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Efficacy, safety and response predictors of adjuvant astragalus for diabetic kidney disease (READY): study protocol of an add-on, assessor-blind, parallel, pragmatic randomised controlled trial

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ABSTRACT

Introduction Diabetic kidney disease (DKD) is a prevalent and costly complication of diabetes with limited therapeutic options, being the leading cause of end-stage kidney disease in most developed regions. Recent big data studies showed that add-on Chinese medicine (CM) led to a reduced risk of end-stage kidney disease and mortality among patients with chronic kidney disease (CKD) and diabetes. Astragalus, commonly known as huang-qi, is the most prescribed CM or used dietary herb in China for diabetes and DKD. *In vivo* and *in vitro* studies showed that astragalus ameliorated podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis. Nevertheless, the clinical effect of astragalus remains uncharacterised. This pragmatic clinical trial aims to evaluate the effectiveness of add-on astragalus in patients with type 2 diabetes, stage 2–3 CKD and macroalbuminuria, and to identify related response predictors.

Methods and analysis This is an add-on, assessor-blind, parallel, pragmatic randomised controlled clinical trial. 118 patients diagnosed with DKD will be recruited and randomised 1:1 to receive 48 weeks of add-on astragalus or standard medical care. Primary endpoints are the changes in estimated glomerular filtration rate and urine albumin-to-creatinine ratio between baseline and treatment endpoint. Secondary endpoints include adverse events, fasting blood glucose, glycated haemoglobin, lipids and other biomarkers. Adverse events are monitored through self-complete questionnaire and clinical visits. Outcomes will be analysed by regression models. Subgroup and sensitivity analyses will be conducted for different epidemiological subgroups and statistical analyses. Enrolment started in July 2018.

Ethics and dissemination This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West/East/Kowloon Central clusters (UW 16-553/HKEC-2019-026/REC (KC/KE)-19-0049/ER-4). We will report the findings in medical journals and conferences. The dataset will be available on reasonable request.

Strengths and limitations of this study

- ► Existing epidemiological data suggested that Chinese medicine (CM) was associated with retarded progression of renal function among diabetic kidney disease (DKD) patients. It is timely to perform a clinical trial on astragalus, the most used herbs in diabetes and DKD with unclear clinical effectiveness.
- ► The inclusion/exclusion criteria, primary outcome measurement and the corresponding analyses are designed according to conventionally used parameters to facilitate further meta-analysis with other clinical studies for a wide range of audience.
- ► A responder analysis is built into the trial as the secondary analysis to identify possible factors (including biomarkers and symptom-based diagnosis) that could lead to more personalised the use of astragalus.
- ► We conducted a focus group interview series to explore the expectations of patients and clinicians (both conventional and CM) to refine the study design (drug form, dosage, administration route, frequency, health services delivery and outcome measurement) for better clinical translation.
- ► As the trial is open-label, subjective outcomes including quality of life could not be assessed.

Trial registration number NCT03535935

INTRODUCTION

In 2019, it was estimated that 463 million (9.3%) people were living with diabetes worldwide and the figure was projected to reach 578 million by 2030, with the highest prevalence in North America at present.[1] In 2017, the healthcare expenditure on diabetes reached US$850 billion globally (11.6% of global health expenditure).[2 3] Diabetic

kidney disease (DKD) refers to the chronic kidney disease (CKD) caused by long-standing diabetes. DKD presents in more than one third of all diabetic patients and is the leading cause of end-stage kidney disease in many developed regions which requires replacement therapy in the form of dialysis and transplantation.[4 5] In Hong Kong, the incidence of diabetes-related end-stage kidney disease increased from 26.2% in 1996 to 49.6% in 2013[6] and end-stage kidney disease increased 5.23 times the annual direct medical cost to the local public health system.[7] Furthermore, DKD was accounted for 23.4% (31.1% vs 7.7%) absolute increase in 10-year mortality in the USA[8] and 16 years shorter life expectancy in Taiwan[9] when compared with those without diabetes and kidney diseases.

