International Journal of General Medicine

Dovepress
Taylor & Francis Group

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CLINICAL TRIAL REPORT

Traditional Chinese Medicine Ion Introduction Therapy Reduces the Incidence of Acute Exacerbation of Idiopathic Pulmonary Fibrosis: A Prospective Cohort Study

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Objective: To evaluate the effectiveness and safety of traditional Chinese medicine (TCM) ion introduction therapy in the treatment of patients with acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF).

Methods: This study adopts a prospective cohort study design, with 60 AE-IPF patients as the research subjects. Divided into an exposed group and a non exposed group, with 30 cases in each group, based on the frequency of TCM ion introduction treatment as the exposure factor. Follow-up for 1 year to observe the acute exacerbation of the patient. The main indicator is the annual incidence of acute exacerbation, and the secondary indicators are hospitalization time, readmission rate, time to first acute exacerbation, mortality rate, all-cause mortality rate, inflammatory indicators, quality of life, etc.

Results: 51 patients completed a one-year clinical observation, including 27 in the exposed group and 24 in the non exposed group. Compared to the non exposed group, significant differences were observed in the annual incidence of acute exacerbation [incidence rate ratios (IRR) = 0.556, 95% CI: 0.315, 0.980; P = 0.035] and hospitalization time (P = 0.040), readmission rate (IRR = 0.533, 95% CI: 0.288, 0.988; P = 0.037), time to first acute exacerbation (P = 0.045), and quality of life (P < 0.05). However, there was no statistically significant difference in mortality rate and all-cause mortality rate between the two groups (P > 0.05).

Conclusion: Compared to the non exposed group, TCM ion introduction can reduce the annual incidence of acute exacerbation of IPF patients. Hospitalization time, readmission rate, time to first acute exacerbation, quality of life improved, but mortality rate and all-cause mortality rate did not improve.

Keywords: TCM, ion introduction, idiopathic pulmonary fibrosis, acute exacerbation, incidence

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease characterized by irreversible fibrosis of the lung structure.[1] Out of every 100,000 patients, 20 to 80 develop IPF, with the majority being males with a history of smoking.[2] The median survival time of patients after diagnosis is only 3 to 5 years.[3] Most patients have a long course of illness, and some patients may experience acute respiratory deterioration, also known as acute exacerbation of IPF (AE-IPF), during the progression of their condition.[4] The incidence rate of AE-IPF is relatively high.[5] AE can occur at various stages of IPF and is an important cause of patient mortality.[6] The in-hospital mortality rate exceeds 50%,[7] resulting in over 46% IPF mortality rate.[8] Every year, 10%–20% of patients have acute exacerbation,[9] and the three-month survival rate is 41%.[10] Therefore, seeking safe, effective, and economical treatment methods is currently a difficult and hot research topic.

Received: 27 September 2024
Accepted: 25 December 2024
Published: 6 January 2025

Although significant progress has been made in understanding IPF, the etiology and mechanism of IPF are not yet fully understood.[11] In terms of preventing and treating IPF, the current guidelines recommend western drugs including Nintedanib and Pirfenidone.[12] Pirfenidone and Nintedanib are recommended as effective treatment options to improve forced lung capacity and delay disease progression.[13,14] Pirfenidone can reduce the incidence of death. Even if a single disease progression event occurs, continuing to use Pirfenidone treatment is still beneficial.[15] The emergence of these two drugs has provided new treatment options for IPF patients.[16] But these two drugs are expensive, limiting their scope of use, and have adverse reactions such as photosensitivity and gastrointestinal discomfort.[17,18] Lung transplantation is still the only curative measure, but it cannot be accepted by most patients.[19] Limited prevention and treatment measures bring serious burdens to patients and society. So seeking safe, effective, and economical treatment methods is a difficult and hot research topic.[20–23]

