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Efficacy of Shugan Hewei formula combined with rabeprazole in refractory gastroesophageal reflux disease: randomized, double-blind, placebo-controlled trial

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Abstract

Objectives To assess the efficacy of the Chinese herbal medication Shugan Hewei formula (SHF) combined with rabeprazole in patients with refractory gastroesophageal reflux disease (rGERD).

Method A total of 264 participants were randomly assigned to the treatment group ($n=132$) receiving SHF granules (20 mg) combined with rabeprazole (10 mg) and the control group ($n=132$) receiving placebo SHF granules (20 mg) combined with rabeprazole (20 mg). Both groups undergo 8 weeks of treatment and 2 weeks of follow-up.

Results The treatment group showed higher total clinical symptom efficacy and lower total symptom scores compared to the control group. The treatment group was superior to the control group in reducing rGERD major symptom scores, including heartburn, retrosternal pain, regurgitation and belching, and acid regurgitation. Additionally, treatment group ($Z=8.169$, $P<0.001$) and control group ($Z=9.800$, $P<0.001$) treatments were all significantly attenuated esophageal inflammation, demonstrating comparable efficacy. Patients with esophagitis grade A decreased from 40.34% to 17.23%, and those with grade B decreased from 11.76% to 3.78% in the treatment group. The results of the SF-36 scale showed that combination therapy was more effective in improving role limitations due to physical health, vitality, general health, total somato-physical health, and psychiatric mental health.

Conclusion Our study reveals that the combined treatment of SHF with rabeprazole is more efficacious in managing patients with rGERD when contrasted with sole rabeprazole treatment.

Keywords Chinese herbal medicine, Proton pump inhibitor, SF-36 quality of life scale

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Introduction

Gastroesophageal reflux disease (GERD) is a comprehensive disease with reflux symptoms caused by reflux of gastric or duodenal contents into the esophagus or pharynx [1]. The current prevalence of GERD varies, ranging from 8 to 33%, and it is anticipated that this prevalence will continue to increase in the future [2]. The pharmaceutical approach to managing GERD focuses on reducing gastric acid secretion and preventing exposure of the esophagus to acid [3]. Proton pump inhibitors (PPIs) are the preferred medication for managing GERD as they can effectively decrease acid reflux [4, 5]. Nevertheless, it is essential to note that PPIs provide relief for only about half of individuals with reflux symptoms [5, 6]. The ineffectiveness of double-dose PPIs for more than 4 weeks of continuous treatment, coupled with symptoms such as retrosternal heartburn or regurgitation occurring at least 3 times per week, is often referred to as refractory GERD (rGERD), even though rGERD has never been distinctly defined [7–9]. The rGERD significantly affects the quality of life and places a substantial burden on healthcare resources, making it a prominent health concern [10]. Therefore, it is imperative to explore supplementary or alternative treatments to enhance treatment outcomes for individuals with rGERD.

Traditional Chinese medicine (TCM), known for its lower occurrence of adverse effects and demonstrated therapeutic benefits, has gained widespread acceptance and extensive research in many Asian countries. It has been widely applied for the treatment of GERD in China [11]. Various TCM improve symptoms in GERD patients. Modified Xiaochaihu Decoction, BanxiaXiexin Decoction, and Hewei Jiangni Decoction all relief symptoms in GERD patients [12–14]. In addition, the combination of TCM and traditional Western medicine may be a potentially effective strategy in the treatment of rGERD. Combined treatment of rikkunshito and rabeprazole significantly reduced mental component summary scores and improved acid-related dysmotility symptoms in female and elderly patients with non-erosive reflux disease refractory [15]. The combination of Sini Zuojin Decoction and traditional gastric medication shows superiority over traditional gastric medication alone, particularly in improving symptoms like heartburn, retrosternal chest pain, acid reflux, and regurgitation [16]. Consequently, exploring the combination of TCM and Western medicine treatment holds significant importance in enhancing the therapeutic outcomes for patients with rGERD.

In the present study, we explored the efficacy of SHF combined with rabeprazole in the treatment of rGERD. We found that SHF combined with rabeprazole was more efficacious than rabeprazole alone in improving the symptoms and enhancing the quality of life of patients with rGERD. The efficacy and safety of SHF combined with rabeprazole in the treatment of rGERD are significant, suggesting that it could be used as a combination of traditional Chinese and Western medicine for the treatment of rGERD.

Methods

Study design

This clinical trial was conducted in strict accordance with the Declaration of Helsinki (Edinburgh 2000 version) and relevant Chinese clinical trial research norms and regulations. The study protocol received approval from the Ethics Committee of Yueyang Hospital of Integrative Medicine affiliated with Shanghai University of Traditional Chinese Medicine (Ethics No. 2013-060). The written informed consent was obtained from all participating patients. The subjects for this study were sourced from outpatients and inpatients at Yueyang Hospital of Integrative Medicine affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, and Shuguang Hospital of Shanghai University of Traditional Chinese Medicine. All participating investigators received standardized training in accordance with standard operating procedures (SOP) for clinicians. The study followed the principles of center-stratified paired randomized grouping. Case collection began in April 2014 and ended in March 2016.

Inclusion criteria: (1) This study included patients diagnosed with rGERD [Los Angeles (LA) Classification grade A–D] as confirmed by endoscopic examination. The patient exhibits typical symptoms related to rGERD, such as heartburn, acid reflux, burning sensation behind the sternum, belching, difficulty swallowing or throat discomfort, esophageal inflammation-related issues, like coughing during sleep or lying flat, and inflammation confirmed by endoscopy and biopsy from pathological examination after 8 weeks of PPI therapy. (2) Meeting the diagnostic criteria for TCM: referring to the consensus opinions of Chinese gastroesophageal reflux disease experts (2009 edition). (3) Those who have failed to take four or more consecutive weeks of standard-dose first-generation PPIs for GERD prior to this study. (4) Individuals aged 18 to 70 years, with no gender restrictions. (5) Patients who signed the informed consent.

Exclusion criteria: (1) Patients with the following medical conditions: peptic ulcer; gastrinoma; malignant lesions in the upper gastrointestinal tract; had a history of gastroesophageal and duodenal surgery; primary esophageal disorders (such as esophageal achalasia scleroderma, primary esophageal spasms); drug-induced esophagitis; individuals with psychiatric disorders. (2) Pregnant and lactating women. (3)

Individuals with liver or kidney function abnormalities exceedingly twice the normal reference range for aspartate aminotransferase (AST), alanine aminotransferase (ALT), or creatinine are excluded. (4) Patients with possible esophageal functional diseases other than GERD were excluded using high-resolution esophageal manometry.

24-h esophageal pH monitoring

The 24-h esophageal pH monitoring was performed using an antimony pH catheter (Orion-Ohmega, the Netherlands). The sensor was positioned 5 cm above the lower esophageal sphincter and secured with tape on the nose and neck. Patients were told to keep their usual diets, avoiding acidic foods and alcohol, and not to take any medications that might interfere with the results.

To calculate the distal pH variables, the DeMeester score was employed, assessing the percentage of total time with pH < 4, the longest reflux event, the number of reflux events longer than 5 min, and the number of reflux episodes in 24 h. A DeMeester score > 14.72 indicated significant esophageal acid exposure. An elevated classification level of rGERD resulted in a higher DeMeester score (Supplementary Fig. 1).

SHF reagents and groupings

Granules of LHF and dummy SHF were sourced from Jiangyin Tianjiang Pharmaceutical Co., Ltd (Jiangsu, China). SHF included 12 Chinese herbs: *Spinosa pedunculata*, *Magnolia officinalis*, *Coptis chinensis*, *Evodia rutaecarpa*, *ginger*, *Concha arcae*, *Inula japonica Thunb*, *radix bupleuri*, *Corydalis yanhusuo*, *Cyperus rotundus*, *Gardenia jasminoides*, *Fructus Aurantii*, and *Polygonatum sibiricum*. The dummy SHF granules were formulated by cyclodextrin (90%), the SHF (5%), food colorants, and bitters using the same manufacturing procedure as the genuine therapeutic medication. The dummy SHF granules was essentially the same in appearance, size, color, dosage form, weight, taste and odor as the SHF granules. This study included two groups: the treatment group, which received treatment with SHF granules (20 mg) in combination with rabeprazole capsules (10 mg), and the control group, which received treatment with equal doses of dummy SHF (20 mg) and rabeprazole capsules (20 mg). In the treatment group, the SHF granules were reconstituted with 100 mL of warm water, and taken orally once a day in two divided doses. The SHF granules and rabeprazole capsules were taken more than 30 min apart each time. The control group received the same treatment regimen as the treatment group. The entire treatment lasted 8 weeks.