The risk factors and pathogenesis of DKD are heterogeneous[5] involving metabolic,[10 11] inflammatory,[12–14] haemodynamic[15–18] and many other pathways.[5 19] Thickening of glomerular basement membrane, mesangial expansion, effacement of foot process, formation of Kimmelstiel-Wilson nodules, glomerulosclerosis and interstitial fibrosis are the classical histopathological features of diabetic nephropatchy .[15 20] Conventional blockade on the renin–angiotensin–aldosterone system (RAAS) offers limited effect on clinical outcomes.[21–24] In a previous meta-analysis of 9797 patients with stage 3–5 CKD, RAAS blockade did not reduce all-cause mortality and only provided a mild risk reduction in the composite endpoint of replacement therapy initiation or doubling of serum creatinine when compared with placebo or other antihypertensive agents.[22] RAAS blockade with combined ACE inhibitor (ACEI) and angiotensin II receptor blocker (ARB) resulted in increased adverse events but not the expected synergistic effect.[23 25] More therapies with different working mechanisms are needed.

Chinese medicine (CM) has been extensively used among patients with diabetes and DKD in Asia.[26 27] Previous observational studies from Taiwan with 47 876 and 24 971 subjects showed that the use of add-on prescribed CM is associated with 40% reduction of mortality[27] and 59% risk reduction of end-stage kidney disease, respectively.[26] *Astragalus membranaceus*, commonly known as huang-qi, is the most frequently used CM or dietary herb for DKD.[28] Systematic reviews showed that astragalus could enhance creatinine clearance, reduce albuminuria and reduce blood pressure among patients with CKD and DKD.[29–31] Meta-analysis also showed that astragalus' effect in improving renal clearance and reducing albuminuria was better than routine care (without ACEI or ARB) and the efficacy was comparable to ACEI or ARB.[31] *In vivo* and *in vitro* evidence suggested that astragaloside IV, an active ingredient of astragalus, could ameliorate podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis through regulating the nuclear factor kappa B (NF-κB) and transforming growth factor beta 1 (TGF-β_1) signalling pathways, which partly explained the renoprotective effect.[32 33] Nevertheless, the methodological reporting and quality of the existing clinical trials were inadequate and further evaluation is needed. Based on our preliminary result of ongoing trials, CM formulations containing astragalus are likely to retard the progression of DKD.[34 35] Considering the extensive current use of astragalus, clinical study could be considered before preclinical investigation as suggested by the WHO.[36]

METHODS/DESIGN

Objective

This pragmatic clinical trial aims to evaluate the effectiveness of add-on astragalus on patients with type 2 diabetes with stage 2–3 chronic kidney disease and macroalbuminuria and to identify related response predictors for subsequent large-scale health services research.

Study design

Add-on, assessor-blind, parallel, pragmatic randomised controlled trial. The WHO Trial Registration Data Set (online supplemental appendix 1) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (online supplemental SPIRIT checklist) are enclosed.

Inclusion and exclusion criteria

Patients with (1) type 2 diabetes for at least 5 years; (2) estimated glomerular filtration rate (GFR) ≥30 and < 90 mL/min/1.73 m^2 confirmed by repeated testing over 3 months calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) study equation[37 38]; (3) persistent macroalbuminuria with spot urine albumin-to-creatinine ratio (UACR) ≥300 mg/g confirmed by at least two consecutive first morning void urine samples; (4) age between 35 and 80 years old; (5) stable dose of antidiabetic agent(s) including insulin for at least 12 weeks and (6) stable dose of ACEI or ARB for at least 12 weeks will be recruited.

Patients will be excluded if with (1) UACR ≥5000 mg/g; (2) a known history of glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus or any suggestive evidence of non-diabetic glomerulopathy; (3) known history of kidney transplant; (4) concurrent severe disorders of heart, brain, liver and hematopoietic system, tumour, mental disorder; (5) deranged liver function; (6) poorly controlled blood pressure; (7) known history of intolerance or malabsorption of oral medications; (8) uncontrollable urinary infection; (9) experiencing pregnancy and (10) participating in other clinical trial(s) within 30 days.

