (markers of kidney damage): albuminuria (urinary albumin excretion rate [UAER] ≥ 30 mg/24 h or urinary albumin-to-creatinine ratio [UACR] ≥30 mg/g), urinary sediment abnormalities, tubular disorders, histological abnormalities, structural abnormalities detected via imaging, or a history of kidney transplantation; accompanied by a decline in eGFR: eGFR < 60 mL/min^{-1}/1.73 m$^{2\ -1}$;
(3) Age between 18 and 80 years, inclusive; no gender restrictions;
(4) NYHA functional class II–III;
(5) Chronic kidney disease stage G2–G3 (based on eGFR);
(6) The patient provides informed consent and signs the informed consent form.

Exclusion Criteria

(1) Patients with concurrent severe primary diseases involving hepatic, hematological, or endocrine systems; patients with malignancies; and patients with severe neuroendocrine disorders or psychiatric illnesses;
(2) Patients with concurrent high-mortality-risk factors, such as acute coronary syndrome (within the past 30 days), cardiogenic shock, acute myocarditis, hypertension refractory to medical treatment (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure≥110 mmHg), refractory malignant arrhythmias, hypertrophic obstructive cardiomyopathy, severe valvular heart disease requiring surgical intervention, or pulmonary embolism;
(3) Patients with chronic heart failure requiring device-based therapy in the near future;
(4) Women who are pregnant, planning to become pregnant, or currently breastfeeding;
(5) Patients with an allergic constitution or a known allergy to the study medication;
(6) Patients who have participated in other clinical drug trials within the past month;
(7) Patients who, in the investigator's judgment, are unable to complete the study or unable to adhere to the study's follow-up schedule.

Interventions and Study Plan

Interventions

Prior to enrollment, all eligible patients must provide written informed consent. Following enrollment, patients in both groups will receive standardized baseline treatment based on current guidelines, such as the *Clinical Practice Guidelines for the Diagnosis and Treatment of Cardiorenal Syndrome (2023 Edition)* and the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. This baseline treatment commences on the day of enrollment and continues until the conclusion of the follow-up period. To minimize confounding effects from interventions, the concomitant use of other proprietary Chinese medicines or herbal decoctions possessing properties of "replenishing Qi and activating blood circulation" or "treating both the heart and kidney" is, in principle, to be avoided during the study period. Should the patient's clinical condition necessitate the addition of such medications, the name of the drug, its start and end dates, and the rationale for its use must be recorded in detail and accounted for during the statistical analysis.

Non-Exposure Group: Baseline pharmacotherapy.

Exposure Group: Baseline pharmacotherapy supplemented with Qishen Yiqi Dropping Pills (Tianjin Tasly Pharmaceutical Group Co., Ltd.; Approval No. Z20113048). The medication is administered orally at a dose of 0.5 g three times daily for a continuous period of 90 days.

During the study period, QSYQ is, in principle, administered at a fixed dosage, with no routine dosage adjustments. If suspension, dosage reduction, or discontinuation of the medication becomes necessary due to adverse reactions, changes in clinical condition, conflicts with concomitant medications, or issues regarding patient compliance, the date of occurrence, duration, specific reason, and outcome of the management measures must be fully documented. Given that medication

compliance and the accurate measurement of actual drug exposure directly impact the validity and credibility of clinical study results,[24] this study employs a combined approach comprising "verification of remaining medication," "patient medication diaries," and "clinical interview inquiries" to monitor compliance and enhance the accuracy of the trial's findings. During the visit on Day 90, medication boxes from the Exposure Group will be collected to verify the quantity of remaining medication; this objective verification will be cross-referenced with the patients' self-reported records to accurately document actual medication intake. For patients who miss doses consecutively, discontinue the medication prematurely, or interrupt and subsequently resume treatment, their actual exposure status will be recorded accordingly.

