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Original Research Article

A clinical study on the efficacy of modified Sangsu Guiling Decoction in the treatment of pulmonary hypertension due to left-sided heart disease

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Abstract

Purpose: *To evaluate the efficacy/effectiveness of modified Sangsu Guiling Decoction (SSGD) formula when used in combination with standard Western medicine in the treatment of pulmonary hypertension caused by left-sided heart disease (PH-LHD).*
Methods: *A randomized controlled study was carried out on 60 PH-LHD patients recruited from Changzhou Traditional Chinese Medicine Hospital. The patients were randomly assigned to 2 groups, each with 30 subjects. The conventional Western medicine treatment for the control group comprised oral intake of 5 mg of andrisentan daily, 0.5 g of amoxicillin capsules every 6 to 8 h (for the patients who had infections, with daily dose not exceeding 4 g); 2.5 mg of enalapril, once daily, and 25 mg of metoprolol, twice daily. The study group received 400 mL of the modified SSGD formula in soup form, in addition to the conventional Western medicine therapy. The treatments lasted three months. In both groups, Traditional Chinese Medicine (TCM) symptom scoring, 6-minute walk test (6MWT), WHO functional classification, echocardiography, and assay of biochemical indicators were carried out, both before and after the 3-month treatment course.*
Results: *After 3-month treatments, there were significant improvements in the study group ($p < 0.05$) in terms of clinical symptom scores, high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), left ventricular ejection fraction (LVEF), 6MWT distance, systolic pulmonary artery pressure (sPAP), WHO functional classification, and soluble suppression of tumorigenesis-2 (sST2) levels, relative to the control group ($p < 0.05$).*
Conclusion: *The combined use of modified SSGD formula and standard Western medicine improves the conditions of PH-LHD patients, enhances physical endurance, and reduces pulmonary systolic pressure. The combination treatment also mitigates inflammatory response, and minimizes the adverse effects caused by TCM, resulting in the enhancement of overall quality of life. Subsequent studies should involve long-term follow-up in order to determine the long-term effects of treatment.*

Keywords: *Modified Sangsu Guiling Decoction, Pulmonary hypertension, Left-sided heart disease, 6-minute walk test, WHO functional classification*

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INTRODUCTION

Pulmonary hypertension (PH) is often characterized by a range of pathological changes resulting from various underlying factors and mechanisms. This condition typically leads to remodeling of the pulmonary blood vessels, resulting in increased resistance and pressure within the pulmonary artery. The symptoms of PH comprise shortness of breath, palpitations, fatigue, chest pain and discomfort [1]. As the disease progresses, patients may develop right-sided heart failure which may ultimately be fatal [2]. Pulmonary hypertension (PH) caused by left-sided heart disease (PH-LHD) is characterized by a series of physiological and pathological changes resulting from structural and functional alterations within the left ventricle. Left heart disease (LHD) usually leads to PH [3]. Left heart disease (LHD) refers to a group of conditions that affect the left side of the heart, including the left atrium and left ventricle. A variety of factors may cause LHD. These factors include heart valve problems, coronary artery disease, hypertension, and cardiomyopathy, among others. Indeed, LHD is a common cause of heart failure, a debilitating and life-threatening condition. The treatment for LHD typically involves addressing the underlying causes and managing symptoms through lifestyle changes, medications, and in some cases, surgery, physiotherapy or sports therapy [4].

The co-existence of LHD and PH presents a complex and challenging clinical scenario that is refractory to traditional treatments. For instance, while targeted therapies are available for pulmonary hypertension (PH) caused by other conditions, e.g., idiopathic pulmonary arterial hypertension (IPAH), there are currently no specifically approved targeted therapies for PH-LHD [3]. This is due to the complex pathophysiology of PH-LHD which involves multiple factors such as left ventricular dysfunction, pulmonary vascular remodeling, and neurohormonal activation, thereby posing serious challenge to the development of effective targeted therapies [3]. As a result, the current treatment strategies for PH-LHD primarily focus on managing the symptoms and improving cardiac function through a combination of medications such as diuretics and vasodilators, in addition to lifestyle modifications [5].