In TCM, IPF belongs to the categories of lung dysfunction and lung obstruction. Research has pointed out that the pathogenesis of IPF is based on the accumulation and damage of positive deficiency and collateral obstruction, with phlegm and blood stasis as the standard.[24,25] TCM has certain therapeutic effects and advantages in treating IPF.[26–28] TCM ion introduction is a treatment method that uses electric current to introduce drug ions into the skin or mucous membrane. It has the effects of dredging meridians, regulating qi and blood, and reducing swelling and pain. TCM ion introduction has the characteristics of simplicity, convenience, cost–effectiveness, and efficacy. It is widely used in clinical practice and has achieved good therapeutic effects in respiratory diseases. At present, the number of literature on the treatment of AE-IPF with TCM ion therapy is small, the sample size is small, the level of evidence is low, and the intervention measures are complex, making it difficult to determine the efficacy of TCM ion therapy. Although TCM ion introduction therapy for AE-IPF has certain efficacy and advantages, the lack of rigorous research design, non-standard operation process of TCM ion introduction, and unreasonable therapeutic indicators affect the authenticity and reliability of research conclusions. The effectiveness and safety of TCM ion therapy for AE-IPF still need to be re evaluated and considered. Therefore, this study adopts a prospective cohort study design to evaluate the clinical efficacy of TCM ion introduction therapy for AE-IPF patients, hoping to provide reference for further research.

Materials and Methods

Study Design

This study adopts a prospective cohort study design, with 60 AE-IPF patients as the research subjects. The exposure factor is the continuous use of TCM ion therapy for ≥10 times or intermittent use of TCM ion therapy for ≥14 times within a year. Continuous refers to using it every day, while intermittent refers to not using it every day, with intervals in between. According to the exposure situation, AE-IPF patients were divided into an exposed group and a non exposed group, with 30 cases in each group. Baseline data was extracted from inpatient medical records. Mainly through telephone follow-up, supplemented by face-to-face interviews. Ask AE-IPF patients about acute exacerbation within 1 year after discharge. This study was conducted at the First Affiliated Hospital of Henan University of TCM, Henan Provincial Hospital of TCM, and the First People's Hospital of Xinxiang City.

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Henan University of TCM (Ethical approval number: 2021HL-117-02). This study has been registered with the Chinese Clinical Trial Center (registration number: ChiCTR2200060405). All participants provided informed consent forms in accordance with the Helsinki Declaration.

Subjects

The research subjects of this study are 60 AE-IFP patients admitted to the hospital after July 2021. Diagnostic criteria refer to the Chinese Expert Consensus on Diagnosis and Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis.[29]

Inclusion and Exclusion Criteria

Our inclusion criteria are: (1) According to the hospitalization medical records, the patient met the AE-IPF diagnostic criteria upon admission; (2) Age range from 40 to 80 years old; (3) Voluntarily participate in the study and sign an informed consent form. Our exclusion criteria are: (1) Pregnant or lactating women; (2) Combining active pulmonary tuberculosis, bronchiectasis, and other severe respiratory diseases; (3) Merge severe liver, kidney, cardiovascular and cerebrovascular diseases; (4) Merge malignant tumors.

Treatments

The conventional treatment plan of Western medicine follows the Chinese expert consensus on the diagnosis and treatment of acute exacerbation of idiopathic pulmonary fibrosis.[29] The main drugs used for TCM iontophoresis are blood activating and stasis removing formulas, such as safflower, stir-fried peach kernels, vinegar frankincense, vinegar myrrh, angelica, soapberry thorn, peony bark, Chuanxiong, Xinjiang purple grass, white atractylodes, red peony, etc. The specific operation is as follows: Soak an appropriate amount of TCM decoction in a medication pad (5–6 layers of velvet cloth, about 10cm × 5cm), wrap two lead plate electrodes, place them on the lung floor, and use elastic bandages to press and fix the corresponding surface position with the most obvious Velcro rales. Connect the ion introduction device (T99-C computer intermediate frequency electrotherapy device, Beijing Tianchangfu Medical Equipment Manufacturing Co., Ltd), and the stimulation intensity should be based on the patient's comfortable feeling. Generally, a slight acupuncture sensation is sufficient, 20 minutes each time, once a day.

Primary Outcomes

The main outcome measure of this study is the annual incidence of acute exacerbations, specifically calculating the proportion of acute exacerbations occurring in AE-IPF patients within one year after discharge.

Secondary Outcomes

(1) The hospitalization time specifically refers to the time it takes for a patient to be admitted to and discharged from the hospital; (2) The readmission rate specifically refers to the proportion of patients who are readmitted due to acute exacerbation after discharge; (3) The time to first acute exacerbation specifically refers to the time from discharge to the first occurrence of acute exacerbation in patients; (4) The mortality rate specifically refers to the proportion of patients who die of IPF; (5) The all-cause mortality rate specifically refers to the proportion of patients who die of various causes; (6) Inflammatory indicators specifically refer to recording the levels of blood routine, C-reactive protein, and other indicators of patients upon admission and discharge; (7) The quality of life is specifically measured using the Idiopathic Pulmonary Fibrosis Patient Reported Outcome (IPF-PRO) scale, which is recorded once at admission, once at discharge, and once at 1-year follow-up.