Study Plan

On the day of enrollment, basic patient information will be collected, including demographic data, smoking and alcohol history, comorbidities, and current medications, respiratory rate, blood pressure, and heart rate. The baseline visit is defined as Day 0; the endpoint assessment for the exposure period is scheduled for Day 90; and follow-up assessments are scheduled for Days 120, 180, and 270. To enhance practical feasibility, a 7-day window (±7 days) is permitted for each visit. At baseline and on Day 90, the following parameters will be monitored: respiratory rate, heart rate, blood pressure, NYHA functional class, NT-proBNP, Cr, BUN, eGFR, CRP, TMAO, 6MWT, VSAQ, and KCCQ. On Days 120, 180, and 270, the following data will be collected: respiratory rate, heart rate, blood pressure, NYHA functional class, 6MWT, VSAQ, KCCQ, and MARCE. MARCE events will be adjudicated according to pre-specified outcome definitions, utilizing data from electronic medical record systems, discharge summaries, or telephone verification whenever possible. If a subject fails to complete a scheduled on-site visit, the research team will prioritize telephone follow-up to obtain supplementary information regarding clinical outcomes and safety; subjects for whom critical information remains unobtainable will be classified as lost to follow-up.

Assessment of Efficacy

Primary Outcomes

As the primary outcome measure in this trial, the 6MWT effectively assesses patients' exercise tolerance and cardiopulmonary functional status during routine physical activity; it closely simulates the conditions of patients' daily lives, evaluates their overall functional capacity, and serves as an independent predictor of mortality in patients with chronic kidney disease.

Secondary Outcomes

NYHA functional classification, NT-proBNP, Cr, BUN, eGFR, CRP, TMAO, MARCE, VSAQ, and KCCQ.

Given that MARCE is not a fully standardized outcome—and definitions vary somewhat across different studies—it was prospectively defined within the context of this study. As referred to herein, MARCE primarily encompasses kidney-related death; a sustained decline in eGFR of ≥50% (confirmed by a second measurement taken at least 28 days later); end-stage renal disease events (defined as requiring maintenance dialysis for at least 28 days, undergoing a kidney transplant, or having an eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement taken at least 28 days later); cardiac death; non-fatal myocardial infarction; non-fatal stroke (specifically ischemic stroke); re-hospitalization or receipt of intensified anti-heart failure treatment in an emergency or outpatient setting due to worsening heart failure; and repeat coronary revascularization.[25–27] The composition and structure of the evaluation endpoints adopted in this study protocol are illustrated in Figure 2.

Safety Assessment

Throughout the trial, patients' vital signs and adverse events were continuously monitored and recorded. Adverse events were defined as any untoward medical occurrences, whether newly emerging during treatment or representing an aggravation of pre-existing symptoms, regardless of whether a definitive causal relationship with the study drug could be established. For each adverse event, the following details were recorded: the name of the event, time of onset, duration, severity, management measures taken, outcome, and the investigator's assessment of its relationship to QSYQ. In the event of a serious adverse event, prompt notification was provided to the Ethics Committee, and the event was handled in accordance with relevant regulations.