Sample size calculation

Since the primary objective of this trial is to evaluate key clinical outcomes and to perform a preliminary analysis on potential response predictors, we calculated the sample size based on the control of inflation factor (IF) to the estimation of sample size for the subsequent large-scale studies.[39 40] One hundred and eighteen patients (around 60 per group) are needed.

$$IF = S_{ucl}/S_{obs} = \mathrm{sqrt}[(n-1)/x^2_{1-\alpha,\,n-1}]$$

$$N_{adj}/N_{unadj} \approx IF^2 \approx n_{unadj} \times IF^2$$

$$N \approx [2(Z_{1-\alpha/2} + Z_{1-\beta})^2 (IF * s)^2]/(\mu_1 - \mu_2)^2]$$

$$= [2(Z_{1-\alpha/2} + Z_{1-\beta}) s^2]/(\mu_1 - \mu_2)^2]$$

$$Z_{1-\beta} = Z_{1-\alpha/2}(IF^{-1} - 1) + Z_{1-\beta} * IF^{-1}$$

where

IF=Inflation factor.

S_{ucl}=SD of upper CI.

S_{obs}=Observed SD in pilot study.

α=Chosen confidence level.

ß=Nominal power set for main study.

ß′=Actual power achieved for main study by using pilot SD for sample size calculation.

n=Sample size of pilot study.

N=Sample size of main study.

N_{unadj}=Sample size of main study with no adjustment on SD.

N_{adj}=Sample size of main study with adjustment on SD.

The SD used for sample size calculation for large-scale main studies is often underestimated by small-scale pilot studies; therefore, an IF is needed for adjustment in sample size calculation.[39 40] IF is calculated based on the size of pilot study and the confidence level of achieving at least the desired power in subsequent main studies. Therefore, the actual achieved power of the main studies depends on the nominal power set for the main study and the IF.

In order to be 95% confident (two-sided) that the main study achieves a power of 70% with nominal power set at 80% (ie, a 10% power forfeit), the IF should be controlled to less than 1.13. At IF=1.13, a sample size of 100 is therefore needed to attain 95% one-sided confidence that the main studies will achieve the nominal power to test the hypothesis of add-on astragalus could be more effective in stabilising the GFR among patients with DKD when compared with standard care. To allow a 15% attrition rate, a sample size of 118 patients is therefore needed for this pilot study.

Currently, there is limited evidence on the symptom-based response predictors of astragalus. A general recommendation for power estimation is to have 10 events per variable.[41] From the previous systematic review, we estimate that around 60% of patients will have stabilised GFR after receiving astragalus.[31] One hundred and eighteen subjects with 15% attrition will power up to six variables for the screening of predictors. A univariable screening on the 11 prespecified potential symptom-based predictors will be conducted to reduce the number of predictors for the subsequent multivariable regression analysis, in order to maximise the power of the regression analysis.

Recruitment and randomisation

Patients will be recruited from general and specialist outpatient clinics of Queen Mary Hospital, Queen Elizabeth Hospital, Hospital Authority Hong Kong East Cluster through consultations and the community via public health campaigns. The details of study will be explained by principal investigators (PIs) or co-investigators (Co-Is) before written consent is obtained from each participating patient. All patients will undergo a 2-week run-in period, during which the dosage of their medications will be stabilised. Blood and urine samples will be sent to an independent local laboratory for screening. Patients are considered eligible for the study if their liver functions are normal and fulfil the inclusion criteria. Recruitment started in July 2018 and the recruitment is ongoing.

A random sequence was generated and encrypted with computer by an independent staff of the University of Hong Kong and kept in sealed opaque envelopes. The password of the sequence is kept in a sealed, duly signed opaque envelop locked by research assistants (RAs). The allocation sequence is concealed from PIs, Co-Is, CM physicians and all research staffs that are responsible for patient screening, randomisation or sample analysis. Eligible patients will be randomised 1:1 to either receive active intervention along with standard care or standard care alone. The allocation is masked from the outcome assessor (technicians from an independent laboratory). The study subjects could not be masked due to the nature of treatment. Since the primary clinical outcomes under investigation are objectively assessed and the outcome assessor is blinded, placebo effect and outcome measurement bias should be minimised. The flow of study is presented in figure 1. Under no circumstances the primary outcome assessors will be unblinded.