Variable assignment

(1) Center: Yueyang Hospital of Integrative Medicine affiliated with Shanghai University of Traditional Chinese Medicine was "1"; Shanghai University of Traditional Chinese Medicine was "2"; Shuguang Hospital of Shanghai University of Traditional Chinese Medicine was "3". (2) Groups: Treatment group was "1"; Control group was "2". (3) Gender: Male was "1"; Female was "2". (4) Age: 18–44 years old was "1"; 45–59 years old was "2"; 60–70 years old was "3". (5) Obesity level: Lean (BMI < 18.5) was "1"; Normal (BMI: 18.5–23.9) was "2"; Overweight (BMI: 23–24.9) was "3"; Obesity (BMI: 25–29.9) was "4". (6) Course of disease (BC): Less than 1 year was "1"; 1–2 years was "2"; 2–3 years was "3"; More than 3 years was "4".

Sample size estimation

Based on the clinical experience, the effective rate of GERD after 8 weeks of treatment with rabeprazole was 58.3%. The trial was planned to perform a superiority test of two independent sample proportions, employing a margin of 0.02, with an alpha risk of 0.05 and a beta risk of 0.20, while taking into account an anticipated attrition rate of about 20%. Consequently, the estimated sample size required for the study was $N = 264$, with an equal 1:1 ratio of 132 patients in both the treatment and control groups.

Randomization and blinding

To ensure that the key influencing factors were balanced between the groups, this study considered two primary factors: gender and disease type. We used these factors for stratified randomization, pairing them based on the treatment center. Furthermore, a statistician affiliated with Shanghai University of Traditional Chinese Medicine, who was not part of the clinical trial team, oversaw the blinded randomization of drug allocation. Random sequences for the allocation of participants into the treatment and control groups were generated using SPSS 21.0 statistical software. The number of blinded cases was 264, divided into treatment and control groups of 132 cases each. Each subject's drug box received a unique number, and an emergency letter was prepared for each case. The envelope holding the emergency letter was clearly marked with the patient's center number, patient number, drug code, and randomization number. It also showed the patient's assigned group and the exact medication type and dosage for that group in case of emergency unblinding. These emergency letters were given to each study center with the study medication and were kept by the principal investigator at each center. In the event of severe adverse events or complications occurring during

the clinical trials, the blinding of the study should be promptly unsealed, and instances of unblinding should be considered as cases of participant dropout. Before the trial was over, the amount of blind leakage or emergency letter opening could not exceed 20%.

Allocation

The process of randomization was handled by a person responsible for issuing the appropriate drugs according to the subject's number and randomization number, without altering the order of drug numbers. The implementation of randomization was managed as part of the quality control of the clinical study.

Baseline scoring

The baseline levels of the treatment and control groups were assessed by measuring the following indicators: demographic characteristics (gender, age, BMI index), medical history data (type of PPI administration before enrollment, duration of PPI administration, concomitant medication for GERD, allergic history, concomitant diseases, and treatment of concomitant diseases), vital signs (temperature, breathing, heart rate, systolic pressure, and diastolic pressure), and physical examination (digestive system, circulatory system, respiratory system, nervous system, endocrine system, skeletal system, urogenital system).

Clinical symptom scoring

In this study, the GERD-Q scores mainly included clinical symptom scoring and SF-36 scoring. The scoring method was employed to assess each efficacy indicators. The clinical symptom score was developed following the diagnostic criteria outlined in the 2006 China Consensus on Gastroesophageal Reflux Disease and adheres to the "Guiding Principles for Clinical Research of New Traditional Chinese Medicine". (Supplementary Table 1). In addition, electronic endoscopic scoring was employed to assess the improvement of esophageal mucosa before and after treatment using the LA Classification [17]. The definitions for each category within the LA Classification: (1). recovery (esophageal mucosa appeared normal under endoscopy); significant effect (2 points); effective (1 points); invalid (score of 0 or negative).

Criteria for determining symptomatic efficacy

The clinical efficacy was evaluated as follows: recovery: regurgitation symptoms have completely disappeared, and the symptom score has been reduced by $\geq 95\%$; marked efficacy: reflux symptoms have essentially disappeared, with occasional symptoms that quickly vanish, and the symptom score has been reduced by $\geq 70\%$; effective: reflux symptoms have not disappeared but have decreased, and the symptom score has been reduced by $\geq 30\%$; ineffective: reflux symptoms have not disappeared, and the symptom score has been reduced by $< 30\%$.

Quality of life scoring

The SF-36 scale mainly reflects patients' quality of life from eight dimensions, specifically including physical functioning (PF); role limitations due to physical health (RP); role limitations due to emotional problems (RE); vitality (VT); mental health (MH); social functioning (SF); body Pain (BP); general health (GH). Two comprehensive scores were calculated by integrating eight dimensions, namely the physical component summary (PCS) and the mental component summary (MCS). Among them, PCS included PF, RP, BP, and GH, representing the overall physiological health score. MCS included VT, SF, RE, and MH, representing the overall mental health score. Ultimately, the accumulated points were transformed into a conclusive score ranging from 0 to 100, standard score = (actual score − lowest possible score/general average possible score) × 100. A higher score signified an enhanced quality of life, while a lower score implied a diminished quality of life.

Safety indicator detection

Following 8 weeks of treatment, patients underwent comprehensive testing, including blood, urine, and fecal routine tests, evaluation of liver function (ALT and AST), assessment of renal function (Cr and BUN), as well as electrocardiogram examinations.

Endpoints

The primary endpoint was clinical symptoms total efficacy, and secondary endpoints included clinical symptom score, SF-36 score, safety indicator, and adverse events.

Follow-up

The treatment duration was 8 weeks, followed by a 2-week follow-up period. Detailed information is shown in Supplementary Table 2.

Analytical planning

The full analysis set (FAS) primarily comprised eligible cases and dropout cases while excluding excluded cases. This analysis set consisted of cases who have taken the investigational drug at least once and have at least one baseline efficacy data. The per-protocol set (PPS) was a subset of the FAS, comprising cases that meet inclusion criteria, did not meet exclusion criteria, and completed the treatment plan. Safety set (SS) referred to actual data from at least one treatment with documented safety indicators. Statistical analysis was conducted on the clinical

efficacy, endoscopic mucosal improvement, and quality of life of this study based on the FAS and PPS datasets.

Statistical analysis

Hypothesis tests were conducted using a two-tailed test, with statistical significance set at $P \leq 0.05$. Data analysis was performed using SPSS 21.0. The confidence interval was set at 95%. In descriptive statistical analysis, normally distributed data were described using mean ± standard deviation (mean ± SD), and the range with minimum and maximum values (min, max). Non-normally distributed data were described using the median (M), lower quartiles (P25), upper quartiles (P75), and the range with minimum and maximum values (min, max). Statistical comparisons between the two groups for categorical variables was conducted using the Chi-squared test, Fisher's exact probability method, and the Wilcoxon rank-sum (WRS) test. The t-test was used to compare continuous variables that conformed to a normal distribution. The Wilcoxon rank-sum test was employed for comparing those that conformed to a non-normal distribution. Multiple parametric groups were compared using a one-way analysis of variance (ANOVA) test. For comparing continuous observation indicators at multiple time points between groups, a generalized estimation equation (GZZ) was used.

Results

Demographic factors and baseline characteristics

The present study was conducted between April 2014 and March 2016, involving a total of 264 cases from three different hospitals: Yueyang Hospital of Integrative Medicine affiliated with Shanghai University of Traditional Chinese Medicine (150 patients); Shanghai Hospital of Traditional Chinese Medicine (72 patients); and Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine (42 patients). These patients were suffering from rGERD. Patients from each of the three hospitals were randomly divided into treatment and control groups in a 1:1 ratio. Ultimately, the treatment group consisted of 132 patients, and the control group also included 132 patients. During the study period, a total of 22 patients were shed and the dislodgement rate was 8.33%, which included 11 lost to follow-up, 8 cases refused treatment, 2 patients left due to adverse events, and 1 case were pregnant (Tables 1and 2). There were no statistically significant differences in demographic characteristics (gender, age, BMI index), medical history data (type of PPI administration before enrollment, duration of PPI administration, concomitant medication for rGERD, allergic history, concomitant diseases, and treatment of concomitant diseases), as well as vital signs and physical examination results (Tables 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14).