Traditional Chinese Medicine (TCM) is a holistic approach that acts on multiple targets and pathways. Moreover, TCM is effective in alleviating heart failure symptoms, reducing hospital admissions, preventing ventricular remodeling, and improving the quality of life of patients [6]. However, there are a limited number of clinical studies on the integration of TCM and Western medicine for the treatment of PH-LHD.

The modified *Sangsu Guiling* Decoction (SSGD) is a TCM formula that has been adapted from the original Guiling Decoction, a classic TCM formula used for the treatment of heart failure. The modified SSGD formula contains additional herbs that address the specific symptoms and pathophysiological mechanisms of PH-LHD. The modified SSGD consists of 15 g of white *mulberry root bark,* 15 g of *Fructus Perillae* 10 g of *almonds,* 6 g of *cassia twig,* 10 g of *Wolfiporia extensa,* 10 g of Alisma *plantago-aquatica,*10 g of *Pericarpium arecae*, 10 g of Citri Exocarpium Rubrum, 10 g of *Pinellia ternate*, 10 g of *Polyporus umbellatus*, 30 g of *Radix Astragali preparata,* 10 g of *Rhodiola rosea*, 20 g of *Salvia miltiorrhiza,* and 10 g of *Ligusticum striatum*. In his book *Yichunshengyi,* Fei Boxiong, a well-known figure of the Menghe Medical School during the Qing Dynasty, documented SSGD as a decoction primarily intended for treating thoracic fluid retention. In recent times, SSGD is highly effective in the treatment of pulmonary edema and pulmonary heart disease [7,8]. Studies have shown that SSGD exhibits diuretic, anti-inflammatory, cough and asthma-relieving, and immunoregulatory effects, and has been proven to be effective against heart failure [9].

This study was carried out to evaluate the efficacy of combined use of the modified SSGD formula and standard Western medicine in the treatment of PH-LHD, with the aim of providing a more comprehensive and effective treatment approach for patients with this complex condition.

METHODS

Subjects

Between January 2021 and January 2022, 60 PH-LHD patients were enrolled in a study conducted at the cardiovascular division of Changzhou Traditional Chinese Medicine Hospital in Changzhou, China. The patients comprised 25 men and 35 women who ranged in age from 50 to 80 years. Using a random number table, the patients were divided into a study group and control group, with 30 patients in each group [10].

The study was approved by the Ethical Committee of Changzhou Traditional Chinese Medicine Hospital in Changzhou, China, (approval no. 2021-LL-03-L). Each patient signed a written informed consent for participation in the study.

Diagnostic criteria

Diagnostic criteria in Western medicine

The patients were diagnosed with PH-LHD in line with the Chinese Guidelines for Diagnosis and Treatment of Pulmonary Hypertension 2021 [11]. The diagnosis was based on hemodynamic criteria which included a mean pulmonary artery pressure (mPAP) of 25 mmHg at rest, and a pulmonary artery wedge pressure (PAWP) greater than 15 mmHg. In addition, the patients presented with clinical evidence of LHD. The diagnosis of PH-LHD was confirmed if all the above criteria were met.

Diagnostic criteria used for syndrome differentiation in TCM

The TCM diagnosis of heart failure due to *qi* deficit and blood stasis was made in accordance with the Guiding Principles for Clinical Study of TCM Herbs [12], while the diagnosis of gasp syndrome due to edema with heart involvement was based on the Internal Medicine of TCM. The criteria for TCM syndrome differentiation for PH-LHD were established by two senior professional TCM practitioners. The primary syndromes comprised shortness of breath and wheezing, general lassitude, and edema of the lower extremities. The secondary syndromes consisted of dim complexion, purple and dark lips, cough and expectoration, faint and low voice, poor appetite, low urine volume, and cold limbs. Tongue examination revealed a dark purple tongue with or without bruises or petechiae, and a white and thin coating, while examination of pulse showed a fine and sunken pulse, or an unsmooth or empty pulse with little strength.