Intervention and control

The intervention under investigation is astragalus. Patients under intervention will receive astragalus daily on top of standard medical care for 48 weeks. The CM physicians will advise on the dose and possible adverse

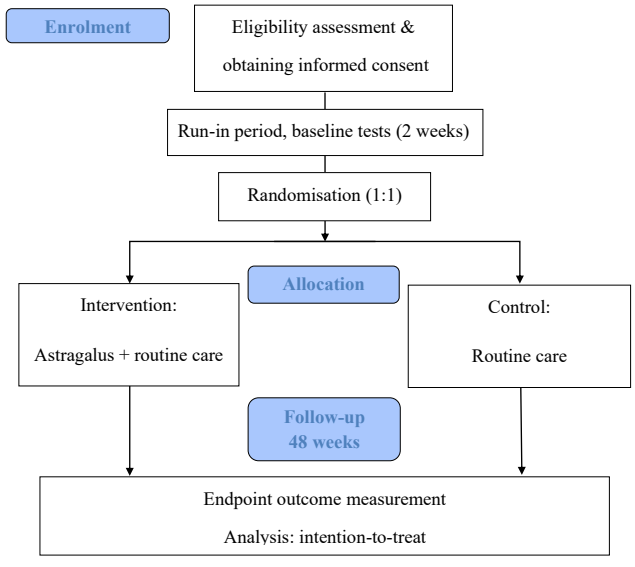

Figure 1 The flow of research.

events of astragalus based on his/her professional knowledge. Existing literature supports a safe dosage of raw astragalus from 15 g/day to 50 g/day.[42 43] According to the China Pharmacopeia, the recommended therapeutic dosage of astragalus is below 30 g/day. To ensure the safety of patients, CM physicians are reminded not to propose dosage exceeding 30 g/day. All patients will continue their standard medication and follow-up with the same consultation schedule with CM physicians. Standard care is used as control to best reflect the real-world practice and the future application scenario of this trial.[44]

Herbal safety

Soluble herbal granules prepared by PuraPharm (listed in US Pharmacopeia as dietary ingredient: VER-DI-PUR-09) are used. The production process is in strict compliance with standards of Good Manufacturing Practice. Fully registered CM physicians from the School of Chinese Medicine, The University of Hong Kong, will be responsible for the clinical diagnosis and prescription. After 4–6 weeks of randomisation, all patients will undergo liver function tests and renal function tests to monitor acute changes of renal and liver function.

Outcome measurement

The primary outcome measures are the changes of estimated GFR[45] and UACR from baseline (week 0) to treatment endpoint (week 48). As the progression of kidney disease is slow, we believe reporting 1-year (48-week) change in GFR is necessary to avoid extrapolation while extended observation may lead to substantial attrition and is limited by resources. Secondary outcome measures include adverse events and changes in CKD stage, haemoglobin A_{1c} (HbA_{1c}), lipids, urinary monocyte chemotactic protein 1 (MCP-1) and urinary cystatin C from baseline to the midpoint (week 24) and the end of treatment.

Data collection

Patient demographics including age, gender, body mass index (BMI), duration of diabetes, other medical history and concurrent medications will be retrieved by the electronic clinical management system of hospital authority by Co-Is and RAs. Estimated GFR, UACR, HbA_{1c}, lipids and liver function tests will be assessed by an independent laboratory (Chan & Hou Medical Laboratories Limited) which is accredited by College of American Pathologists, Royal College of Pathologists Australasia and Quality Control for Molecular Diagnostics, UK. MCP-1 and cystatin C will be assessed at lead PI's research laboratory by an independent RA with commercially available kits. Blood pressure will be taken during consultation. Blood and urine samples will be taken at an overnight (>8 hours) fasting state.

Estimated GFR will be calculated using the MDRD equation with serum creatinine, age, ethnicity and gender. Clinical presentations and CM symptom-based diagnosis will be assessed in a structured consultation developed for this purpose. To ensure consistency and reliability of assessment and to minimise bias from investigators across the study, only three synchronised CM physicians will assess the patients.

A self-complete questionnaire will be distributed to the subjects to monitor adverse events, and they are advised to inform the PIs, Co-Is, CM physicians or RAs immediately if adverse events arise. All adverse events will be coded based on Common Terminology Criteria for Adverse Events (CTCAE) 5.0, following the recommendation of Consolidated Standards of Reporting Trials extension for Chinese herbal medicine formulas.[46]

Follow-up consultations will be held for all patients bi-weekly in the first month and monthly subsequently until the end of treatment for all patients. Minor adjustments are allowed based on clinical needs. Evaluation of outcomes will be performed at baseline, week 24 (treatment midpoint) and week 48 (end of treatment). The follow-up schedule is summarised in table 1.