SHF combined with rabeprazole treatment improved clinical symptoms total efficacy of rGERD patients

As the trends in the results of the FAS and PPS data analyses were essentially identical, the subsequent data analysis primarily relied on the FAS data analysis. WRS test showed that after 2 weeks of treatment, there was no significant difference in clinical efficacy between the treatment and control groups ($Z=0.248$, $P=0.804$). After 4 weeks, 6 weeks, and 8 weeks of treatment, there were statistically significant differences in clinical efficacy between the two groups ($Z=1.964$, $P=0.050$ at

Table 1 Distribution of case shedding and excluding in three centers

Centers	Groups	Number of participants	Shedding		Excluding		Statistics
			Numbers	Rate of shedding (%)	Numbers	Rate of excluding (%)	
Yueyang Hospital	Treatment group	75	5	6.67	0	0.00	70
	Control group	75	7	9.33	0	0.00	68
	Totals	150	12	8.00	0	0.00	138
Shanghai Hospital of Traditional Chinese Medicine	Treatment group	36	4	11.11	0	0.00	32
	Control group	36	2	5.56	0	0.00	34
	Totals	72	6	8.33	0	0.00	66
Shuguang Hospital	Treatment group	21	3	14.29	0	0.00	18
	Control group	21	1	4.76	0	0.00	20
	Totals	42	4	8.52	0	0.00	38
Totals	Treatment group	132	12	9.09	0	0.00	120
	Control group	132	10	7.58	0	0.00	122
	Totals	264	22	8.33	0	0.00	242

Table 2 Case-specific causes of shedding and excluding

Numbers	Drug No.	Groups	Centers	Shedding/excluding	Reason	Whether to enter the dataset		
						FAS	PPS	SS
1	34	Treatment group	1	Shedding	Loss to follow-up	Yes	No	Yes
2	37	Control group	1	Shedding	Loss to follow-up	Yes	No	Yes
3	38	Treatment group	1	Shedding	Adverse event	Yes	No	Yes
4	45	Treatment group	1	Shedding	Treatment refusal	Yes	No	Yes
5	48	Treatment group	1	Shedding	Loss to follow-up	Yes	No	Yes
6	53	Control group	1	Shedding	Loss to follow-up	Yes	No	Yes
7	56	Control group	1	Shedding	Loss to follow-up	Yes	No	Yes
8	57	Control group	1	Shedding	Loss to follow-up	Yes	No	Yes
9	67	Control group	1	Shedding	Loss to follow-up	Yes	No	Yes
10	85	Treatment group	1	Shedding	Loss to follow-up	Yes	Yes	Yes
11	356	Control group	1	Shedding	Loss to follow-up	Yes	No	Yes
12	371	Control group	1	Shedding	Treatment refusal	Yes	No	Yes
13	202	Control group	2	Shedding	Treatment refusal	Yes	No	Yes
14	208	Treatment group	2	Shedding	Loss to follow-up	Yes	No	Yes
15	227	Treatment group	2	Shedding	Treatment refusal	Yes	No	Yes
16	235	Treatment group	2	Shedding	Pregnancy	Yes	No	Yes
17	246	Control group	2	Shedding	Treatment refusal	Yes	No	Yes
18	249	Treatment group	2	Shedding	Treatment refusal	Yes	No	Yes
19	306	Treatment group	3	Shedding	Loss to follow-up	Yes	No	Yes
20	328	Treatment group	3	Shedding	Treatment refusal	Yes	No	Yes
21	330	Treatment group	3	Shedding	Adverse event	Yes	No	Yes
22	331	Control group	3	Shedding	Treatment refusal	Yes	No	Yes

Table 3 Comparison of gender composition between two groups

Datasets	Groups	Numbers	Male	Female	χ^2	*P*
FAS	Treatment group	132	71(53.8)	61(46.2)	0.061	0.805*
	Control group	132	73(55.3)	59(44.7)		
	Totals	264	144(54.5)	120(45.5)	–	–
PPS	Treatment group	120	68 (56.7)	52(43.3)	0.161	0.688*
	Control group	122	66(54.1)	56(45.9)		
	Totals	242	134(55.4)	108(44.6)	–	–

*Represents $P > 0.05$

Table 4 Comparison of the age of patients in the two groups

Datasets	Groups	Numbers	$\bar{x} \pm s$	Min	Max	*t*	*P*
FAS	Treatment group	132	53.32 ± 12.54	22.34	70.17	1.341	0.181*
	Control group	132	51.29 ± 12.00	21.14	70.10		
	Totals	264	52.30 ± 12.29	21.14	70.17	–	–
PPS	Treatment group	120	53.83 ± 12.35	22.34	70.17	1.379	0.169*
	Control group	122	51.68 ± 11.95	21.14	70.10		
	Totals	242	52.75 ± 12.17	21.14	70.17	–	–

*Represents $P > 0.05$

Table 5 Comparison of obesity levels between the two groups

Datasets	Groups	Numbers	Lean	Normal	Favor obese	Obesity	Severe obesity	Mean rank	*Z*	*P*
FAS	Treatment group	132	12	63	37	16	4	136.22	0.871	0.384*
	Control group	132	7	78	33	12	2	128.78		
	Totals	264	19	141	70	28	6	–	–	–
PPS	Treatment group	120	11	58	32	15	4	125.10	0.793	0.428*
	Control group	122	6	71	32	11	2	117.96		
	Totals	242	17	129	64	26	6	–	–	–

*Represents $P > 0.05$

Table 6 Comparison of disease duration (months) between the two groups

Datasets	Groups	Numbers	M	Q1	Q3	Min	Max	Mean rank	*Z*	*P*
FAS	Treatment group	132	36	12.0	60.0	5	240	134.67	0.466	0.641*
	Control group	132	24	12.0	60.0	3	240	130.33		
	Totals	264	36	12.0	60.0	3	240	–	–	–
PPS	Treatment group	120	36	12.0	60.0	5	240	125.28	0.837	0.402*
	Control group	122	24	12.0	60.0	3	240	117.79		
	Totals	242	36	12.0	60.0	3	240	–	–	–

*Represents $P > 0.05$

Table 7 Comparison of the composition of the types of PPIs taken before enrollment between the two groups

Datasets	Groups	Numbers	Omeprazole	Lansoprazole	Pantoprazole	χ^2	*P*
PAS	Treatment group	132	90	28	14	1.673	0.433*
	Control group	132	89	34	9		
PPS	Treatment group	120	83	26	11	0.829	0.661*
	Control group	122	81	32	9		

*Represents $P > 0.05$

Table 8 Comparison of the course of PPI administration before enrollment

Datasets	Groups	Numbers	4 weeks	8 weeks	12 weeks	Half a year	One year	χ^2	*P*
FAS	Treatment group	132	17	40	32	21	22	4.966	0.288*
	Control group	132	22	52	28	13	17		
PPS	Treatment group	120	14	34	29	21	22	7.990	0.092*
	Control group	122	20	49	26	11	16		

*Represents $P > 0.05$

Table 9 Comparison of comorbid medications prior to enrollment

Datasets	Groups	Numbers	No co-medication	H2-receptor antagonists	Gastric mucosal protector	Prokinetic drugs	χ^2	*P*
FAS	Treatment group	132	36	3	37	56	1.509	0.680*
	Control group	132	32	1	38	61		
PPS	Treatment group	120	32	3	33	52	1.361	0.715*
	Control group	122	30	1	37	54		

*Represents P > 0.05

Table 10 Comparison of allergy history between the two groups

Datasets	Groups	Numbers	No history of allergies	Have a history of allergies	χ^2	*P*
FAS	Treatment group	132	125	7	1.841	0.175*
	Control group	132	130	2		
PPS	Treatment group	120	114	6	2.423	0.120*
	Control group	122	121	1		

*Represents $P > 0.05$

Table 11 Comparison of concomitant diseases in the two groups

Datasets	Groups	Numbers	Comorbidity		χ^2	*P*
			No	Yes		
FAS	Treatment group	132	86	46	0.850	0.356*
	Control group	132	93	39		
PPS	Treatment group	120	80	40	0.411	0.522*
	Control group	122	86	36		

*Represents P > 0.05

Table 12 Comparison of treatment of concomitant diseases in the two groups

Datasets	Groups	Number of combined diseases	Whether to treat		χ^2	*P*
			No	Yes		
FAS	Treatment group	46	23	23	0.125	0.724*
	Control group	39	18	21		
PPS	Treatment group	120	17	23	0.029	0.864*
	Control group	122	16	20		

*Represents $P > 0.05$

Table 13 Comparison of vital signs between the two groups (FAS)