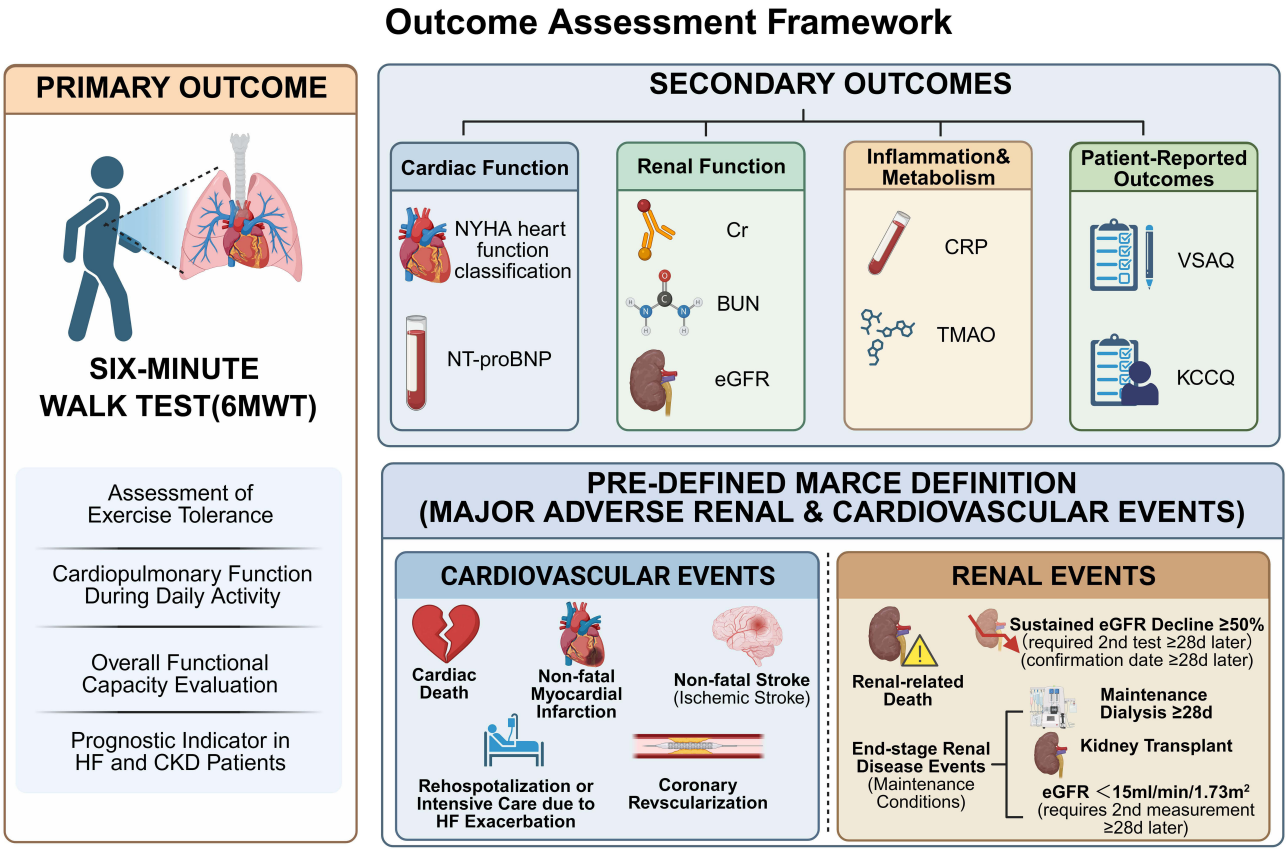

Figure 2 Outcome assessment framework and predefined composite endpoint structure. This figure presents the multidimensional outcome assessment framework of the study. The primary outcome is the 6MWT, selected to evaluate exercise tolerance, cardiopulmonary functional performance during daily activity, and overall functional capacity in patients with chronic CRS. Secondary outcomes include four major domains: cardiac function (NYHA functional classification and NT-proBNP), renal function (Cr, BUN, and eGFR), inflammation and metabolism (CRP and TMAO), and patient-reported outcomes (VSAQ and KCCQ). The lower panel shows the predefined MARCE composite endpoint, which comprises cardiovascular events (cardiac death, non-fatal myocardial infarction, non-fatal ischemic stroke, worsening heart failure requiring rehospitalization or intensified care, and repeat coronary revascularization) and renal events (renal-related death, sustained eGFR decline ≥50%, end-stage renal disease events, maintenance dialysis, kidney transplantation, and eGFR <15 mL/min/1.73 m^2 confirmed by repeat assessment). This figure illustrates the logic of the study's integrated evaluation system spanning functional status, organ-specific biomarkers, patient-reported outcomes, and longer-term clinical events. Created with BioRender.com.

Sample Size

$$n_2 = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (sd_1^2 + sd_2^2)(1 + 1/k)}{2(mean_1 - mean_2)^2},\ n_1 = k \times n_2$$

The sample size estimation for this study is based on the primary outcome measure: the 6MWT. Low-incidence events—such as MARCE—and certain multivariate analyses were primarily exploratory and were not used to determine the sample size. According to the *Chinese Expert Consensus on the Clinical Application of the 6-Minute Walk Test*, the minimum clinically important difference (MCID) for the 6MWT, when used to assess disease progression, exercise rehabilitation, or other therapeutic interventions is 30 m,[28] Furthermore, Daynes et al confirmed through data analysis that the pooled MCID for adults with chronic diseases is 26 meters, consistent with the 30-meter threshold. Consequently, this study designates an inter-group difference of 30 meters as the target difference possessing clinical significance.[29] Prior clinical studies involving TCM have indicated that TCM interventions can improve patients' 6MWT performance, with the overall therapeutic efficacy in the treatment group often surpassing that of the control group. Based on these precedents, the mean and standard deviation of the 6MWT following treatment were estimated at 416.52 ± 102.74 for the treatment group and 368.08 ± 67.95 for the control group. With a sample size ratio of 1:1 between the treatment and control groups, and setting the Type I error (α) for hypothesis testing at 0.05 and the Type II error (β) at 0.2 (where, $z_{1-\alpha/2} = 1.96$, $z_{1-\beta} = 0.84$), the calculated sample size required is 51 subjects for the treatment group and 51 subjects for the control group. Incorporating the results of preliminary clinical surveys

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conducted for this study, which indicated an anticipated loss-to-follow-up rate of 15%, a minimum sample size of 60 subjects is required for the treatment group and 60 subjects for the control group. Accordingly, this study is planned to enroll 120 subjects.[30]

Criteria for Determining Loss to Follow-up: A study subject is deemed "lost to follow-up" if both their official household registration and actual residence have been relocated outside the study area, and their whereabouts remain unknown despite multiple attempts at contact; alternatively, a subject is classified as lost to follow-up if, despite multiple search attempts yielding a confirmed location, it remains impossible to conduct long-term follow-up to obtain information regarding endpoint events.