Data management

A trial management committee (TMC) formed by lead PI, Co-Is and RAs will centralise all trial data. Co-Is and RAs will collect, clean and send the data to TMC weekly. All data will be double entered, secured and cleaned before analysis to prevent data entry errors. TMC will have regular meetings monthly to discuss the progress and double check the data of the trial. Only PI, Co-Is and regulatory bodies will have access to the patient data to protect data privacy. An independent Data and Safety Monitoring Board (DSMB) (VCH Chung, W Wong, JWF Yeung) has been established with expert in methodology, biostatistics and clinical medicine to monitor the progress of the trial, including adverse events and change in protocol. DSMB will have meetings one to two times a year. No competing interests have been reported from DSMB. Trial result will be published in academic journal and trial subjects will be notified.

Handling of withdraw and dropout

In order to maximise subjects' compliance, we will provide a triple thorough consent process for all participants covering details of the study schedule, potential side effects of treatment and the responsibilities of the subjects. An independent e-mail account and a direct telephone line is available for this study to enable active communication with patients. Extra visits will be arranged for patients if necessary. To monitor the adherence of study medication, we will arrange irregular visits for patients and count the unfinished medication.

Termination criteria

The treatment will be terminated for a specific subject if he/she (1) develops serious adverse event (SAE); (2) develops hypersensitivity towards astragalus and (3) participates in other clinical trial. The whole study will be terminated under the following circumstances: (1) presence of clustered SAE(s) related to astragalus with

Table 1 Follow-up schedule

	Study period				
	Enrolment	Allocation	Post allocation—treatment period		
Timepoint	Before treatment	Week 0, Day 1	Week 1–4 (±3 days)	After 4–6 weeks (±7 days)	After 24 and 48 weeks (±7 days)
Enrolment					
Eligibility screen	X				
Informed consent	X				
Medical history	X				
Allocation		X			
Interventions					
Intervention (interventional group)		X	X	X	X
Routine care (all patients)		X	X	X	X
Assessments					
Renal and liver function tests, other biomarkers (blood and urine tests)	X			X	X
Blood pressure, weight, hip–waist circumference		X	X	X	X
Demographics		X			
Clinical presentations		X	X	X	X
Adverse events		X	X	X	X

supportive evidence and (2) completion of all follow-up assessments.

SAE includes adverse events that result in death, require either hospitalisation or the prolongation of hospitalisation, are life-threatening, result in a persistent or significant disability/incapacity, result in a congenital anomaly/birth defect or events classified as grade 3 or above in CTCAE 5.0. Other important medical events, based on appropriate medical judgement, may also be considered SAEs if a patient's health is at risk and intervention is required to prevent an outcome mentioned.

Data analysis

Missing values will be imputed by multiple regression. The analysis will follow intention-to-treat principle that all randomised patients will be included in the analysis. STATA and GraphPad Prism will be used for the analysis.

Demographics will be presented as mean±SD or percentage. UACR will be log-transformed and reported as geometric means. Smoking history will be stratified into non-smoker, ex-smoker and current smoker. Rapid renal progression is predefined as a consecutive annual GFR drop of over 5 mL/min/1.73 m^2 or a cumulative GFR drop of over 25 mL/min/1.73 m^2 for 5 years.[47 48] Differences in mean and proportion between groups will be tested by t-test and χ^2 test.

Mixed regression models will be used to compare the rate of change in estimated GFR and UACR. Analysis of covariance will be used to compare the adjusted mean of outcomes at week 48 between intervention group and control group with the corresponding baseline values as covariates. Data will be presented as the difference in adjusted means between the groups with 95% CI and the corresponding p value.

The adverse events will be recorded according to CTCAE 5.0 and categorised into five grades (grade 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, no intervention indicated; grade 2: moderate, minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living; grade 3: severe or medically significant but not immediately life-threatening, hospitalisation or prolongation of hospitalisation indicated, disabling, limiting self-care activities of daily living; grade 4: life-threatening consequences, urgent intervention indicated and grade 5: death related to adverse events). The percentage of all adverse events with more than one case will be compared between groups. SAE will be analysed case by case descriptively.

