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Effect of sequential treatment with TCM syndrome differentiation on acute exacerbation of chronic obstructive pulmonary disease and AECOPD risk window☆

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ABSTRACT

Objective: To evaluate the efficacy and safety of the comprehensive interventions based on three Traditional Chinese medicine (TCM) patterns therapy in acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and AECOPD risk window.
Methods: A prospective, multi-center, single-blinded, double-dummy and randomized controlled clinical trial is being conducted to test the therapeutic effects of a sequential two stage treatment. A total of 364 patients were enrolled into this study with 182 in each treatment group (TCM and conventional). Patients received medication (or control) according to their assigned group. TCM treatment according to syndrome differentiation for AECOPD were administered twice daily to patients with AECOPD over 7–21 days, followed by TCM for AECOPD risk window (RW) over 28 days. All patients were followed up for 6 months. Exacerbations were used as the primary outcome measures. Forced expiratory volume in the first second (FEV_1) and the modified medical research council dyspnea (MMRC) scale, quality of life and mortality rate were used as secondary outcome measures.
Results: Of 364 randomized patients, 353 were included in the intention-to-treat analysis and 290 in the per-protocol analysis. In the TCM group, 16 patients (10.4%) reached the primary end point; 24 (17.7%) in the conventional group (RR 0.59, 95% CI 0.33–1.06; p = 0.074). Among patients with a re-exacerbation, the median time to event was 107.5 days (interquartile range [IQR], 39.5–129.0) in the TCM and 50 days (IQR, 31–130.5) in the conventional group (P = 0.011). After exacerbation therapy and a further 180-days follow-up, patients in the TCM group had significant improvements in dyspnea, as measured by MMRC (*P* = 0.003), Patients in the TCM group also had improvements in health-related quality of life (P = 0.002), as measured COPD Assessment Test (CAT). There was no difference between groups in death, and recovery of lung function. There were no differences between the TCM and conventional treatment group in adverse events.
Conclusions: In patients presenting to the respiratory department with acute exacerbations of COPD, TCM treatments with syndrome differentiation will have beneficial effects with regard to re-exacerbation, relieving symptoms, improving quality of life for COPD patients.

☆ This study is registered with the Chinese Clinical Trials Registry, ChiCTR-TRC-11001460.

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1. Introduction

Acute exacerbation of chronic obstructive pulmonary disease (COPD) are a risk factor for disease deterioration,[1] and patients with frequent exacerbations result in poorer quality of life,[2] faster decline in lung function,[3] and increased mortality.[4] Many patients with COPD experienced frequent exacerbations requiring pharmacological treatment.[5] Therefore, the management of exacerbations places a considerable burden on the health services both in terms of physician consultation time and healthcare cost.[6] A reduction in exacerbation frequency would have a number of benefits for patients and health services alike.[7] Therefore, preventing exacerbations is a key treatment goal. The global initiative for chronic obstructive lung diseases (GOLD) document suggests a follow-up at 4–6 weeks after a hospitalized exacerbation.[8] However, there is evidence that exacerbations tend to cluster in time, with a high-risk period of recurrence during weeks following the first exacerbation.[9] This has important implications for the target of preventative interventions. Therefore, we have identified acute exacerbation of chronic obstructive pulmonary disease risk-window (AECOPD RW).[10] It seems give intervene in this period will lead to better outcome.

Traditional Chinese medicine (TCM) is commonly used for COPD in Asia. It has long been known that TCM is effective in relieving symptoms, reducing the incidence of COPD exacerbations and improving quality of life in COPD patients.

Our previous study showed that in an exacerbation period the treatment principle was to eliminate exogenous pathogens. When exacerbation finished and go to AECOPD RW, the treatment principle should be supporting body resistance.[11] Our hypothesis was that a sequential TCM treatment aimed at eliminating pathogens and strengthening vital qi with syndrome differentiation may reduce exacerbation frequency in patients with AECOPD.