Inclusion criteria

The study enrolled both male and female patients between the ages of 50 - 80 years who met the diagnostic criteria for PH-LHD in line with the diagnostic criteria in both Western and Chinese medicine.

Exclusion criteria

The excluded patients were those with idiopathic pulmonary hypertension, secondary pulmonary hypertension caused by lung hypoxia or lung diseases, chronic thromboembolic pulmonary hypertension, acute phase of acute myocardial infarction, and obstructive hypertrophic cardiomyopathy. In addition, patients with congenital heart disease, severe valvular heart disease, severe liver or kidney failure, cognitive dysfunction, and malignancies, as well as those who were uncooperative in the treatments, were excluded from the study.

Treatments

The recruited patients were divided into two groups: control group and study group. Both groups received the usual Western medicine therapy in line with the guidelines, i.e., oral intake of 5 mg of Andrisentan daily, 0.5 g of Amoxicillin capsules every 6 to 8 h (for the patients who had infections, with daily dose not exceeding 4 g); 2.5 mg of Enalapril, once daily, and 25 mg of Metoprolol, twice daily. In addition to the Western medicine treatment, the study group received the modified SSGD which was home-made by the Traditional Chinese Medicine Study Team of Menghe Medical School at Changzhou, China. The modified SSGD consisted of 15 g of white *mulberry root bark,* 15 g of *Fructus Perillae* 10 g of *almonds,* 6 g of *cassia twig,* 10 g of *Wolfiporia extensa,* 10 g of Alisma *plantago-aquatica,*10 g of Pericarpium Arecae, 10 g of Citri Exocarpium Rubrum, 10 g of *Pinellia ternate*, 10 g of Polyporus umbellatus, 30 g of *Radix Astragali preparata,* 10 g of *Rhodiola rosea*, 20 g of *Salvia miltiorrhiza,* and 10 g of *Ligusticum striatum*. The concoction was prepared by the TCM pharmacy of Changzhou TCM Hospital. Each bag of herbs prescribed was boiled in water to a total volume of 400 mL, divided equally, sub-packaged and taken orally in two doses (morning and evening). Clinical treatment efficacy was determined after three months of treatment. Patients in the control and study groups received standard Western medicine therapy, while only the patients in the study group were given additional treatment with the modified SSGD.

Evaluation of parameters/indices

Changes in clinical symptom scores

The TCM symptom scoring and 6-MWT were done before treatment and three months thereafter. The diagnosis criteria for PH-LHD involved a scoring system that assessed the severity of symptoms based on mean pulmonary artery pressure (mPAP) value. In the scoring system, different points were assigned to different levels of mPAP to indicate the severity of symptoms. The symptoms were considered absent if mPAP was less than 25 mmHg, and no points were assigned. Mild symptoms, with mPAP values of 25-40 mmHg, were assigned 2 points, while moderate symptoms, with mPAP levels of 41-55 mmHg, were assigned 4 points. In contrast, mPAP values higher than 55 mmHg

indicated severe symptoms which were assigned the highest score of 6 points [13].

6-Minute walk test (6MWT)

The 6-minute walk test (6MWT) was used to categorize the degree of heart failure: <150 m was considered severe, 150-450 m was considered moderate-to-severe, while >450 m was considered mild [14].

WHO functional classification

The WHO functional classifications (classes I to IV) of patients were evaluated during their first visit [15].

Echocardiography

Systolic pulmonary arterial pressure (sPAP) and left ventricular ejection fraction (LVEF) were measured using echocardiography prior to therapy and at three months thereafter.

Biochemical indicators

High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), soluble suppression of tumorigenesis-2 (sST2), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured in fasting venous blood samples taken before and after three months of treatment.

Statistical analysis

The SPSS 26.0 software was used for statistical analysis. Measurement data are presented as mean ± standard deviation (SD). Independent-sample *t*-test was used to compare measurement data between groups. Measurement data that did not follow normal distribution are presented as percentages, and comparison between the two groups was done with chi-squared (χ^2) test. Statistical significance was set at $p<0.05$.