Statistical Analysis

SPSS 25.0 statistical software was used for statistical analysis. The measurement data were described by mean ± standard deviation or median (interquartile spacing), and the counting data were described by frequency (component ratio). When the baseline distribution of the two groups was balanced, chi-square test was used for counting data and independent sample *T*-test or Mann–Whitney *U*-test was used for measurement data comparison between groups. $P < 0.05$ was considered statistically significant.

Results

Subjects Characteristics

From July 2021 to July 2022, a total of 60 AE-IPF patients were finally included. After one year of discharge, the patient was lost to follow-up (n = 7) and had poor compliance (n = 2). Nine cases were excluded, and ultimately 51 patients completed one year of clinical observation, including 27 in the exposed group and 24 in the non exposed group.

Baseline Data

Baseline Characteristics

There was no statistically significant difference in gender, age, course of disease, BMI, blood pressure, number of acute exacerbations in the past year, number of hospitalization due to acute exacerbations in the past year, cough score, sputum score, wheezing score, chest tightness score, shortness of breath score, fatigue score, and comorbidities between the exposed and non exposed groups ($P > 0.05$), and the two groups were comparable. Please refer to Table 1 for details. Please refer to Figure S1 in the Supplementary Materials for symptom scoring.

Comparison of Medication Use During Hospitalization Between Two Groups

There was no statistically significant difference in medication use between the exposed group and the non exposed group during hospitalization ($P > 0.05$), indicating comparability between the two groups. Please refer to Table 2 for details.

Comparison of Ion Introduction Between Two Groups of TCM

Twenty-seven patients in the exposure group were all treated with TCM ion introduction therapy, and all met the criteria of continuous use of TCM ion introduction therapy ≥10 times or intermittent use of TCM ion introduction therapy ≥14 times within 1 year. Nine patients in the non exposure group were treated with TCM ion introduction therapy, and the number of times of TCM ion introduction therapy was divided into 9, 6, 3, 3, 3, 3, 2, 2, and 2. The number of times of TCM ion introduction therapy was less than 10 times within 1 year; The single treatment time for both groups of TCM ion introduction is 20 minutes.

Table 1 Comparison of Basic Information Between Exposed and Non Exposed Groups

Project	Exposure Group	Non Exposure Group	Statistic	*P*
Male/female	11/16	16/8	3.428	0.064
Age(years)	63.37±8.30	65.21±8.46	−0.782	0.438
Course of disease (month)	36.00 (5.00, 60.00)	36.00 (15.00, 69.50)	−0.786	0.432
BMI (kg/m^2)	22.98±3.21	23.85±5.76	−0.724	0.469
Systolic pressure (mmHg)	125.00±5.17	121.00±6.29	−1.366	0.172
Diastolic pressure (mmHg)	76.00±3.73	75.00±5.64	−0.684	0.494
Number of acute exacerbations in the past year	3.00±1.18	2.00±1.30	−1.816	0.069
Number of hospitalizations in the past year	3.00±1.18	2.00±1.30	−1.693	0.090
Symptom score				
Cough score	50.00±23.32	55.00±17.93	−0.799	0.424
Phlegm score	40.00±24.58	40.00±17.64	−0.287	0.774
Wheezing score	50.00±12.34	60.00±17.69	−1.420	0.156
Chest tightness score	50.00±11.76	65.00±18.85	−1.766	0.077
Shortness of breath rating	50.00±11.76	60.00±18.15	−1.644	0.100
Fatigue score	40.00±19.08	35.00±21.43	−0.855	0.393
Comorbidities				
Hypertension	8 (29.6%)	9 (37.5%)	0.354	0.552
Cerebral infarction	2 (7.4%)	1 (1.4%)	0	1
Coronary heart disease	3 (11.1%)	4 (16.7%)	0.028	0.867
Diabetes	2 (7.4%)	5 (20.8%)	0.966	0.326
Hepatitis B	0 (0%)	1 (4.2%)	/	0.471*
Osteoporosis	1 (3.7%)	0 (0%)	/	1*

Notes: *Adopting Fisher's exact probability method. Symptom score: We used visual simulation scoring, where 0 represents no symptoms and 100 represents the most severe symptoms. Please refer to the supplementary materials for details.
Abbreviation: BMI, Body mass index.