2. Methods

2.1. Study design and patients

Details of our study's rationale, design, and analysis plan have been published elsewhere.[10] The trial was approved by the institutional review boards of participating hospitals. All patients provided written informed consent. This study report adheres to the consolidated standards for the reporting of randomized trials.[12] From September 2011 through July 2012, consecutive patients with exacerbated COPD were screened for eligibility at the respiratory departments of 8 China teaching hospitals. Inclusion criteria were exacerbation of COPD as defined by the presence of at least 2 of the following: change in baseline dyspnea, cough, or sputum quantity or purulence,[13,14] age older than 40 years, meet the TCM diagnostic criteria (syndrome of exogenous cold-evil and internalization, syndrome of accumulation of phlegm-dampness in the lung, syndrome of phlegm-heat obstructing in the lung) and give written informed consent to participate. Exclusion criteria were a history of asthma, ratio of FEV_1 to forced vital capacity (FVC) greater than 70% as evaluated by bedside post-bronchodilator spirometry prior to randomization, radiological diagnosis of pneumonia, estimated survival of less than 6 months due to severe comorbidity, pregnancy or lactation, and inability to give written informed consent.

2.2. Study drugs, randomization, and masking

Eligible patients will be randomized to one of the two arms: placebo or Chinese medical herb (11.65 g twice daily). There are 3 TCM formulas for exacerbation will be administered orally for 7–21 days according to syndrome differentiation: sanhanhuayinfang for syndrome of interior phlegm with exopathic cold, qingrehuatanfang syndrome of phlegm heat obstructing lung, zaoshihuatanfang syndrome of phlegm obstructing lung, There are also 3 TCM formula for AECOPD-RW will be administered orally for 4 weeks, they are bufeijianpifang for syndrome of lung and spleen qi weaken, bufeiyishenfang for syndrome of qi deficiency of lung and kidney, yiqizishenfang for syndrome of deficiency of both qi and yin (Table 1). All drugs were made into granules by Jiangyin Tianjiang Pharmaceutical Co., Ltd. In this study, the subjects and statisticians will be blinded to treatment assignment. Randomization of subjects will occur centrally using a random number generator and will be stratified by syndrome differentiation of TCM.

2.3. Procedures

In addition to the study medication, all patients received a broad-spectrum antibiotic for 7 days and an inhaled, nebulized, short-acting bronchodilator 4–6 times daily as needed while hospitalized. Physiotherapy, supplemental oxygen, and ventilatory support were administered according to American Thoracic Society/European Respiratory Society guidelines.[13] Endpoints were assessed daily during hospitalization, 7, 14, 28 days during AECOPD-RW, as well as on follow-up days 30, 90, and 180 (Fig. 1).

2.4. End points

The primary endpoint was exacerbation rate in 6 follow-up months. We defined exacerbation and types according to Anthonisen et al.[14] The exacerbation was assessed from patients' diary card report or documented hospital visits due to respiratory disorders, and confirmed by investigators based on Anthonisen's criteria.[14]

Time to next COPD exacerbation during a follow-up of 6 months was also evaluated, defined as an acute clinical deterioration beyond usual day-to-day variation, requiring interaction with a clinician. This would occur during follow-up.

Secondary end points were all cause mortality, change in FEV_1, and clinical performance (assessed using questionnaires for the Medical Research Council dyspnea scale, and CAT score).[15]

2.5. Statistical analysis

Statistical analyses were done with SAS (SAS Institute, version 9.3) and SPSS (SPSS Corp, version 20). Categorical variables are summarized by absolute numbers and percentages of total. Differences in time to next exacerbation or time to death were assessed using the Kaplan-Meier method in combination with the log-rank test and Cox proportional hazards models. The proportional hazard assumption was tested using Schoenfeld residuals. Patients lost to follow-up were censored at the time of last contact. Differences in categorical variables were assessed with the $\chi 2$ test or Fisher exact test. The time course of clinical parameters (FEV_1, dyspnea scale, quality-of-life score, self-assessed performance) was analyzed using mixed linear models. Time and group were treated as categorical variables. Their interaction was also included in the model and served to test the null hypothesis of parallel time course patterns.