Vital signs	Groups	Numbers	$\bar{x} \pm s$	*t*	*P*
Temperature	Treatment group	132	36.76 ± 0.27	0.260	0.795*
	Control group	132	36.76 ± 0.26		
Breathing	Treatment group	132	16.89 ± 1.81	0.100	0.920*
	Control group	132	16.92 ± 1.88		
Heart rate	Treatment group	132	75.20 ± 8.21	1.894	0.059*
	Control group	132	73.30 ± 8.11		
Systolic pressure	Treatment group	132	120.98 ± 8.73	0.828	0.408*
	Control group	132	120.16 ± 7.25		
Diastolic pressure	Treatment group	132	77.12 ± 6.36	0.715	0.475*
	Control group	132	76.58 ± 6.03		

*Represents $P > 0.05$

4 weeks; $Z = 2.054$, $P = 0.040$ at 6 weeks; and $Z = 9.422$ at 8 weeks; $P < 0.05$; Table 15). Additionally, the results of the GEE analysis revealed a statistically significant difference between the treatment group and the control group (Wald $\chi^2 = 25.657$, $P < 0.001$). The clinical efficacy of the treatment group was significantly better than that of the control group. The repeated measurement ANOVA (rmANOVA) also revealed significant differences in clinical efficacy between the two groups at various time points, including 2 weeks, 4 weeks, 6 weeks, 8 weeks treatments (Wald $\chi^2 = 272.697$, $P < 0.001$). Notably, the clinical efficacy became increasingly pronounced as the treatment duration extended in two groups (Table 16).

SHF combined with rabeprazole treatment reduced total symptom scores

There were no differences in total symptom scores between the treatment and control groups before interventions ($F = 0.549$, $P = 0.459$), suggesting the same baseline between the two groups. WRS test showed that

Table 14 Comparison of the 7 major systems of physical examination between the two groups of patients (FAS)

System	Groups	Numbers	Normal or not		χ^2	*P*
			Normal	Abnormal		
Digestive system	Treatment group	132	132	0	0.000	1.000*
	Control group	132	131	1		
Circulatory system	Treatment group	132	130	2	0.000	1.000*
	Control group	132	130	2		
Respiratory system	Treatment group	132	132	0	–	–
	Control group	132	132	0		
Nervous system	Treatment group	132	132	0	–	–
	Control group	132	132	0		
Endocrine system	Treatment group	132	132	0	–	–
	Control group	132	132	0		
Skeletal system	Treatment group	132	131	1	0.000	1.000*
	Control group	132	132	0		
Urogenital system	Treatment group	132	131	1	0.000	1.000*
	Control group	132	132	0		

*Represents $P > 0.05$

Table 15 Comparison of efficacy between the two groups at different times (FAS)

Treatment time	Group	Recovery	Marked efficacy	Effective	Ineffective	Totals	Mean rank	*Z*	*P*
2 weeks	Treatment group	1	14	77	34	126	127.00	0.248	0.804△
	Control group	0	13	81	35	129	128.97		
4 weeks	Treatment group	2	49	67	5	123	116.11	1.964	0.050*
	Control group	2	37	73	12	124	131.83		
6 weeks	Treatment group	13	66	41	1	121	113.66	2.054	0.040*
	Control group	6	62	48	6	122	130.27		
8 weeks	Treatment group	72	42	6	0	120	81.60	9.422	< 0.001**
	Control group	8	64	44	6	122	160.75		

△ represents $P > 0.05$, *Represents $P \leq 0.05$, and **Represents $P \leq 0.001$

Table 16 Generalized estimating equation to estimate the total efficacy of clinical symptoms (FAS)

Parameter	*B*	Standard error	Hypothesis-testing			Exp(B)	95% Exp (B) confidence interval	
			Wald χ^2	df	*P*		Lower limit	Upper limit
[zzlxfj12 = 1]	− 4.254	0.2308	339.809	1	0.000	0.014	0.009	0.022
[zzlxfj12 = 2]	− 1.650	0.1910	74.633	1	0.000	0.192	0.132	0.279
[zzlxfj12 = 3]	1.496	0.1791	69.774	1	0.000	4.464	3.142	6.341
[group = 2]	0.937	0.1850	25.657	1	0.000**	2.553	1.776	3.669
[group = 1]	0					1		
[time = 5]	− 3.733	0.2312	260.721	1	0.000**	0.024	0.015	0.038
[time = 4]	− 2.495	0.1749	203.464	1	0.000**	0.083	0.059	0.116
[time = 3]	− 1.510	0.1429	111.630	1	0.000**	0.221	0.167	0.292
[time = 2]	0					1		

**Represents $P \leq 0.001$

there was a statistically significant difference between pre-treatment and 8 weeks of treatment in both the treatment group ($F=435.172$, $P<0.001$) and the control group ($F=322.442$, $P<0.001$). At 6 weeks of treatment ($F=5.579$, $P=0.019$) and 8 weeks of treatment ($F=74.490$, $P<0.001$), a statistically significant difference emerged between the two groups, with the treatment group demonstrating superiority over the control group (Table 17). Results from the rmANOVA analysis indicated a statistically significant divergence between the total clinical symptom scores of all patients before and after treatment ($F=752.547$, $P<0.001$). Furthermore, there was an interaction between time and group ($F=13.565$, $P<0.001$; Table 18). Based on the graph, both the treatment group and the control group showed a similar decreasing trend in total clinical symptom scores before, after 2 weeks, and after 4 weeks treatment. However, the treatment group exhibited a faster reduction in total clinical symptom scores at 6 weeks and 8 weeks of treatment (Fig. 1).

Table 18 Repeated measures ANOVA results of total clinical symptom scores in the two groups (FAS)

Source of variation	SS	df	MS	*F*	*P*
Time	51,168.618	2.111	24,243.960	752.547	< 0.001**
Time*group	922.337	2.111	437.008	13.565	< 0.001**
Intra-group error	16,318.529	506.537	32.216	–	–
Groups	389.118	1	389.118	3.028	0.083△
Inter-group error	30,838.215	240	128.493	–	–

△ represents $P>0.05$, *Represents $P<0.05$, and **Represents $P\leq0.001$

SHF combined with rabeprazole treatment reduced major symptom scores

Subsequently, we investigated the impact of SHF on primary symptoms of rGERD, which encompassed heartburn, retrosternal pain, regurgitation and belching, and acid regurgitation. Before the interventions, there were no differences in these main symptoms between the treatment and control groups ($P>0.05$), which indicated that baseline was same for both groups. WRS test showed that after 2 weeks, 4 weeks, and after 6 weeks of treatment, there was no statistically significant difference in these main symptoms between the two groups ($P>0.05$). After 8 weeks of treatment, a statistically significant difference was observed in these main symptoms between the two groups of patients ($P<0.05$). Based on the mean rank, it could be concluded that the treatment group exhibited superior efficacy in managing these main symptoms compared to the control group. The results of the GEE analysis showed that there was no statistically significant difference between the treatment and control groups in the main symptom scores of heartburn, retrosternal pain, regurgitation and belching, and acid regurgitation after 8 weeks of treatment ($P>0.05$). Furthermore, compared with pre-treatment, the results of the rmANOVA revealed statistically significant differences in these symptom scores both in the two groups after 2 weeks, 4 weeks, 6 weeks, and 8 weeks of treatment ($P<0.05$). Moreover, as the treatment duration increased, both groups showed improved treatment effects (Tables 19, 20, 21, 22, 23, 24, 25and26).