To minimise type I error inflation, the analysis will follow a hierarchical approach in the order of (1) comparison of baseline to end of treatment on estimated GFR and UACR; (2) comparison of baseline to end of treatment on other outcome measurements; (3) comparison of baseline to treatment midpoints on estimated GFR and UACR and (4) comparison of baseline to treatment midpoints on other outcome measurements.

For the assessment of predictive factors as secondary analysis, the dependent variable will be the treatment response which is categorised into:

1. Improved or stabilised renal function, defined as estimated GFR after 48-week treatment being higher or equal to baseline.

2. Non-responder, defined as patients having estimated GFR decreased at a rate of less than 5 mL/min/1.73 m^2 after 48-week treatment compared with baseline.
3. Rapid deteriorating renal function, defined as estimated GFR of more than 8 mL/min/1.73 m^2 after 48-week treatment compared with baseline.

Potential prognostic variables (baseline values) will include:

1. Demographics: age, gender, BMI, systolic blood pressure, history and duration of smoking and alcohol consumption.
2. Symptom-based diagnosis: presence of CM-based symptom-based subtype (eg, *spleen and kidney qi deficiency*) based on the presentation of standardised and commonly documented signs and symptoms.[49]
3. Biochemical profile: GFR, UACR, HbA_{1c}, lipids.

All potential predictors will first be included into univariable regression models followed by multivariable stepwise regression analysis. Variables that are not significant at a 5% level will be excluded.

Subgroup analyses will be performed for (1) CKD stages stratified into stages 2, 3a and 3b[50]; (2) UACR levels stratified by 100 mg/mmol[51]; (3) gender and (4) age groups. Sensitivity analyses will be performed for (1) per-protocol cohort; (2) estimation of GFR by c-MDRD[52] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[53] equations; (3) missing data imputed with last-observation-carried-forward and (4) different analytical approaches (change score) and categorisations of primary outcomes.

Patient and public involvement

We conducted a focus group interview series to collate the experience and expectations of patients and clinicians (both conventional medicine and CM) on the study design (drug form, dosage, administration route, frequency, health services delivery and outcome measurement) for this trial.[54] The study results will be disseminated to diabetes patient groups and the participants via public workshops and talks.

ETHICS AND DISSEMINATION

This study was approved and monitored by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West/East/Kowloon Central clusters (Ref: UW 16-553/HKEC-2019-026/REC (KC/KE)-19-0049/ER-4). The patient information sheet and consent form are enclosed in Appendix 2. Result will be disseminated as conference presentations and journal publications on completion.

DISCUSSION

Diabetes and DKD are significant public health burdens, and astragalus is the most used herbs among these patients with unclear clinical effectiveness. There is an urgent need to characterise the effect and the associated response predictors of astragalus to prevent unnecessary consumption and increase the cost-effectiveness of administration. Also, the assessment of response predictors of both biomarkers and symptom-based factors will facilitate the integration and clinical translation of generated evidence between conventional medicine and CM physicians. Based on our preliminary result of ongoing trials, CM formulations containing astragalus are likely to retard the progression of DKD.[34 35] This trial aims to evaluate the effect of astragalus and identify related response predictors for more personalised application and further large-scale health services research.

To facilitate further meta-analysis with other clinical studies for wide range of audience, the inclusion/exclusion criteria, primary outcome measurement and the corresponding analyses are designed according to conventionally used parameters similar to other pharmaceutical studies.[55] A responder analysis is included as secondary analysis to identify possible factors (including biomarkers and symptom-based diagnosis) that could lead to more personalised use of astragalus. Besides, we conducted a focus group interview series to explore the expectations of patients and clinicians (both conventional medicine and CM) to refine the study design for better clinical translation.[54] The major limitation of this trial is the open-label nature. The study subjects could not be masked due to the nature of treatment. Since the clinical outcomes under investigation are objective and the outcome assessor is blinded, placebo effect and outcome measurement bias should be minimised. However, subjective outcomes including quality of life could not be assessed.

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Contributors KWC and SCWT conceived the study. KWC, ASKK, PNT, SCYC, GCWC, MM-YW, KCBT and WFC recruited the patients and provided clinical consultation. WHY provided expert opinion and support in biochemical analysis. LL, Z-JZ and YZ provided expert opinion on the study design. KWC and SCWT drafted the manuscript. All authors involved in the manuscript revision.

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