Potential interactions between treatment and other factors, also used to assess heterogeneity of results across subgroups, were tested using likelihood ratio tests for time-to-event outcomes and F tests for quantitative outcomes. Statistical significance was defined at the level of 5%.

Med-Information Management System of Traditional Chinese medicine hospital of Guangdong province (Guangzhou, China) an independent contract research organization took responsibility for

Table 1
The detail of TCM formulae.

	formulas	Traditional Chinese medicine
3 TCM formulas for exacerbation	sanhanhuayinfang	Ephedra, Cassiabarktree Twig, Dried Ginger, White Peony Root, Manchurian Wildginger Herb, Prepared Pinellia Tuber, Chinese Magnoliavine Fruit, Cultivated Purple Perilla Fruit, almond, Officinal Magnolia Bark, Prepared Liauorice Root
	qingrehuatanfang	mongolian snakegourd fruit, Pinellia Tuber, Chekiang Fritillary Bulb, gardenia, White Mulberry Root-bark, Baikal Skullcap Root, almond, Chinese Pulsatilla Root, Heartleaf Houttuynia Herb, Dwarf Lilyturf Root Tuber, Tangerine Peel
	zaoshihuatanfang	Prepared Pinellia Tuber, Officinal Magnolia Bark, Tangerine Peel, Longstamen Onion Bulb, Indian Buead, Ephedra (processed with honey), White Mustard Seed, Cultivated Purple Perilla Fruit, Dry Radix Ginseng, Cassia Bark, Manchurian Wildginger Herb, Fresh Ginger
3 TCM formula for AECOPD-RW	bufeijianpifang	Pilose Asiabell Root, Mongolian Milkvetch Root, Largehead Atractylodes Rhizome, Indian Buead, Chekiang Fritillary Bulb, almond, Earth-worm, Officinal Magnolia Bark, Tatarian Aster Root and Rhizome, Cultivated Purple Perilla Fruit, Short-horned Epimedium Herb, Tangerine Peel, Prepared Liauorice Root
	bufeiyishenfang	Ginseng, Mongolian Milkvetch Root, Barbury Wolfberry Fruit, Common Macrocarpium Fruit, Chinese Magnoliavine Fruit, Short-horned Epimedium Herb, Chekiang Fritillary Bulb, Chinese Eaglewood, Cultivated Purple Perilla Fruit, Red Peony Root, Earth-worm, Tangerine Peel, Prepared Liauorice Root
	yiqizishenfang	Ginseng, Mongolian Milkvetch Root, Prepared Rehmannia Root, Siberian Solomonseal Rhizome, Barbury Wolfberry Fruit, Dwarf Lilyturf Root Tuber, Chinese Magnoliavine Fruit, Cassia Bark, Cultivated Purple Perilla Fruit, Chekiang Fritillary Bulb, Tree Peony Root-bark, Earth-worm, Sessile Stemona Root Tuber, Tangerine Peel, Prepared Liauorice Root

Abbreviations: TCM, Traditional Chinese medicine. AECOPD, acute exacerbations of chronic obstructive pulmonary disease. AECOPD-RW, AECOPD risk window.