SHF combined with rabeprazole treatment improved reflux esophagitis

WRS test showed that there were no differences in the incidence of reflux esophagitis between the treatment and control groups prior to the interventions ($F=0.129$, $P=0.897$), indicating that all groups had the same baseline. After 8 weeks treatment, there was no statistically significant difference in the severity of reflux esophagitis between the two groups ($F=1.410$, $P=0.159$; Table 27). After 8 weeks of treatment, compared with pre-treatment, there was a statistically significant difference in the both the treatment ($Z=8.169$, $P<0.001$) and control groups ($Z=9.800$, $P<0.001$; Table 28). Analysis based on the FAS indicated that in

Table 17 Comparison of total symptom scores between the two groups at different treatment times (FAS)

Groups	Statistic	Treatments before	Treatment for 2 weeks	Treatment for 4 weeks	Treatment for 6 weeks	Treatment for 8 weeks	Before-and-after comparison	
							F	*P*
Treatment group	$\bar{x}$	22.68	12.29	8.17	5.28	1.64	435.172	< 0.001**
	s	8.22	6.97	4.76	3.86	2.82		
Control group	$\bar{x}$	21.86	12.48	8.72	6.73	5.95	322.442	< 0.001**
	s	9.02	7.71	6.11	5.51	4.70		
Comparison between groups	*F*	0.549	0.038	0.619	5.579	74.490	–	–
	P	0.459△	0.846△	0.432△	0.019*	< 0.001**	–	–

△ represents $P>0.05$, *Represents $P<0.05$, and **Represents $P\leq0.001$

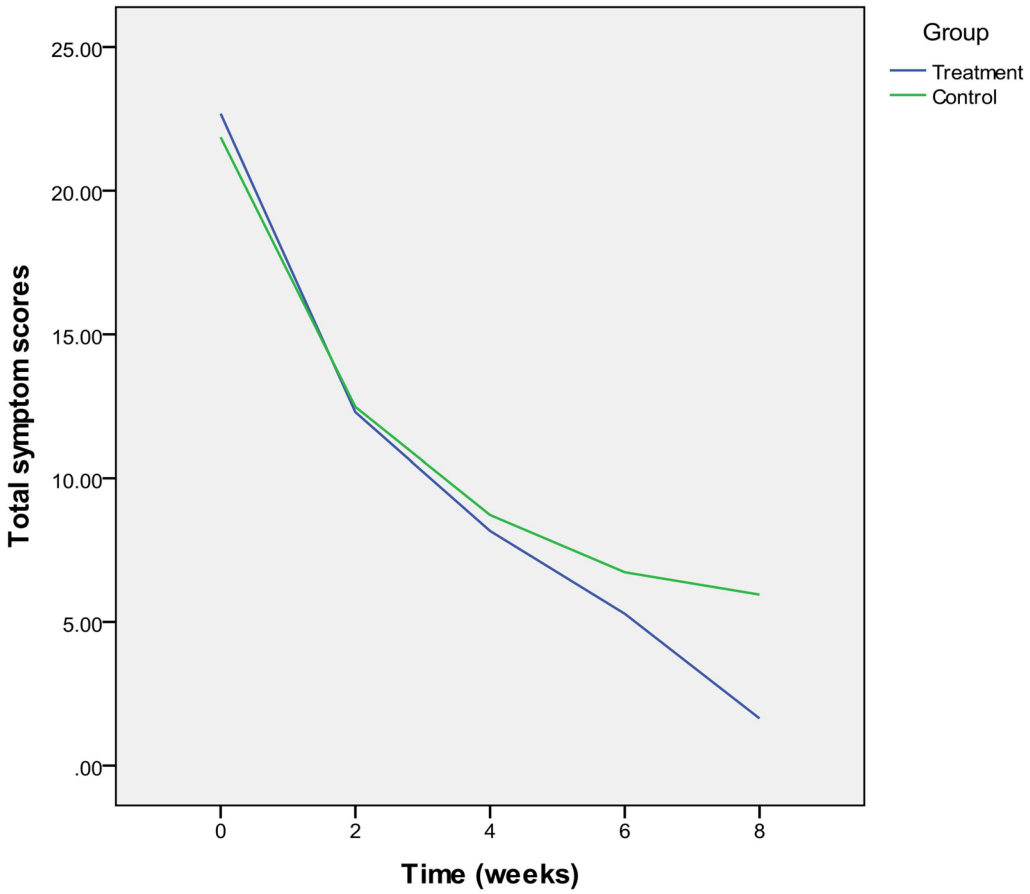

Fig. 1 Trends in total clinical scores at different times in two groups (FAS)

Table 19 Comparison of the degree of heartburn in the two groups at different times (FAS)

Treatment time	Group	0 points	2 points	4 points	6 points	Totals	Mean rank	*Z*	*P*
Pre-treatment	Treatment group	41	35	36	20	132	133.44	0.209	0.834△
	Control group	46	25	45	16	132	131.56		
2 weeks	Treatment group	71	40	13	2	126	128.17	0.042	0.966△
	Control group	74	38	14	3	129	127.83		
4 weeks	Treatment group	83	38	3	0	124	126.76	0.616	0.538△
	Control group	88	32	3	1	124	122.24		
6 weeks	Treatment group	100	20	2	0	122	117.98	1.396	0.163△
	Control group	91	28	3	0	122	127.02		
8 weeks	Treatment group	117	3	0	0	120	112.51	3.825	< 0.001**
	Control group	101	20	1	0	122	130.34		

△ represents $P > 0.05$, **Represents $P \leq 0.001$

the treatment group, patients with esophagitis grade A decreased from 40.34% to 17.23%, and those with grade B decreased from 11.76% to 3.78%. In the control group, patients with esophagitis grade A decreased from 40.25% to 15.35%, and those with grade B decreased from 11.20 to 2.49% (Fig. 2). This suggested that both groups exhibited similar efficacy in improving the degree of esophageal inflammation.

SF-36 scale reliability analysis

SF-36 was used to assess quality of life for patients with rGERD. The assessment of the SF-36 scale's

Table 20 Generalized estimating equations results of heartburn score (FAS)

Parameter	*B*	Standard error	Hypothesis-testing			Exp(B)	95% Exp (B) Confidence interval	
			Wald χ^2	df	*P*		Lower limit	Upper limit
[SX1 = 0]	− 1.035	0.176	34.740	1	0.000	0.355	0.252	0.501
[SX1 = 2]	0.556	0.162	11.811	1	0.001	1.744	1.270	2.395
[SX1 = 4]	2.209	0.216	104.909	1	0.000	9.104	5.966	13.893
[group = 2]	0.157	0.214	0.535	1	0.465△	1.170	0.769	1.780
[group = 1]	0					1		
[time = 5]	− 3.344	0.224	222.774	1	0.000**	0.035	0.023	0.055
[time = 4]	− 2.440	0.166	215.054	1	0.000**	0.087	0.063	0.121
[time = 3]	− 1.988	0.137	212.122	1	0.000**	0.137	0.105	0.179
[time = 2]	− 1.408	0.110	164.007	1	0.000**	0.245	0.197	0.303
[time = 1]	0					1		

△ represents $P > 0.05$, ** represents $P \leq 0.001$

Table 21 Comparison of the degree of retrosternal pain in the two groups at different times (FAS)

Treatment time	Group	0 points	2 points	4 points	6 points	Totals	Mean rank	*Z*	*P*
Pre-treatment	Treatment group	46	32	26	28	132	135.88	0.751	0.453△
	Control group	56	23	26	27	132	129.12		
2 weeks	Treatment group	69	35	18	4	126	131.35	0.809	0.418△
	Control group	80	24	21	4	129	124.73		
4 weeks	Treatment group	86	31	6	1	124	122.52	0.533	0.594△
	Control group	83	30	11	0	124	126.48		
6 weeks	Treatment group	99	21	2	0	122	118.47	1.237	0.216△
	Control group	91	28	3	0	122	126.53		
8 weeks	Treatment group	114	6	0	0	120	113.03	3.320	0.001**
	Control group	99	22	1	0	122	129.84		

△ represents $P > 0.05$, ** represents $P \leq 0.001$

Table 22 Results of generalized estimation equation for estimating retrosternal pain (FAS)

Parameter	*B*	Standard error	Hypothesis-testing			Exp(B)	95% Exp (B) Confidence interval	
			Waldχ^2	df	*P*		Lower limit	Upper limit
[XGHTT1 = 0]	− 0.726	0.1415	26.353	1	0.000	0.484	.367	0.638
[XGHTT1 = 2]	0.595	0.1403	17.993	1	0.000	1.813	1.377	2.387
[XGHTT1 = 4]	1.848	0.1752	111.308	1	0.000	6.347	4.503	8.947
[group = 2]	0.103	0.1250	0.675	1	0.411△	1.108	0.867	1.416
[group = 1]	0					1		
[time = 5]	− 2.809	0.2289	150.569	1	0.000**	0.060	0.038	0.094
[time = 4]	− 2.101	0.1920	119.699	1	0.000**	0.122	0.084	0.178
[time = 3]	− 1.600	0.1790	79.934	1	0.000**	0.202	0.142	0.287
[time = 2]	− 1.095	0.1755	38.952	1	0.000**	0.334	0.237	0.472
[time = 1]	0					1		

△ represents $P > 0.05$, **Represents $P \leq 0.001$

Table 23 Comparison of the degree of regurgitation and belching between two groups of patients at different times (FAS)