Table 2 Comparison of Medication Use During Hospitalization Between the Exposed and Non Exposed Groups

Drug Classification	Exposure Group	Non Exposure Group	$\chi 2$	*P*
Antibiotic	20 (74.1%)	19 (79.2%)	0.183	0.669
Expectorant drugs	7 (25.9%)	10 (41.7%)	1.417	0.234
Acid suppressants	25 (92.6%)	18 (75.0%)	1.792	0.181
Glucocorticoids	8 (29.6%)	12 (50.0%)	2.212	0.137
Anti fibrotic drugs	20 (74.1%)	16 (66.7%)	0.336	0.562
Doxofylline	27 (100.0%)	21 (87.5%)	1.684	0.194
Montelukast	4 (14.8%)	2 (8.3%)	0.079	0.778
Compound methoxyphenamine	5 (18.5%)	3 (12.5%)	0.042	0.838
Insulin	1 (3.7%)	1 (4.2%)	/	1*
Metformin	1 (3.7%)	2 (8.3%)	0.011	0.916
α Glycosidase inhibitors	0 (0.0%)	2 (8.3%)	/	0.216*
SGLT-2 inhibitor	1 (3.7%)	2 (8.3%)	0.011	0.916
NSAIDs	1 (3.7%)	2 (8.3%)	0.011	0.916
Statins	3 (11.1%)	2 (8.3%)	0	1
ARB	2 (7.4%)	1 (4.2%)	0	1
CCB	4 (14.8%)	4 (16.7%)	0	1
Beta-blocker	5 (18.5%)	5 (20.8%)	0	1
Chinese patent drug	26 (96.3%)	20 (83.3%)	1.171	0.279
TCM Slices/Granules	26 (96.3%)	20 (83.3%)	1.171	0.279

Notes: *Adopting Fisher's exact probability method.
Abbreviations: CCB, Calcium channel blocker; NSAIDs, Non-steroidal anti-inflammatory drugs; ARB, Angiotensin II receptor blocker; SGLT-2, Sodium-dependent glucose transporters 2.

Table 3 Comparison of TCM Syndrome Types Between Exposed and Non Exposed Groups

Tcm Syndrome	Exposure Group	Non Exposure Group	$\chi 2$	*P*
Lung spleen qi deficiency syndrome	1 (3.7%)	1 (4.2%)	/	1*
Syndrome of phlegm heat obstructing the lung	2 (7.4%)	2 (8.3%)	0	1
Phlegm turbidity obstructing lung syndrome	3 (11.1%)	3 (12.5%)	0	1
Syndrome of phlegm stasis and internal obstruction	2 (7.4%)	3 (12.5%)	0.019	0.890
Phlegm dampness accumulation in the lungs syndrome	2 (7.4%)	1 (4.2%)	0	1
Phlegm turbidity obstructing lung syndrome+lung spleen qi deficiency syndrome	4 (14.8%)	1 (4.2%)	0.648	0.421
Syndrome of phlegm heat obstructing the lung+lung kidney qi deficiency syndrome	6 (22.2%)	5 (20.8%)	0.014	0.904
Syndrome of phlegm heat obstructing the lung+qi-yin deficiency syndrome	2 (7.4%)	1 (4.2%)	0	1
Syndrome of phlegm stasis and internal obstruction+lung kidney qi deficiency syndrome	5 (18.5%)	7 (29.2%)	0.801	0.371

Notes: *Adopting Fisher's exact probability method.

Comparison of TCM Syndrome Types Between Two Groups

There was no statistically significant difference in TCM syndrome types between the exposed group and the non exposed group ($P > 0.05$), indicating comparability. Please refer to Table 3 for details.

Outcome Indicators

Annual Incidence of Acute Exacerbation

A total of 26 patients in the exposed and non exposed groups experienced acute exacerbation within 1 year after discharge, with 10 cases in the exposed group (37.0%) and 16 cases in the non exposed group (66.7%). The incidence ratio (IRR) was 0.556 [95% CI, 0.315–0.980], and the difference was statistically significant ($P = 0.035$). Please refer to Table 4 for details.