RESULTS

Baseline data

There were 60 PH-LHD patients in this study, with the control and study groups having 30 patients each. The gender distribution, age, sPAP, LVEF, NT-proBNP, 6MWT, and WHO functional classification of the two groups were comparable ($p>0.05$). Based on the WHO functional classification, majority of the patients were in classes II, III, and IV. These data are shown in Table 1.

TCM symptom scores

The TCM symptom ratings in the control and study groups before and after treatment are displayed in Table 2. In the control group, the average score was reduced from 18±2.34 before therapy to 11 ± 1.52 after therapy ($p < 0.05$). In the study group, the average score of 17 ± 2.15 prior to therapy fell to 7 ± 1.13 following treatment ($p < 0.05$). After therapy, the TCM symptom score in the study group was significantly lower than the corresponding score in the control group ($p < 0.001$). This implies that, compared to traditional Western medicine treatment alone, the modified SSGD significantly reduced the clinical symptoms of patients with PH-LHD ($p < 0.001$).

Table 1: Comparison of baseline information between the two groups of patients (mean ±SD; n=30)

Data	Control group	Study group	t/(χ^2)	*P*-value
Gender (male/female)	11/19	14/16	0.617	0.432
Age (years)	70.36 ± 6.01	69.03 ± 6.82	0.803	0.438
sPAP (mmHg)	54.30 ± 7.61	55.10 ± 9.22	-0.367	0.715
LVEF	40.23 ± 4.38	41.03 ± 4.25	-0.718	0.476
NT-proBNP	991.21±428.24	864.96±426.99	1.143	0.258
6MWT (m)	278.81 ± 83.26	288.65 ± 76.92	1.152	0.658

Table 2: Comparison of TCM symptom scores between the two groups before and after treatment (mean ±SD; n=30)

Group	Pre-treatment	Post-treatment	*P*-value
Control	18.0 ± 2.34	11.0±1.52[a]	<0.05
Study	17.0 ± 2.15	7.0±1.13[a,**]	<0.001
P-value	0.362	<0.001	

Note: [a]$P < 0.05$ vs. pre-treatment level in the same group; **$p < 0.001$ vs. control group after treatment

WHO functional classification and 6MWT distance

Table 3 shows the WHO functional classification and 6MWT distance of patients in the control and study groups before and after therapy. In both groups, there were no patients in WHO classification I before therapy. However, 14 patients in the control group and 24 patients in the study group attained WHO classification I status after therapy. Following therapy, there were significant improvements in 6MWT distance in both groups ($p < 0.05$). In the study group, there were significant improvements in 6MWT distance from 288.65 ± 76.92 m to 482.72 ± 56.24 m ($p < 0.05$), while in the control group, 6MWT distance was significantly improved from 278.81 ± 83.26 m to 380.64 ± 90.27 m ($p < 0.05$). There was better progress in 6MWT distance in the study group than in the control group ($p < 0.05$).

sPAP, LVEF, and NT-ProBNP

The results in Table 4 reveal that before treatment, the sPAP and LVEF values of the two groups were comparable. However, after treatment, there was a significant drop in sPAP in the study group, when compared to the control group ($p = 0.028$). Additionally, the study group had a significantly higher LVEF value than the control group ($p = 0.027$), while the NT-proBNP level in the study group was significantly lower ($p = 0.020$).

hs-CRp, IL-6, and sST2

Prior to therapy, the control group and study group did not differ significantly in hs-CRP (10.62 ± 1.78 vs 10.24 ± 1.52 mg/L), IL-6 (35.64 ± 5.82 vs 34.26 ± 5.17 µg/L), and sST2 (43.50 ± 4.826 vs 42.30 ± 4.843 µg/L). However, following treatment, the study group had significantly lower hs-CRP levels than the control group (3.96 ± 1.47 vs 6.58 ± 1.56 mg/L, $p = 0.026$). Similarly, IL-6 level was significantly lower in the study group than in the control group (20.36 ± 4.73 vs 26.98 ± 4.62 µg/L, $p = 0.013$). In addition, there was significantly lower sST2 level in the study group than in the control group (34.63 ± 3.64 vs 37.63 ± 3.36 µg/L, $p = 0.002$). These results are shown in Table 5.