Treatment time	Group	0 points	2 points	4 points	6 points	Totals	Mean rank	*Z*	*P*
Pre-treatment	Treatment group	18	37	46	31	132	131.03	0.324	0.746△
	Control group	24	27	45	36	132	133.97		
2 weeks	Treatment group	43	51	26	6	126	123.31	1.064	0.288△
	Control group	38	51	32	8	129	132.59		
4 weeks	Treatment group	53	64	6	1	124	120.80	0.896	0.370△
	Control group	53	51	18	2	124	128.20		
6 weeks	Treatment group	76	44	2	0	122	117.24	1.349	0.177△
	Control group	68	45	8	1	122	127.76		
8 weeks	Treatment group	112	6	2	0	120	99.33	6.468	< 0.001**
	Control group	69	48	4	1	122	143.30		

△ represents $P > 0.05$, ** represents $P \leq 0.001$

Table 24 Results of generalized estimation equation for estimating regurgitation and belching (FAS)

Parameter	*B*	Standard error	Hypothesis-testing			Exp(B)	95% Exp (B) Confidence interval	
			Waldχ^2	df	*P*		Lower limit	Upper limit
[FWAQ1 = 0]	− 2.098	0.1615	168.773	1	0.000	0.123	0.089	0.168
[FWAQ1 = 2]	− .144	0.1354	1.129	1	0.288	0.866	0.664	1.129
[FWAQ1 = 4]	1.501	0.1525	96.930	1	0.000	4.488	3.328	6.051
[group = 2]	.445	0.1117	15.907	1	0.000**	1.561	1.254	1.943
[group = 1]	0					1		
[time = 5]	− 3.452	0.2060	280.813	1	0.000**	0.032	0.021	0.047
[time = 4]	− 2.760	0.1900	211.103	1	0.000**	0.063	0.044	0.092
[time = 3]	− 2.127	0.1799	139.699	1	0.000**	0.119	0.084	0.170
[time = 2]	− 1.451	0.1803	64.784	1	0.000**	0.234	0.165	0.334
[time = 1]	0					1		

**Represents $P \leq 0.001$

Table 25 Comparison of the degree of acid regurgitation in the two groups at different times (FAS)

Treatment time	Group	0 points	2 points	4 points	6 points	Totals	Mean rank	*Z*	*P*
Pre-treatment	Treatment group	37	30	47	18	132	135.61	0.688	0.491△
	Control group	42	33	37	20	132	129.39		
2 weeks	Treatment group	77	37	11	1	126	125.30	0.662	0.508△
	Control group	74	40	14	1	129	130.64		
4 weeks	Treatment group	91	31	1	1	124	125.35	0.247	0.805△
	Control group	93	28	2	1	124	123.65		
6 weeks	Treatment group	104	17	1	0	122	121.93	0.203	0.839△
	Control group	103	18	1	0	122	123.07		
8 weeks	Treatment group	114	6	0	0	120	116.05	2.365	0.018*
	Control group	105	17	0	0	122	126.86		

△ represents $P > 0.05$ and*represents $P \leq 0.05$

reliability revealed that the Cronbach's α for the pre-treatment scale exceeded 0.8, indicating a high level of reliability in the researcher's evaluation of the patients' health status. In the case of the post-treatment scale, Cronbach's α exceeded 0.8 across all groups, with the exceptions of 0.796 in the control group at the Shanghai Hospital of Traditional Chinese Medicine and 0.761 in the treatment group at Shuguang Hospital.

Table 26 Results of generalized estimation equation for estimating acid regurgitation (FAS)

Parameter	*B*	Standard error	Hypothesis-testing			Exp(B)	95% Exp (B) Confidence interval	
			Waldχ^2	df	*P*		Lower limit	zzz
[FS1 = 0]	− 1.223	0.1548	62.447	1	0.000	0.294	0.217	0.399
[FS1 = 2]	0.397	0.1412	7.921	1	0.005	1.488	1.128	1.962
[FS1 = 4]	2.051	0.1867	120.644	1	0.000	7.776	5.393	11.212
[group = 2]	0.064	0.1312	0.241	1	0.624△	1.066	0.825	1.379
[group = 1]	0					1		
[time = 5]	− 3.532	0.2531	194.811	1	0.000**	0.029	0.018	0.048
[time = 4]	− 3.008	0.2198	187.285	1	0.000**	0.049	0.032	0.076
[time = 3]	− 2.367	0.1920	151.951	1	0.000**	0.094	0.064	0.137
[time = 2]	− 1.657	0.1801	84.645	1	0.000**	0.191	0.134	0.271
[time = 1]	0					1		

△ represents $P > 0.05$, ** represents $P \leq 0.001$

Table 27 Comparison of severity of reflux esophagitis between the two groups at different times

Datasets	Treatment time	Group	0 grade	A grade	B grade	C grade	D grade	Totals	Mean rank	*Z*	*P*
FAS	Pre-treatment	Treatment group	0	96	28	7	1	132	132.97	0.129	0.897△
		Control group	0	97	27	7	1	132	132.03		
	8 weeks	Treatment group	53	41	9	1	0	104	112.85	1.536	0.125△
		Control group	66	37	6	0	0	109	101.42		
PPS	Pre-treatment	Treatment group	0	85	27	7	1	120	122.90	0.393	0.695△
		Control group	0	89	26	7	0	122	120.12		
	8 weeks	Treatment group	53	41	9	1	0	104	112.85	1.536	0.125△
		Control group	66	37	6	0	0	109	101.42		

△ represents $P > 0.05$

Table 28 Comparison of reflux esophagitis in the treatment and control groups before treatment and at 8 weeks of treatment

Datasets	Group	Treatment time	0 grade	A grade	B grade	C grade	D grade	Totals	Mean rank	*Z*	*P*
FAS	Treatment group	Pre-treatment	0	96	28	7	1	132	147.12	8.169	< 0.001**
		8 weeks	53	41	9	1	0	104	82.17		
	Control group	Pre-treatment	0	97	27	7	1	132	156.88	9.800	< 0.001**
		8 weeks	66	37	6	0	0	109	77.55		
PPS	Treatment group	Pre-treatment	0	85	27	7	1	120	141.63	8.056	< 0.001**
		8 weeks	53	41	9	1	0	104	78.89		
	Control group	Pre-treatment	0	89	26	7	0	122	151.99	9.611	< 0.001**
		8 weeks	66	37	6	0	0	109	75.72		

** represents $P \leq 0.001$

This suggested that the researcher's second assessment of the patients' health status following treatment remained highly reliable. The combined Cronbach's α for the pre-treatment assessments was 0.900, while for the post-treatment assessments, it was 0.877 (Table 29).

SHF combined with rabeprazole treatment improved the quality of life of patients with rGERD

Before interventions, there were no differences in the scores of each indicator between the treatment group and the control group ($P > 0.05$). In terms of all eight evaluation dimensions, both groups exhibited a significant

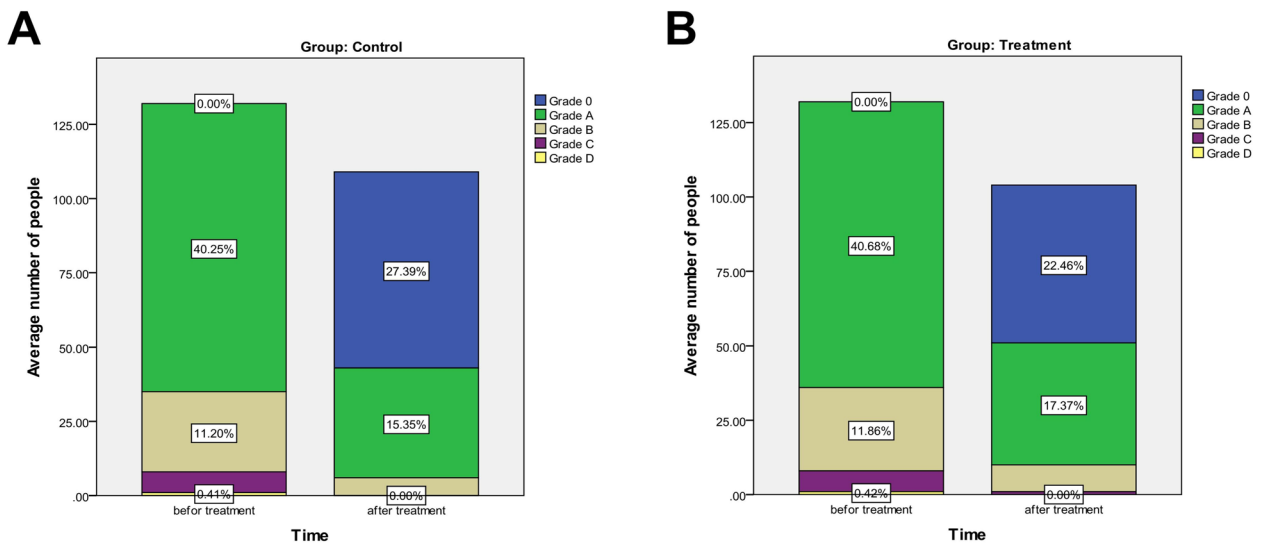

Fig. 2 Distribution of esophagitis types (FAS) before and after treatment in both groups