Table 4 Comparison of the Annual Incidence of Acute Exacerbation Between Exposed and Non Exposed Groups

Group	Number of Cases	Annual Incidence of Acute Exacerbation (n,%)	IRR (95% CI)	*P*
Exposure group	27	10 (37.0%)	0.556 (0.315–0.980)	0.035
Non exposure group	24	16 (66.7%)		

Abbreviation: IRR, Incidence rate ratios.

Table 5 Comparison of Hospitalization Time Between Exposed and Non Exposed Groups

Group	Number of cases	Hospitalization time (days)	*Z*	*P*
Exposure group	27	10.81±2.58	−2.053	0.040
Non exposure group	24	14.88±8.09		

Hospitalization Time

The difference in hospitalization time between the exposed and non exposed groups was statistically significant (P = 0.040). Please refer to Table 5 for details.

Readmission Rates

A total of 24 patients in the exposed group and non exposed group were readmitted due to acute exacerbation within 1 year after discharge. There were 9 cases (33.3%) in the exposed group and 15 cases (62.5%) in the non exposed group, with an IRR of 0.533 [95% CI, 0.288–0.988], and the difference was statistically significant (P = 0.037). Please refer to Table 6 for details.

Time to First Acute Exacerbation

There was a statistically significant difference (P = 0.045) between the exposed group and the non exposed group in terms of the time to first onset of acute exacerbation. Please refer to Table 7 for details.

Mortality Rate

There were 4 deaths in the non exposure group, of which 3 (12.5%) died of acute exacerbation of IPF, and 1 (4.2%) died of novel coronavirus infection. There was no death in the exposure group, with no statistically significant difference (P > 0.05). Please refer to Table 8 for details.

Table 6 Comparison of Readmission Rates Between Exposed and Non Exposed Groups

Group	Number of Cases	Readmission Rate (n,%)	IRR (95% CI)	*P*
Exposure group	27	9 (33.3%)	0.533 (0.288–0.988)	0.037
Non exposure group	24	15 (62.5%)		

Abbreviation: IRR: Incidence rate ratios.

Table 7 Comparison of the Time to First Acute Exacerbation Between the Exposed and Non Exposed Groups

Group	Number of Cases	Time to First Acute Exacerbation (days)	*t*	*P*
Exposure group	27	106.00±58.45	2.120	0.045
Non exposure group	24	61.38±48.08		

Table 8 Comparison of Mortality Rate Between Exposed and Non Exposed Groups

Case Fatality Rate	Exposure Group	Non Exposure Group	χ^2	*P*
AE-IPF (n,%)	0 (0%)	3 (12.5%)	1.684	0.194
Novel coronavirus infection (n,%)	0 (0%)	1 (4.2%)	/	0.471*

Note: *Adopting Fisher's exact probability method.

Table 9 Comparison of All-Cause Mortality Rate Between the Exposed and Non Exposed Groups

Group	Number of Cases	All-Cause Mortality (n,%)	$\chi 2$	*P*
Exposure group	27	0 (0%)	2.849	0.091
Non exposure group	24	4 (16.7%)		

All-Cause Mortality Rate

There were a total of 4 deaths in the exposed and non exposed groups within 1 year after discharge, with no deaths in the exposed group and 4 deaths in the non exposed group (16.7%), with no statistically significant difference ($P > 0.05$). Please refer to Table 9 for details.

Quality of Life

Physiological Field Scores

After repeated measures of analysis of variance, there was an interaction effect between time and group ($F = 18.414$, $P < 0.001$), and the impact of the interaction effect on physiological domain scores was statistically significant. A separate effect analysis was conducted for time and group. Please refer to Table 10 for details.

Psychological Field Scores

After repeated measures analysis of variance, there was an interaction effect between time and group ($F = 4.982$, $P = 0.018$), and the impact of the interaction effect on the psychological field score was statistically significant. A separate effect analysis was conducted for time and group. Please refer to Table 10 for details.

Table 10 Comparison of Quality of Life Before and After Treatment

Group	No of Cases	On Admission	At Discharge	12 Months After Discharge
Physiological field score				
E	27	14.59±4.37	11.15±2.81	6.48±2.48
N	24	16.33±3.69	15.33±4.73	14.88±5.74
Group effect		*F*=25.236, *P*<0.001		
Time effect		*F*=37.290, *P*<0.001		
Time*Group		*F*=18.414, *P*<0.001		
Psychological field scores				
E	27	2.52±1.92	2.22±1.73	1.52±1.52
N	24	5.38±1.86	4.50±1.79	3.50±1.71
Group effect		*F*=25.738, *P*<0.001		
Time effect		*F*=52.572, *P*<0.001		
Time*Group		*F*=4.982, *P*=0.018		

(*Continued*)

https://doi.org/10.2147/IJGM.S498350

Table 10 (Continued).