Table 3: Comparison of WHO functional classification and 6MWT distance between the two groups **(n=30)**

Parameter	Control group		Study group	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**
WHO Class I	0.0	14.0	0.0	24.0
Class II	17.0	15.0	15.0	5.0
Class III	10.0	1.0	10.0	1.0
Class Ⅳ	3.0	0.0	5.0	0.0
6MWT	278.81 ± 83.26	380.64±90.27 **[a]**	288.65 ± 76.92	482.72±56.24**[b,a]**

[a]$P < 0.05$, vs. pre-treatment level in the same group; [b]$p < 0.05$, vs. control group in the same period. Values are expressed as mean ± SD

Table 4: Comparison of sPAP, LVEF, and NT-ProBNP between the two groups (n = 30)

Group	sPAP		LVEF		NT-ProBNP	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	54.30±7.61	49.96± 7.77*	40.23±4.38	45.97±7.11*	991.21±428.24	116.06±91.12*
Study	55.10±9.22	45.03±9.07**[a]***	41.03±4.25	50.93±9.68**[b]***	864.96±426.99	69.95±52.84**[c]***
t	-0.367	2.261	-0.718	-2.265	1.143	2.398
P-value	0.715	0.028	0.476	0.027	0.258	0.020

[a]$P = 0.028$, [b]$p = 0.027$, [c]$p = 0.020$, vs. control group after treatment; *$p < 0.05$, vs. pre-treatment level in the same group. Values are presented as mean ± SD

Table 5: Comparison of hs-CRP, IL-6, and sST2 between the two groups (mean ±SD)

Group	hs-CRP (mg/L)		IL-6 (µg/L)		sST2 (µg/L)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	10.62±1.78	6.58±1.56*	35.64±5.82	26.98±4.62*	43.50±4.826	37.63±3.36*
Study	10.24±1.52	3.96±1.47**[a]***	34.26±5.17	20.36±4.73**[b,]***	42.30±4.843	34.63±3.64**[c,]***
t	0.136	4.372	0.532	6.351	0.961	3.312
P-value	0.721	0.026	0.948	0.013	0.340	0.002

[a]$P = 0.026$, [b]$p = 0.013$, vs. control group after treatment; [c]$p = 0.002$, *$p < 0.05$, vs. pre-treatment level in the same group

Safety of medication

Patients in both groups adhered strictly to their medication requirements. There were no severe complications or deaths during the treatment period. Routine tests on blood, urine, and feces, as well as evaluations of liver and kidney functions and electrolyte levels, did not reveal any abnormalities. These results suggest that the modified SSGD was safe and did not cause any obvious toxicity or adverse side effects.

DISCUSSION

Pulmonary hypertension caused by left-sided heart disease (PH-LHD) is often complicated by severe symptoms, decreased mobility, and a poor prognosis [16]. The mechanisms underlying the pathophysiology of PH-LHD are extremely complex [3]. Traditional Chinese Medicine (TCM) has a long history of use, and it has been shown to be effective in the treatment of a variety of diseases [6,17]. In this study, the combined use of modified SSGD and standard Western medicine treatment produced satisfactory clinical effectiveness in the treatment of PH-LHD. This validates the clinical efficiency of modified SSGD [7-9]. This research showed that both groups experienced improvements in TCM symptom scores, with a greater improvement in the study group, which may likely be due to the reduced side effects associated with TCM herbs.