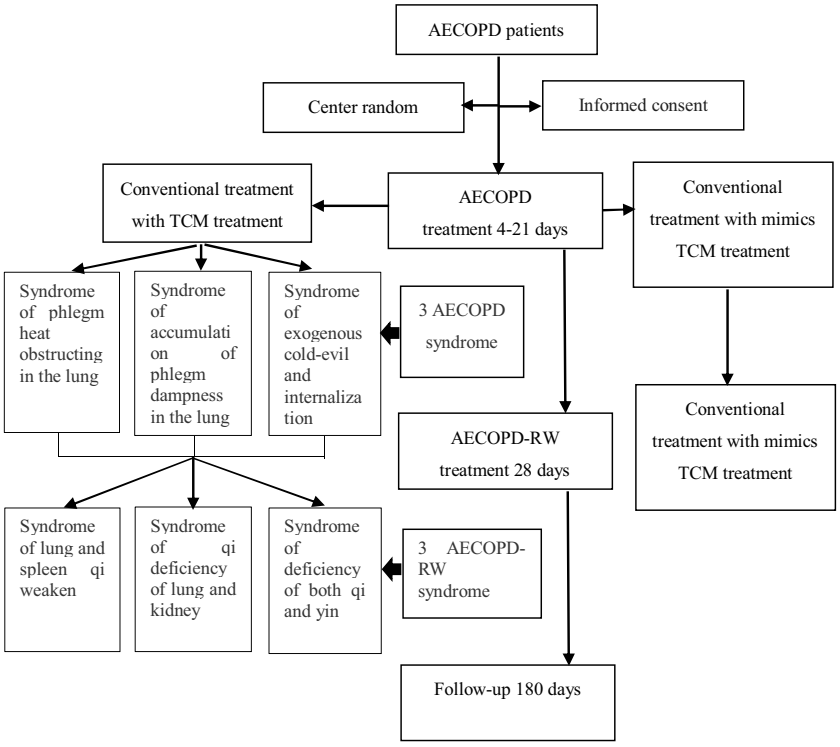

Fig. 1. Procedure of Patients Through the Trial.

data collection, quality assurance, and statistical analysis. SAS (version 9.2) was used for all statistical analyses.

This study is registered with the Chinese Clinical Trials Registry, ChiCTR-TRC-11001460.

3. Results

Baseline characteristics of participants are summarized in Table 2, and results for the primary and secondary end points in Tables 3 and 4.

Table 2
Baseline Characteristics of Study Participants.

	TCM Treatment (n = 173)	Conventional Treatment (n = 180)	p-value
Age, mean (SD), y	68.01 (8.07)	67.87 (8.36)	0.879
Women, No. (%)	47 (27.2)	54 (30)	0.556
Smokers, No. (%)			0.737
Current	70 (40.5)	76 (42.2)	
Past	103 (59.5)	104 (57.8)	
branch-days smoked, median	20.62 (9.32)	22.98 (13.46)	0.142
FEV_1 mean (SD), % predicted	48.0 (17.7)	50(19.8)	0.273
Duration of COPD (month), median	164.54 (101.13)	158.83 (115.45)	0.622
Severity of COPD exacerbation, No. (%)			0.784
moderate	111 (64.2)	62 (35.8)	
severe	118 (65.6)	62 (34.4)	
Medical Research Council dyspnea scale, No. (%)[a]			0.464
0	0	0	
1	3 (1.6)	3(1.6)	
2	38 (20.9)	31 (17.0)	
3	79 (43.4)	81 (44.5)	
4	62 (34.1)	67 (36.8)	
Clinical variables, median (IQR)			
Blood pressure, mm Hg			
Systolic blood pressure	130 (120–134)	130 (122–134)	0.783
Diastolic blood pressure	80 (74–83)	80 (74–84)	0.834
Heart rate, beats/min	84 (80–95)	84 (80–92)	0.254
Respiratory rate, times/min	21 (20–24)	20 (20–24)	0.597

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range.

[a] Grading for severity of breathlessness according to the Medical Research Council questionnaire: 1, breathless only with strenuous exercise; 2, short of breath when hurrying on the level or up a slight hill; 3, walking slower than people of the same age on the level because of breathlessness, or stop for breath when walking at own pace on the level; 4, stop for breath after walking 100 yards or after a few minutes on the level; 5, too breathless to leave the house.

Table 3
Results for the Primary End Point.