Group	No of Cases	On Admission	At Discharge	12 Months After Discharge
Environmental domain scores				
E	27	6.26±2.24	5.26±1.93	3.96±1.97
N	24	7.13±2.59	6.71±1.65	6.96±1.51
Group effect		*F*=11.499, *P*<0.001		
Time effect		*F*=20.913, *P*<0.001		
Time*Group		*F*=16.576, *P*<0.001		
Satisfaction scores				
E	27	3.26±1.58	3.19±1.86	3.00±1.33
N	24	3.92±1.24	3.83±1.27	3.75±1.15
Z		−1.720	−1.961	−1.997
P		0.085	0.050	0.046
Group effect		*F*=3.294, *P*=0.076		
Time effect		*F*=1.492, *P*=0.232		
Time*Group		*F*=0.102, *P*=0.857		

Abbreviations: E, Exposure group; **N**, Non exposure group.

Environmental Domain Scores

After repeated measures analysis of variance, there was an interaction effect between time and group (F = 16.576, P < 0.001), and the impact of the interaction effect on environmental domain scores was statistically significant. A separate effect analysis was conducted for time and group. Please refer to Table 10 for details.

Satisfaction Scores

After repeated measures analysis of variance, there was no interaction effect between time and group (F = 0.102, P = 0.857). Please refer to Table 10 for details.

Comparison of Two Sets of Safety Indicators

There was no statistically significant difference in blood routine tests (white blood cells, neutrophils, lymphocytes) between the two groups at admission, and there was no statistically significant difference in discharge.

Adverse Reactions

Both groups of patients did not experience any adverse reactions during the process of traditional Chinese medicine ion introduction therapy.

Discussion

Our research has found that TCM ion introduction has certain advantages in treating AE-IPF patients. Compared with the non exposed group, TCM ion introduction can reduce the annual incidence of acute exacerbation in patients during the 1-year follow-up period. In addition, hospitalization time, readmission rate, time to first acute exacerbation, quality of life improved. However, the mortality rate and all-cause mortality rate did not improve. Previous studies have shown that TCM has significant therapeutic effects on AE-IPF and low economic costs.[30,31] A previous study showed that TCM ion introduction for IPF has a certain therapeutic effect and fewer adverse reactions.[32] However, there are currently few clinical studies, and our research results may provide reference for clinical applications, especially for AE-IPF patients.

TCM external treatment has certain therapeutic effects and advantages in treating IPF. Acupuncture, acupoint application, and thread embedding are all based on the meridians, and their mechanisms of action are closely related to the meridians. Fibrosis is a process of abnormal tissue repair, which is relatively complex and has a significant impact

on the structure and function of human physiological organs, making it one of the main causes of death worldwide.[33] Therefore, the treatment of fibrotic diseases needs to fully consider meridian factors in order to achieve effective treatment. According to literature,[34] research on biological indicators related to fibrosis has found that acupuncture can effectively slow down the development of fibrosis and reverse the early occurrence of fibrosis, thereby contributing to the treatment of chronic diseases. The main lesions of IPF are bilateral subpleural and bilateral lower lungs, and explosive sounds can be heard during auscultation. Research has shown[35] that in the treatment of lung disease, the electrode plate for ion introduction is usually placed in the most prominent area of the back rale, which can promote lung circulation, promote the absorption of lung rales, and also have the effect of relieving cough and asthma. However, the literature on TCM ion therapy for IPF is limited, with a small sample size, low level of evidence, and complex intervention measures. Further scientific clinical research is needed to determine whether ion therapy is effective in reducing the incidence of acute exacerbation of IPF.