Traditional clinical indicators and tests such as NT-ProBNP, echocardiography, WHO functional classification, and 6MWT serve as indices for assessment of the effectiveness of treatment and prediction of prognosis [13-15]. Due to its sensitivity and specificity, NT-proBNP is a clinically used test for heart failure. However, when heart failure is complicated with PH, it becomes difficult to diagnose or predict with a single indicator. The levels of IL-6 and sST2 have been found to be strongly associated with cardiac functional status in heart failure [18]. Inflammatory response is important in the development of PH, and IL-6 is involved in pulmonary vascular remodeling [18]. Therefore, the combined use of IL-6, sST2, and NT-proBNP as indices of PH-LHD is justified, based on clinical experience. Following treatment, there were more significant improvements in LVEF, NT-proBNP, and sST2 in the study group than in the control group. Patients who received the modified SSGD in combination with Western medicines had better outcomes than those treated with Western medicines alone. The reduction in sPAP after treatment was greater in the study group than in the control group. This may be due to the capacity of the modified SSGD to improve left heart function, thereby reducing PH and delaying disease progression. After treatment, there were greater reductions in inflammatory factors (hs-CRP and IL-6) in the study group, indicating that the modified SSGD reduced inflammatory response and arrested the progression of PH-LHD.

Patients with a prolonged course of PH-LHD often experience deficiency in heart and lung *qi*, general fatigue, panting during physical exertion, and a significant decrease in motor activity. The WHO functional classification and 6MWT are used for assessment of physical endurance in patients [3,14]. After treatment, the 6MWT distance was longer in the study group than in the control group. Additionally, the degree of improvement in WHO functional classification was significantly higher in the study group. These results suggest that the use of modified SSGD in combination with standard Western medicine treatment, improved cardiopulmonary function, exercise tolerance, and quality of life in patients with PH-LHD.

Furthermore, there were no adverse events such as death or severe complications during the treatment period in either group, demonstrating that the combined treatment had favorable safety profile. Overall, this research indicates that integrative Chinese and Western medicine outperformed Western medicine treatment alone in the clinical treatment of PH-LHD caused by *qi* deficiency, blood stasis, and edema with heart involvement.

Traditional Chinese Medicine (TCM) and the *Yichunshengyi* by Fei Boxiong, a famous authority in TCM, do not address the diagnosis, treatment, and concept of PH-LHD. However, modern Chinese medicine approaches PH-LHD by breaking it down into categories based on clinical symptoms such as heart failure, lung-distention, and gasp syndrome. In TCM, it is believed that the pathogenesis of PH-LHD involves heart-lung *qi* deficiency, stasis and obstruction of vessels and *collaterals*, retention of *water-dampness*, and blood stasis and excessive water. These interfere with the purification function of the lungs, leading to disrupted circulation of *qi*, blood, and body fluids. Patients with PH-LHD experience symptoms such as shortness of breath, chest tightness, persistent cough and wheezing, lethargy, fatigue, limb swelling, dizziness, and panic [1]. The main factors involved in the pathogenesis of PH-LHD are heart-lung *qi* deficiency, stasis and obstruction of vessels and collaterals, and *invasion of the heart and lung.* The TCM treatment for PH-LHD focuses on invigorating *qi*

and promoting blood circulation to enhance water metabolism, as well as purging the lungs, thereby relieving asthma and cough [6,17].

The modified SSGD decoction was prepared from various herbs: white mulberry root bark, *Fructus Perillae,* almonds, cassia twig, *Wolfiporia extensa, Alisma plantago-aquatica, Pericarpium Arecae, Citri Exocarpium Rubrum, Pinellia ternata, Polyporus umbellatus, Radix Astragali preparata, Rhodiola rosea, Salvia miltiorrhiza,* and *Ligusticum striatum* [7,8]. These components exert diverse effects. For instance, white mulberry root bark clears and reduces lung *qi*, and dredges and regulates water passage. *Fructus perillae* and almonds reduce *qi*, eliminate phlegm, and relieve cough and asthma [7,8]. Cassia twig warms *yang* for activating *qi* flow and water excretion. *Wolfiporia extensa* strengthens the spleen and regulates the stomach, *clears dampness*, and promotes diuresis. *Polyporus umbellatus* and Alisma plantago-aquatica produce water benefits, and they *permeate dampness*. *Pericarpium arecae* relieves swelling by enhancing *qi* circulation. Citri Exocarpium Rubrum and *Pinellia ternata* harmonize the stomach, eliminate dampness and reduce phlegm [7,8]. *Astragalus membranaceus* benefits *qi,* nourishes blood, and alleviates edema by inducing diuresis [19].