Primary outcome Re-exacerbations	TCM Treatment (n = 154)	Conventional Treatment (n = 136)	Hazard Ratio (95% CI)	*P* Value
Intention to treat	16 (9.24%)	24 (13.3%)	0.69 (0.38–1.26)	0.226
Per protocol	16 (10.4%)	24 (17.7%)	0.59 (0.33–1.06)	0.074

Abbreviation: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 4
Results for Secondary End Points.

Secondary End Point	TCM Treatment (n = 173)	Conventional Treatment (n = 180)	Comparison Measure (95% CI)	*P* Value
Deaths during follow-up	2 (1.16)	7 (3.89)	OR, 0.29 (0.06, 1.41)	0.175[a]
Need for mechanical ventilation	3 (1.73)	7 (3.89)	OR, 0.43 (0.11, 1.70)	0.337[a]
Duration of hospital stay, median (IQR), d j	8 (6–12)	10 (7–12)	HR, 0.82 (0.32–2.14)	0.8[a]
Mean, d	9.01 (3.82)	9.93 (4.10)		

Abbreviations: HR, hazard ratio; IQR, interquartile range; OR, odds ratio.

[a] Fisher exact test.

3.1. Baseline characteristics

Of 717 patients evaluated for eligibility, 364 underwent randomization (Fig. 2). 11 patients were excluded after randomization in a blinded fashion because of erroneous initial COPD diagnoses. The data from the remaining 353 patients were used for all intention-to-treat analyses. A total of 290 patients completed all treatment period according to study protocol and were included in the per protocol analysis. 29 patients (16.8%) in the TCM group and 43 patients (23.9%) in the conventional treatment group were discharged directly from the emergency department and treated as outpatients ($P = 0.18$). The two treatment groups were well balanced in terms of age, sex, and other baseline variables.

3.2. Primary end point

After 6 month of follow-up, we noted 17 acute exacerbations of 16 patients in 154 patients in the TCM treatment group and 26 exacerbations of 24 patients in 136 patients in the conventional treatment group (RR 0.59, 95% CI 0.33–1.06; p = 0.074).

Time to re-exacerbation did differ between groups as demonstrated in the KaplanMeier plots (Fig. 3). Among patients who experienced a re-exacerbation during follow-up, the median time to event was 107.5 days (interquartile range [IQR], 39.5–129.0) in the TCM and 50 days (IQR, 31–130.5) in the conventional treatment group (HR0.56, 90% CI 0.35–0.89; P = 0.011).