Definition of Analysis Sets

The primary efficacy analysis set is defined as subjects who have completed the baseline assessment and possess data for at least one follow-up visit regarding the primary outcome. The safety analysis set is defined as all subjects who have received at least one dose of study-related treatment or have completed at least one safety assessment. To evaluate the robustness of the study results, a sensitivity analysis may be further conducted on subjects with good compliance and no major protocol deviations.

Statistical Analysis

Statistical analyses will be performed using SPSS 29.0 and R 4.4.2 software. Continuous variables will be tested for normality and described using the mean ± standard deviation or median (interquartile range); categorical variables will be described using counts and percentages. Comparisons of baseline characteristics will be conducted using independent-samples *t*-tests, Wilcoxon rank-sum tests, χ^2-tests, or Fisher's exact tests. The primary outcome will be analyzed using Analysis of Covariance (ANCOVA), with the 6MWT result at Day 90 as the dependent variable and the treatment group as the independent variable, adjusted for baseline data and other key confounding factors; the adjusted group difference and its 95% confidence interval will be reported. Ordinal categorical variables, such as the NYHA functional classification, will be analyzed using ordinal logistic regression, reporting the odds ratio and its 95% confidence interval. Continuous secondary outcomes, including NT-proBNP, Cr, BUN, eGFR, CRP, and TMAO will be analyzed using multivariate linear regression models with covariate adjustment; variables with skewed distributions will undergo logarithmic transformation as appropriate, and regression coefficients or group differences, along with their 95% confidence intervals, will be reported. For time-to-first-event outcomes during the follow-up period (eg, MARCE), group comparisons will be performed using the Log rank test, followed by the construction of a Cox proportional hazards regression model to report the hazard ratio and its 95% confidence interval, thereby assessing the association between QSYQ exposure and the risk of event occurrence. Given that this is a observational study, propensity score-based covariate adjustment methods will be employed to control for baseline confounding, and standardized differences will be used to evaluate baseline balance between groups; propensity score matching or weighting analyses will be conducted as sensitivity analyses. Missing data will be handled using multiple imputation under the assumption of data missing at random (MAR), followed by sensitivity analyses. All statistical tests will be two-sided, and a P-value < 0.05 will be considered statistically significant. The analysis of secondary outcomes is primarily exploratory, and the results are interpreted in conjunction with effect sizes and 95% confidence intervals.

Ethics

This study must adhere to the Declaration of Helsinki (1996 version) and relevant Chinese regulations regarding clinical trials. The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine on October 30, 2024 (Approval No.: TYLL2024[K]067). Patients must sign an informed consent form prior to enrollment. Both the protocol and the informed consent form meet ethical and scientific requirements and have been registered on the International Traditional Medicine Clinical Trial Registry Platform (Registration No.: ITMCTR2025000145; November 13, 2024).

Discussion

Research Background and Clinical Significance

Chronic CRS is a clinical syndrome characterized by the long-term mutual influence and progressive deterioration of both the heart and the kidneys.[31] It is distinguished by its clinical complexity, poor prognosis, and significant management challenges.[32,33] Although international understanding of CRS has deepened in recent years, with corresponding updates to classification systems, diagnostic criteria, and management strategies, prospective clinical studies within China, particularly those focused on Chinese patient populations, remain relatively scarce. Notably, there is a distinct lack of high-quality clinical evidence regarding the efficacy of TCM interventions for chronic CRS. Consequently, this study aims to systematically evaluate the clinical potential of QSYQ in patients with chronic CRS within a real-world, multicenter, prospective cohort study. The objective is to provide an evidence base for integrating TCM into the comprehensive management of cardiorenal comorbidities.