A recent pharmacological study showed that *Astragalus* saponins which are bioactive compounds in *Astragalus membranaceus*, effectively reduced pulmonary arterial pressure, pulmonary artery hyperplasia, and pulmonary artery remodeling by inhibiting *in vivo* oxidative stress [19]. *Rhodiola rosea* is benefitial to *qi* for activating blood circulation, clearing the pulse, and controlling asthma. It has been reported that the combined use of *Salvia miltiorrhiza* and *Ligusticum striatum* removed blood stasis by enhancing blood circulation [20]. *Rhodiola rosea* exerts a range of therapeutic effects such as reducing inflammation, preventing oxidative damage, scavenging reactive oxygen species, boosting immunity, and mitigating pulmonary vascular remodeling. *Salvia miltiorrhiza* and *Ligusticum striatum* also exhibit numerous pharmacological properties such as decreasing pulmonary arterial pressure, expanding blood vessels, enhancing tissue microcirculation, increasing tissue perfusion, and preventing platelet aggregation and thrombosis [20]. These herbs which promote circulation and remove stasis, produce anti-hypoxic effects, leading to a decrease in pulmonary arterial pressure without affecting systemic blood pressure. Furthermore, the herbs increase myocardial contractility and coronary blood supply [20]. Meta-analysis has demonstrated that medicinal herbs that minimize water retention by replenishing *qi* and stimulating the blood, also enhance cardiac function, lower levels of NT-proBNP, and increase 6MWT distance, as left heart insufficiency frequently worsens PH-LHD [20].

Through appropriate combination of the medicinal herbs, SSGD produces the desirable effects of invigorating *qi* and stimulating the blood, thereby enhancing diuresis, cleansing the lungs, and relieving asthma and cough.

Limitations of the study

Despite providing valuable information, this study has some potential limitations. The first limitation is the small sample size used. The study was based on only 60 patients. This population may not be sufficient to fully demonstrate the effectiveness and safety of the treatment. The use of larger sample sizes is expected to improve the reliability and generalizability of the findings. The second limitation is in the study design. Although the study used a randomized controlled trial design, it was a single-blind trial, i.e., the patients were not aware of the treatment they received. This could lead to subjective bias in the study results, as patients and doctors may have biases towards the study outcomes. Thirdly, there is a limitation in scope of the study. The study only covered one treatment method, i.e., the use of modified SSGD formula in combination with standard Western medicine treatment. Based on the fact that pulmonary hypertension has complex etiology, other treatment methods may also have impacts on the study results. Therefore, subsequent research should explore other possible treatment options. The fourth limitation pertains to study time frame. The time span of the study was short: it covered only a short period after treatment. Therefore, the study did not fully evaluate the long-term effectiveness of the treatment method used. The fifth limitation is on practicality issues. Although the study showed the potential advantages of the modified SSGD formula, the actual application of this TCM formula presents some challenges such as patient tolerance to the bioactive components, as well as regional differences in TCM formulations. Therefore, more practical experience and research are needed to evaluate the practicality of this TCM formula.

CONCLUSION

The use of Menghe Medical School-modified SSGD along with standard Western medicine treatment effectively improves the condition of PH-LDH patients. The decoction was beneficial

in enhancing physical endurance, reducing pulmonary systolic pressure, mitigating inflammatory response, and strengthening cardiopulmonary function while relieving TCM symptoms, thereby elevating the patients' overall quality of life. The combined use of the modified SSGD and standard Western medicine treatment yielded better results than the use of standard Western medicine treatment alone. Subsequent studies should involve long-term follow-up in order to determine the long-term effects of treatment.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Zhenhua Gu participated in generating the ideas for the study, study design, data analyses, interpretation, and writing of the manuscript. Yichen Wang was involved in study design, data analyses, interpretation, and reviewing of the manuscript. Shuhua Tang participated in data collection, data interpretation, and reviewing of the manuscript. Chunti Shen took part in data collection, data interpretation, study design, data analyses, and reviewing of the manuscript. Zhenhua Gu and Yichen Wang contributed equally to this study.

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