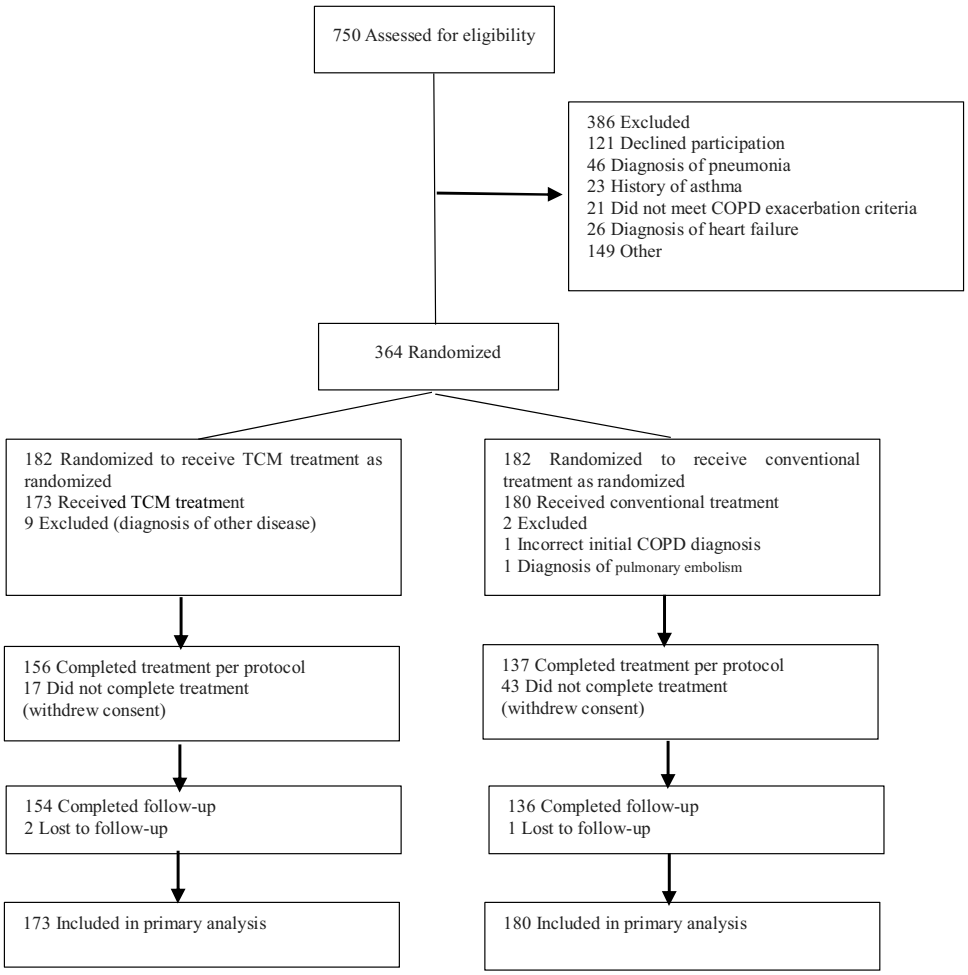

Fig. 2. Flow of Patients Through the Trial.
Patients who were lost to follow-up between the end of intervention and end of the study (day 180) were included in both the intention-to-treat and the per-protocol analyses and censored at the time of last study visit.

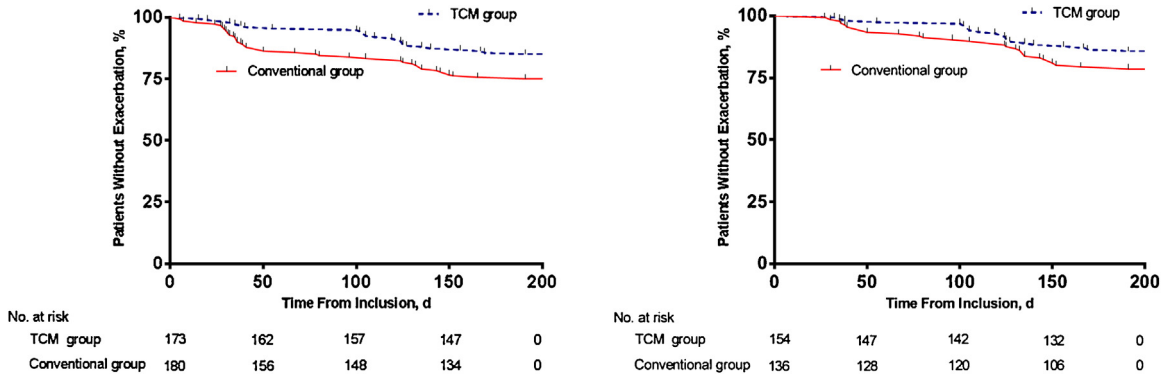

Fig. 3. Time to Re-exacerbation of Chronic Obstructive Pulmonary Disease.
A, Proportions of patients without re-exacerbation in the intention-to-treat analysis. B, Proportions of patients without re-exacerbation in the per-protocol analysis. Survival curves did not differ significantly when compared by the log-rank test. Hazard ratios for the TCM vs conventional treatment group were 0.56 (90% CI, 0.35–0.89; $P = 0.011$) in the intention-to-treat analysis and 0.64 (95% CI, 0.37–1.10; $P = 0.10$) in the per-protocol analysis.