This study found that TCM ion introduction can reduce the incidence of acute exacerbation of IPF. IPF patients are prone to acute exacerbation, and AE is the main cause of death in IPF.[36] The survival period of IPF patients is relatively short,[37] and clinical epidemiological data is scarce. There are few studies on the relationship between TCM ion introduction and reducing the incidence of acute exacerbation of IPF. Although we have taken some measures to control the influencing factors, there may still be a mutual influence between the subjects' other drug treatments and TCM ion therapy, which may lead to some deviation in the results. Please refer to the Supplementary Materials for detailed measures to control influencing factors. Further exploration is needed through large-scale, multicenter, and high-quality research. In terms of hospitalization time, the comparison between the two groups in this study showed that the hospitalization time of the exposed group was lower than that of the non exposed group, indicating that TCM ion introduction can shorten the hospitalization time to some extent. However, the sample size of this study is small, and only the first hospitalization time of patients is counted. The single hospitalization time of patients is easily affected by multiple factors. In the future, large sample studies are still needed to frequently count the hospitalization time of patients, and further exploration and verification are needed. This study found that iontophoresis of TCM can reduce the readmission rate of IPF. Affected by novel coronavirus infection, readmission treatment of patients may be related to the acute exacerbation after novel coronavirus infection, but this study can still provide some reference for the study of reducing the incidence of acute exacerbation of IPF. This study suggests that TCM ion therapy can delay the onset of acute exacerbation in patients with IPF.

In this study, there was no statistical significance in the case fatality rate between the two groups. There were 3 deaths due to AE-IPF, and 1 deaths due to novel coronavirus infection. Consistent with previous research findings, studies have shown that the main cause of death in IPF patients is acute exacerbation.[38,39] Novel coronavirus infection poses a great threat to human health.[40] IPF patients may suffer from acute exacerbation due to novel coronavirus infection.[41] A large number of clinical studies have found that in the recovery period of novel coronavirus infection, some patients' chest CT showed signs of pulmonary fibrosis, especially in severe patients.[42–44] A total of 4 patients died in this study. Consistent with previous research results, the prognosis of AE-IPF patients is poor.[45] Some studies have shown that the median survival period of AE-IPF patients is only 3–4 months. When the condition worsens and acute exacerbation occurs, the mortality rate of patients during hospitalization is higher, even reaching 55% to 80%.[46] The patient reported outcome developed by the research team[46,47] based on TCM theory and in accordance with international standards can not only reflect the health status of patients, but also reflect the factors of concern in diagnosis and treatment, providing a certain basis for the clinical efficacy evaluation of IPF patients. The exposed group outperformed the non exposed group in reducing scores in physiological, psychological, and environmental domains, and the exposed group showed statistical significance compared to the non exposed group at different time points. There was a statistically significant difference in satisfaction scores between the two groups after 12 months of discharge, but there was no significant effect during the follow-up period between the exposure group at discharge and admission.

Limitation

The IPF patients in this study only came from three hospitals, and the severity of the disease and treatment status of the study subjects may not necessarily reflect the characteristics of the overall affected population; This study used telephone follow-up to inquire about the patient's acute exacerbation within the past year, and the patient may have recall bias. Although there are many methods for using TCM external treatment to treat IPF, there are relatively few studies on the use of TCM ion therapy for IPF, and the level of attention paid to the treatment of IPF is still insufficient. Further attention needs to be paid to the treatment of IPF, scientific clinical trial design should be carried out, standardized acupoint selection should be strengthened, unified efficacy evaluation standards should be established, and multi center, large sample, and high-quality randomized controlled trials should be conducted for validation, fully leveraging the advantages of TCM ion introduction.

Conclusion

Compared to the non exposed group, TCM ion introduction can reduce the annual incidence of acute exacerbation of IPF patients. Hospitalization time, readmission rate, time to first acute exacerbation, quality of life improved, but mortality and all-cause mortality rates did not improve.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

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.

Funding

The study was supported by the National Key Research and development Program (No. 2023YFC3502601), Natural Science Foundation of Henan Youth Fund (No. 212300410056), National Natural Science Foundation of China (No.81830116), Henan Province Scientific Research Project - Double First-Class Traditional Chinese medicine (HSRP-DFCTCM-2023-3-16, DFCTCM-2023-4-05), Special Project of Traditional Chinese Medicine Research of Henan Province (20-21ZY2186), Special Project of Traditional Chinese Medicine Research of Henan Province (2023ZY2055), the Henan Province Medical Science and Technology Program (No.LHGJ20220586) and Henan Province Second Batch of Top-notch Chinese Medicine Talent Projects (2021 No.15).

Disclosure

The authors declared no conflicts of interest for this work.

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