Table 29 Reliability analysis of the SF-36 scale for patients (FAS)

Centers	Group	Pre-treatment		Post-treatment	
		Numbers	Cronbach's α	Numbers	Cronbach's α
Yueyang Hospital	Treatment group	75	0.904	70	0.833
	Control group	75	0.911	68	0.902
Shanghai Hospital of Traditional Chinese Medicine	Treatment group	36	0.890	32	0.801
	Control group	36	0.908	34	0.796
Shuguang Hospital	Treatment group	21	0.895	18	0.761
	Control group	21	0.907	20	0.886
Totals	Treatment group	132	0.901	120	0.807
	Control group	132	0.912	122	0.888

improvement in patients' quality of life after 8 weeks of treatment compared to before treatment ($P<0.05$; Table 30). Furthermore, rmANOVA showed that after 8 weeks of treatment, the treatment group demonstrated a significantly greater improvement in quality of life compared to the control group ($P<0.05$). Additionally, there was a significant interaction between time and group for PF, RP, VT, BP, and RE ($P<0.05$), suggesting that the scores in these five dimensions increased more rapidly with prolonged treatment. Statistically, the treatment group outperformed the control group in terms of RP, VT, and GH ($P<0.05$; Table 31), indicating that scores in the treatment group improved more significantly over time compared to the control group.

SHF combined with rabeprazole treatment increased total somato-physical health and psychiatric mental health scores

WRS test showed that there was no statistical difference between the two groups at the pre-treatment in terms of total scores for somatic-physical health ($F=0.954$, $P=0.330$) and psychiatric mental health ($F=0.817$, $P=0.367$), allowing for follow-up comparisons. Both groups significantly improved their scores on somato-physical health and psychiatric mental health scores after 8 weeks of treatment compared to pre-treatment ($P<0.05$; Figs. 3and4). Additionally, following 8 weeks of treatment, there were also statistically significant differences in scores between the two groups ($P<0.05$).

Table 30 Comparison of the dimensions of the SF-36 scale between the two groups (FAS)

Dimension	Group	Numbers	Pre-treatment	8 weeks after treatment	*P*	*F*
(Physical Functioning, PF)	Treatment group	132	27.92 ± 2.52	29.44 ± 1.05	54.514	< 0.001**
	Control group	132	27.39 ± 2.85	28.02 ± 2.53	7.881	0.006*
	Totals	264	27.66 ± 2.70	28.72 ± 2.06	50.084	< 0.001**
	F	–	2.564	35.693	–	–
	P	–	0.111△	< 0.001**	–	–
(Role Limitations Due to Physical Health, RP)	Treatment group	132	6.69 ± 1.63	7.89 ± 0.49	72.294	< 0.001**
	Control group	132	6.42 ± 1.77	7.36 ± 1.15	40.936	< 0.001**
	Totals	264	6.56 ± 1.70	7.63 ± 0.92	110.442	< 0.001**
	F	–	1.611	23.925	–	–
	P	–	0.205△	< 0.001**	–	–
(Body Pain, BP)	Treatment group	132	9.59 ± 1.56	10.84 ± 1.31	66.319	< 0.001**
	Control group	132	9.63 ± 1.65	10.29 ± 1.46	15.879	< 0.001**
	Totals	264	9.61 ± 1.60	10.56 ± 1.41	71.288	< 0.001**
	F	–	0.040	10.116	–	–
	P	–	0.842△	0.002*	–	–
(General Health, GH)	Treatment group	132	15.74 ± 2.93	18.08 ± 2.49	66.903	< 0.001**
	Control group	132	15.69 ± 3.06	16.54 ± 2.77	15.695	< 0.001**
	F	–	0.021	22.600	–	–
	P	–	0.886△	< 0.001**	–	–
(Vitality, VT)	Treatment group	132	16.58 ± 3.43	19.08 ± 2.29	83.317	< 0.001**
	Control group	132	16.37 ± 4.13	17.63 ± 3.42	27.464	< 0.001**
	F	–	0.206	16.477	–	–
	P	–	0.650△	< 0.001*	–	–
(Social Functioning, SF)	Treatment group	132	8.89 ± 1.64	9.70 ± 1.10	32.201	< 0.001**
	Control group	132	8.69 ± 1.86	9.25 ± 1.52	15.876	< 0.001**
	F	–	0.833	7.744	–	–
	P	–	0.362△	0.006*	–	–
((Role Limitations Due to Emotional problems, RE)	Treatment group	132	4.78 ± 1.29	5.48 ± 0.58	68.588	< 0.001**
	Control group	132	4.70 ± 1.35	5.11 ± 0.99	26.488	< 0.001**
	F	–	0.218	14.264	–	–
	P	–	0.641△	< 0.001**	–	–
(Mental Health, MH)	Treatment group	132	19.07 ± 3.35	20.56 ± 2.34	25.988	< 0.001**
	Control group	132	18.55 ± 3.90	19.60 ± 3.20	11.985	0.001*
	F	–	1.364	7.870	–	–
	P	–	0.244△	0.005*	–	–

△ represents $P > 0.05$,*represents $P \leq 0.05$, and ** represents $P \leq 0.001$

Based on the mean values, the treatment group was superior to the control group. The rmANOVA showed that all patients had significantly higher somato-physical health and psychiatric mental health scores after 8 weeks of treatment compared to pre-treatment ($P < 0.05$). There was an interaction between time and group ($F = 17.909$, $P < 0.001$), suggesting that the total somato-physical health and psychiatric mental health scores gradually increased with the prolongation of treatment. After 8 weeks of treatment, the treatment group was significantly faster than the control group in rising scores (Tables 32, 33, 34and35).

Characteristics of the first symptoms of rGERD in Chinese medicine

Two hundred and sixty-four patients diagnosed with rGERD based on Chinese medicine evidence were subjected to systematic cluster analysis using Ward's method and Euclidean distance. The analysis revealed five distinct categories based on the degree of symptom similarity

Table 31 Results of repeated measurement ANOVA for SF-36 dimension (FAS)

Dimension	Source of variation	SS	df	MS	*F*	*P*
(Physical Functioning, PF)	Time	151.127	1	151.127	50.084	< 0.001**
	Time*group	26.407	1	26.407	8.751	0.003*
	Intra-group error	790.570	262	3.017	–	–
	group	126.146	1	126.146	15.815	< 0.001**
	Inter-group error	2089.747	262	7.976	–	–
(Role Limitations Due to Physical Health, RP)	Time	150.913	1	150.913	110.442	< 0.001**
	Time*group	2.331	1	2.331	1.706	0.193△
	Intra-group error	358.007	262	1.366	–	–
	group	20.913	1	20.913	9.128	0.003*
	Inter-group error	600.223	262	2.291	–	–
(Body Pain, BP)	Time	120.540	1	120.540	71.288	< 0.001**
	Time*group	11.194	1	11.194	6.620	0.011*
	Intra-group error	443.012	262	1.691	–	–
	group	8.370	1	8.370	2.983	0.085
	Inter-group error	735.235	262	2.806	–	–
(General Health, GH)	Time	336.003	1	336.003	79.547	< 0.001**
	Time*group	73.055	1	73.055	17.295	< 0.001**
	Intra-group error	1106.680	262	4.224	–	–
	group	83.841	1	83.841	7.180	0.008*
	Inter-group error	3059.559	262	11.678	–	–
(Vitality, VT)	Time	465.864	1	465.864	106.480	< 0.001**
	Time*group	50.915	1	50.915	11.637	0.001*
	Intra-group error	1146.290	262	4.375	–	–
	group	91.633	1	91.633	4.954	0.027*
	Inter-group error	4846.082	262	18.496	–	–
(Social Functioning, SF)	Time	61.979	1	61.979	46.851	< 0.001**
	Time*group	2.177	1	2.177	1.645	0.201△
	Intra-group error	346.597	262	1.323	–	–
	group	13.975	1	13.975	3.985	0.047*
	Inter-group error	918.787	262	3.507	–	–
((Role Limitations Due to Emotional problems, RE)	Time	40.294	1	40.294	91.744	< 0.001**
	Time*group	2.979	1	2.979	6.783	0.010*
	Intra-group error	115.070	262	0.439	–	–
	group	6.741	1	6.741	3.445	0.065△
	Inter-group error	512.618	262	1.957	–	–
(Role Limitations Due to Physical Health, RP)	Time	214.889	1	214.889	36.387	< 0.001**
	Time*group	6.557	1	6.557	1.110	0.293△
	Intra-group error	1547.264	262	5.906	–	–
	group	73.383	1	73.383	4.832	0.029*
	Inter-group error	3978.636	262	15.186	–	–

△ represents $P > 0.05$,*represents $P \leq 0.05$, and ** represents $P \leq 0.001$

(Fig. 5). Further analysis by gender yielded consistent results, suggesting that patients with rGERD could be classified into five categories (Fig. 6).