3.3. Secondary end points

Overall survival did not differ between the treatment groups. The HRs for death for TCM compared with conventional treatment were 0.29 (95% CI, 0.06–1.41, $P = 0.18$) in the intention-to-treat and 0.24 (95% CI, 0.05–1.19, $P = 0.09$) in the per-protocol analysis (Table 4).

During hospital stay, there was no increase in the requirement for mechanical ventilation with the TCM treatment regimen, The HRs were 0.43 (95% CI, 0.11–1.70, P = 0.337). Patients under TCM treatment had a shorter hospital stay with a median of 8 days (IQR, 6–12; 95% CI, 7–9), compared with 10 days (IQR, 7–12; 95%CI, 9–11) in the conventional treatment group ($P = 0.81$)

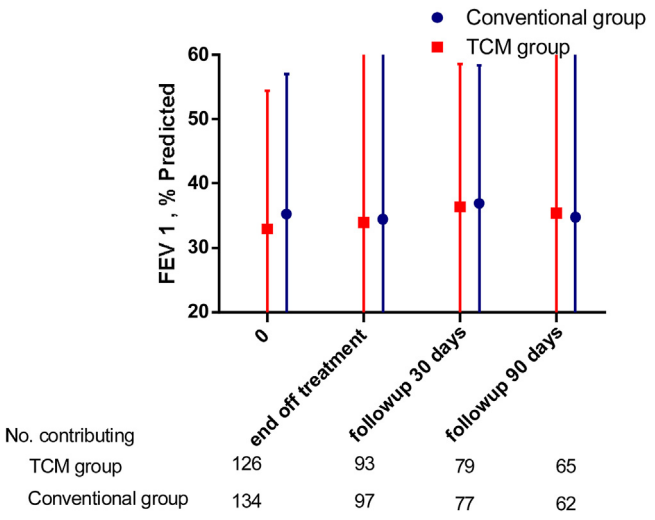

Fig. 4. Measures of Forced Expiratory Volume in One Second.
Time course of forced expiratory volume in the first second (FEV_1), assessed at study entry and end off treatment, as well as on follow-up days on which patients were seen for clinical visits. Data markers represent the mean and the error bars, 95% CI. In the full factorial model with factors group and time, the interaction between group and time was not significant ($P = 0.02$). In the main effects model, the factor time was significant ($P = 0.011$), whereas the factor group was no significant ($P = 0.89$).

The FEV_1 improved no significantly in both groups between baseline and day 28 ($P < 0.05$ for difference) and remained stable thereafter (Fig. 4). In a longitudinal analysis, there were almost no differences between groups.

However, the MMRC (P = 0.003) and CAT scores (P = 0.001) improved significantly in both groups between baseline and end off treatment and remained stable thereafter, occurred during the first 28 days of the study, respective scores did not change significantly thereafter. In a longitudinal analysis, the TCM group improved significantly than the conventional group. (Fig. 5)

4. Discussion

To date, data of TCM therapy in acute exacerbation of COPD have been insufficient. Our results show that in patients with exacerbations requiring hospital admission, provide additional TCM interventions for exacerbations will lead to better outcome. We chose exacerbation rate as a clinically meaningful primary end point with regard to previous study.[16]

Our results show that in patients with exacerbations requiring hospital admission, TCM compared with conventional treatment is superior to conventional treatment course with respect to re-exacerbation. We chose time to next exacerbation as a clinically meaningful primary end point because of earlier trials.[16,17] We therefore expected to observe differences between groups in the first few weeks of follow-up.

There were no detectable differences in forced expiratory volume between groups at any time. Dyspnea and quality of life improved significantly in the TCM treatment group. Duration of hospital stay was significantly shorter in the TCM treatment group. We did not observe significant differences in TCM related adverse effects.

Our study has several limitations. When we designed this trial, there was no standard TCM regimen for the treatment of exacerbated COPD. Since the GOLD document suggests a follow-up at 4–6 weeks after a hospitalized exacerbation, 8 so we take 4-week TCM intervention after discharge.