Strengths and Novelty of This Study

Compared with previous studies, the novelty of the present study primarily lies in three dimensions: the study population, the outcome framework, and the research setting. First, previously published prospective studies on QSYQ have predominantly focused on populations with coronary heart disease complicated by chronic heart failure or ischemic heart failure, rather than specifically targeting patients with chronic CRS, a prototypical population characterized by concurrent cardiac and renal comorbidities. This study expands the scope of evaluation to include patients with chronic CRS; this approach more closely mirrors the common clinical scenario of heart failure complicated by renal impairment and aligns better with current research trends regarding the holistic management of cardiorenal comorbidities. Second, this study features a highly comprehensive outcome framework. While previous studies of this nature often relied on a single cardiac function parameter or a general laboratory marker as their primary endpoint, the present study, in addition to its primary outcome, incorporates patient-reported outcomes, cardiorenal-specific laboratory markers, and long-term adverse clinical events. This approach allows for a multidimensional assessment of the intervention's effects, spanning exercise tolerance, quality of life, organ function, and clinical event outcomes. Such a multidimensional evaluation framework facilitates a more comprehensive reflection of the actual benefits experienced by patients with chronic CRS and aligns with the current trend in clinical research toward prioritizing patient-centered outcomes and composite endpoints.[34] Third, this study employs a prospective, multicenter, observational cohort design; this methodology allows the study to remain closely aligned with clinical practice while more accurately reflecting the actual treatment context for patients with complex comorbidities. In contrast to randomized controlled trials (RCTs), which typically involve stringent patient selection criteria, this prospective, real-world design is better suited to evaluating the practical utility of QSYQ in routine clinical management. Furthermore, by incorporating pre-specified exposure documentation, adherence monitoring, and statistical control for confounding factors, this study strives to maximize the reliability of its findings. Consequently, the value of this study lies not in serving as a substitute for RCTs but rather in providing prospective evidence, highly relevant to real-world clinical decision-making regarding the use of QSYQ in patients with chronic CRS, thereby laying a foundation for subsequent studies of higher methodological rigor.

Outcome Measures and Follow-Up Design

This study established a 90-day exposure period, a decision primarily guided by the natural history of chronic CRS and the characteristic patterns of change observed in key outcome measures. In patients with chronic CRS receiving stable background therapy, improvements in symptoms, quality of life, exercise tolerance, and certain biomarkers typically require several weeks to months to become consistently evident. In accordance with relevant clinical guidelines which suggest that many medications used to treat heart failure and chronic kidney disease often require 2 to 3 months of continuous administration to gradually elicit biological effects and achieve statistically significant clinical benefits.[35,36,] This study designated the duration of exposure as 90 days. Furthermore, this study was not limited to assessing short-term changes occurring during the treatment phase; it also sought to determine whether the benefits persisted following treatment discontinuation and to monitor the cumulative incidence of major adverse clinical events. Consequently,

following the conclusion of the 90-day exposure period, follow-up assessments were conducted at days 120, 180, and 270 to capture, respectively, short-term carryover effects, medium-term maintenance of benefits, and longer-term clinical outcomes. Prior studies have established that a timeframe of 12 to 16 weeks is a standard window for evaluating endpoints such as the KCCQ and 6MWT, while longer-term follow-up is more appropriate for assessing clinical outcomes and the sustained efficacy of treatment.[37,38]

The 6MWT serves as the primary outcome measure in this study, utilized to assess patients' exercise tolerance and overall functional capacity. The clinical burden of chronic CRS is directly reflected in limitations on physical activity and functional decline; consequently, selecting the 6MWT facilitates a direct and intuitive reflection of changes in patients' functional status. Previous studies,[39–41] have substantiated the significant clinical utility of the 6MWT in populations with chronic heart failure; it not only serves as a commonly employed functional outcome measure in interventional studies but is also associated with adverse prognoses, such as mortality and rehospitalization. Furthermore, in patients with end-stage renal disease and those undergoing hemodialysis, the 6MWT similarly provides an effective reflection of functional status and holds predictive value regarding prognosis.[42,43] Given that chronic CRS is characterized by dual features of impaired cardiac function and renal dysfunction, the 6MWT can comprehensively reflect changes in the overall functional capacity of this patient cohort and is therefore well-suited to serve as the primary outcome measure for the present study.