Patients in our trial were treated with inhaled, long-acting-agonists, glucocorticoids, and tiotropium throughout the study period. Therefore, some of them may have been over treated based on current guidelines, which may affect the outcome.

Patients in our trial were treated in hospital and out hospital (The AECOPD-RW days), if patient get exacerbated again during this period, the patient would be stop TCM treatment, which may explain the so many drop off case.

All patients in our study received antibiotic treatment regardless of sputum purulence or procalcitonin levels, which may not always have complied with current guidelines. By standardizing disease management in the exacerbation and follow-up phases, we aimed at eliminating all possible confounding factors so that any

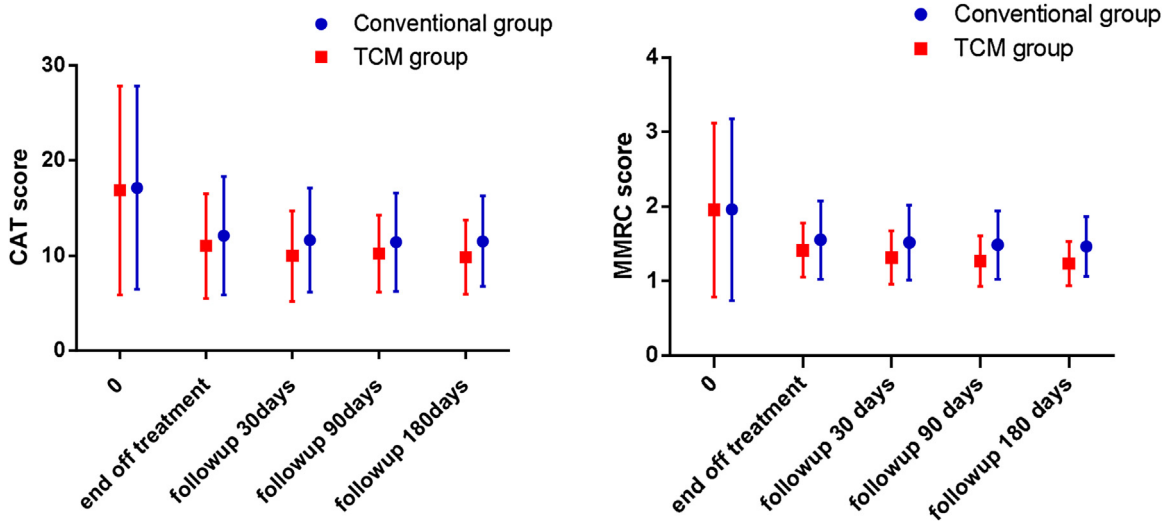

Fig. 5. Measures of MMRC and CAT score.
Time course of MMRC and CAT score, assessed at study entry and end off treatment, as well as on follow-up 30, 90, 180 days on which patients were seen for clinical visits. Data markers represent the mean and the error bars, 95% CI. In the full factorial model with factors group and time, the MMRC interaction between group and time was not significant (P = 0.091). In the main effects model, the factor time was significant (P < 0.001), whereas the factor group was significant ($P = 0.003$). The CAT interaction between group and time was significant (P = 0.006). In the main effects model, the factor time was significant (P < 0.001), whereas the factor group was significant (F = 11.552, $P = 0.001$).

potential difference in outcome could be attributed to the different TCM treatment regimes.

In summary, in patients with chronic obstructive pulmonary disease exacerbation, TCM therapy was associated with improvements in exacerbations, dyspnea, and quality of life, over the exacerbation treatment period and a further 6-months follow-up, with no relevant between-group differences in adverse events.

Conflict of interest

None declared.

Authors' contributions

This project was initiated and developed by L.J.S and W.H.F. L.J.S. and W.H.F. were involved in the design of the study and the interventions of the protocol. W.H.F. and Z.H.L. were involved in drafting and writing the manuscript. Y.X.Q. and L.S.Y. was involved in evaluating the data. The other authors were involved in collecting cases. All authors read and approved the final manuscripts.

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