In addition to the primary outcome measures, we selected MARCE, VSAQ, KCCQ, and laboratory markers of cardiac and renal function as secondary outcome measures to evaluate the clinical efficacy of QSYQ. Regarding patient-reported outcomes, this study utilized VSAQ and KCCQ as supplementary assessment tools. The VSAQ is primarily used to assess patients' self-perceived physical activity capacity and exercise tolerance levels;[44,45] thereby complementing the objective exercise metric—the 6MWT from the perspective of subjective functional status.[46] When combined with the 6MWT, these two instruments facilitate a comprehensive assessment of the clinical benefits of QSYQ across two distinct dimensions: objective physical activity capacity and subjective health status. Furthermore, the NYHA functional classification, NT-proBNP, Cr, BUN, eGFR, and relevant inflammatory and metabolic markers objectively reflect the patient's overall disease state—encompassing symptom severity, cardiac and renal functional status, and systemic inflammatory burden—thereby providing a multidimensional basis for evaluating treatment efficacy and predicting prognosis.[47,48] By selecting the aforementioned indicators, this study establishes an interconnected evaluation framework spanning "functional status—patient perception—organ-specific markers—long-term clinical events." Such a design helps avoid the pitfalls of relying solely on single-organ markers to determine treatment efficacy, aligning more closely with the inherent characteristics of chronic CRS as a complex cardiorenal comorbidity syndrome.

Study Limitations

This study is subject to certain limitations. First, this is a observational cohort study; although methods such as propensity score matching will be employed to control for confounding, it remains difficult to completely eliminate selection bias and residual confounding. Second, the overall sample size is limited; while it is well-suited for primarily evaluating changes in functional status, symptoms, and biomarkers, it may lack sufficient statistical power to assess low-incidence "hard" endpoints. Third, this study does not use a blinded design; patients' awareness of their treatment status may influence outcomes measured with subjective scales. Finally, although the follow-up period spans 270 days, for a chronic, protracted condition such as chronic CRS, this still constitutes a medium-term observation period; future studies involving larger sample sizes, randomized controlled designs, and longer follow-up durations are required to further validate the findings of this study. Furthermore, this study is best interpreted as a prospective validation and an observational study of trends; the results should be interpreted with caution, given the specific characteristics of the study design.

Conclusion

In summary, building upon previous studies investigating the use of QSYQ for heart failure, this study extends its focus to the high-risk population of patients with Chronic CRS. Operating within a real-world, multicenter, and prospective

framework, it establishes a comprehensive evaluation system encompassing exercise tolerance, quality of life, cardiorenal laboratory markers, and long-term adverse events. This study is expected to contribute prospective clinical evidence regarding the utility of QSYQ in the management of Chronic CRS and to provide a foundation for subsequent randomized controlled trials as well as the integration of Traditional Chinese Medicine into comprehensive intervention strategies for cardiorenal comorbidities. Future research involving larger sample sizes, more rigorous designs, and longer follow-up periods will be necessary to further validate the efficacy and safety of this intervention.

Trial Registration and Status

International Traditional Medicine Clinical Trials Registry Platform, ITMCTR2025000145. Registered November 13, 2024, http://itmctr.ccebtcm.org.cn/zh-CN/UserPlatform/ProjectView?pid=a816056d-4aee-4707-ad95-0cbc66940b96

Patient enrollment begins in March 2025 Pre-enrollment preparations are currently underway.

Abbreviations

6MWT, 6-Minute Walk Test; ANCOVA, analysis of covariance; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; Cr, serum creatinine; CRP, C-reactive protein; CRS, cardiorenal syndrome; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; KDIGO, Kidney Disease: Improving Global Outcomes; MAR, missing at random; MARCE, major adverse renal and cardiovascular events; MCID, minimum clinically important difference; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QSYQ, Qishen Yiqi Dropping Pills; SPSS, Statistical Package for the Social Sciences; TCM, Traditional Chinese Medicine; TMAO, trimethylamine N-oxide; UAER, urinary albumin excretion rate; UACR, urinary albumin-to-creatinine ratio; VSAQ, Veterans Specific Activity Questionnaire.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics Approval and Consent to Participate

The study protocol was independently reviewed by experts from the Oriental Huaxia Institute of Cardiovascular Health, Suzhou Industrial Park, Suzhou, China. On October 30, 2024, the Medical Ethics Committee of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine approved the study protocol (TYLL2024[K]067). The protocol and its informed consent complied with ethical and scientific requirements and were registered with the International Traditional Medicine Clinical Trials Registry Platform (registration number: ITMCTR2025000145). All patients were required to provide written informed consent before enrollment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

None of the authors have any competing interests to declare.

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