Cluster analysis of *indicator* system

Using systematic cluster analysis with Ward's method and Euclidean distance, we categorized the primary and secondary symptoms of 264 patients with rGERD based on their initial visit to a Chinese medicine doctor. The analysis identified two categories of symptoms. The first category included symptoms such as heartburn (SX), acid reflux (FS), retrosternal pain (XGHTT), regurgitation belching (FWAQ), dry mouth and bitter mouth (KGKK), and the sensation of pharyngeal obstruction

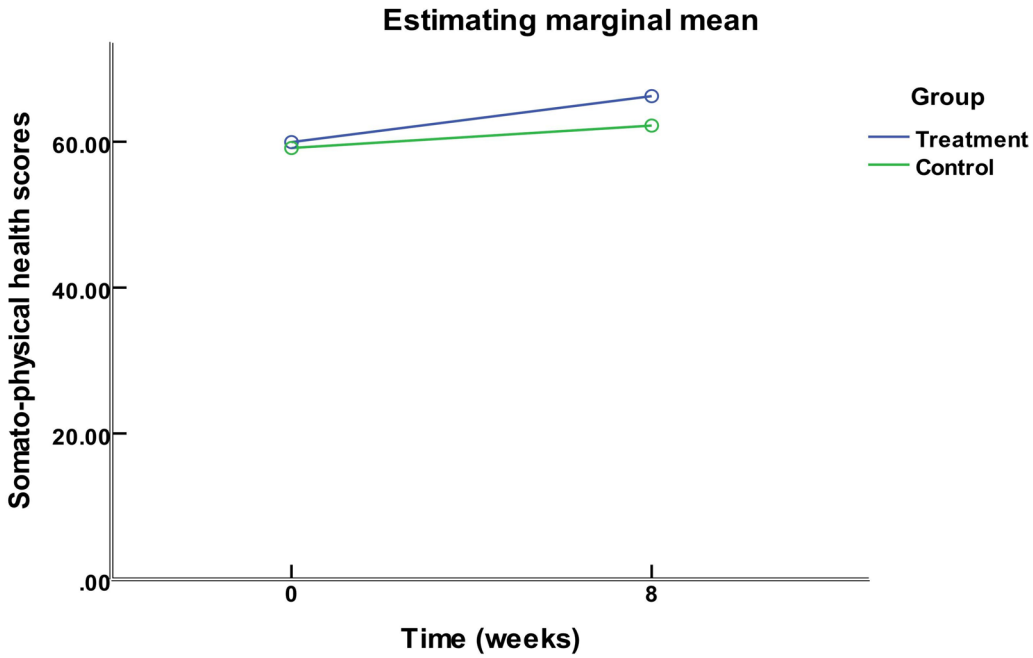

Fig. 3 Time and group interaction plot for somato-physical health scores (FAS)

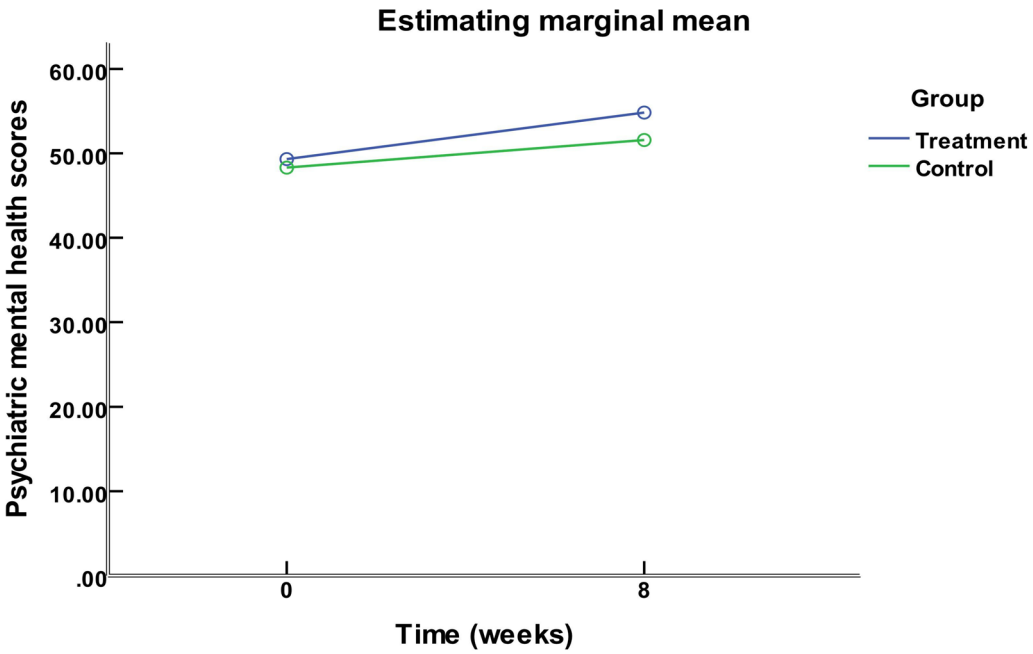

Fig. 4 Time and group interaction plot for psychiatric mental health scores (FAS)

(YBGZG). The second category comprised symptoms like dysphagia (TYKN), dyspareunia (NC), constipation (BM), loose bowel movements (BT), fatigue (SPFL), coldness and limb discomfort (WHZL), cough (KS), dry and sore throat (YGYT), epigastric pain (SFT), abdominal distension (FZ), and heartburn-induced insomnia (XFSM; Fig. 7).

Gender-based cluster analysis revealed distinct patterns in symptom grouping. Among male patients, symptoms such as heartburn (SX), acid reflux (FS),

Table 32 Comparison of total somato-physical health scores

Dataset	Group	Numbers	Pre-treatment	8 weeks after treatment	*F*	*P*
FAS	Treatment group	132	59.95 ± 6.48	66.25 ± 3.70	130.445	< 0.001**
	Control group	132	59.14 ± 6.97	62.21 ± 5.77	34.017	< 0.001**
	Totals	264	59.54 ± 6.73	64.23 ± 5.24	150.995	< 0.001**
	F	–	0.954	45.916	–	–
	P	–	0.330△	< 0.001**	–	–
PPS	Treatment group	120	59.80 ± 6.49	66.07 ± 3.83	116.864	< 0.001**
	Control group	122	59.21 ± 6.92	62.21 ± 5.99	31.415	< 0.001**
	Totals	242	59.50 ± 6.70	64.12 ± 5.39	138.178	< 0.001**
	F	–	0.456	35.409	–	–
	P	–	0.500△	< 0.001**	–	–

△ represents $P > 0.05$, **Represents $P \leq 0.001$

Table 33 Repeated measurement ANOVA of somato-physical health scores

Dataset	Source of variation	*SS*	*df*	*MS*	*F*	*P*
FAS	Time	2903.860	1	2903.860	150.995	< 0.001**
	Time*group	344.415	1	344.415	17.909	< 0.001**
	Intra-group error	5038.670	262	19.232	–	–
	group	775.855	1	775.855	15.668	< 0.001**
	Inter-group error	12,973.756	262	49.518	–	–
PPS	Time	2599.783	1	2599.783	138.178	< 0.001
	Time*group	324.585	1	324.585	17.252	< 0.001
	Intra-group error	4515.552	240	18.815	–	–
	Group	596.186	1	596.186	11.559	0.001
	Inter-group error	12,378.762	240	51.578	–	–

**Represents $P \leq 0.001$

Table 34 Comparison of total psychiatric mental health scores

Dataset	Group	Numbers	Pre-treatment	8 weeks after treatment	*F*	*P*
FAS	Treatment group	132	49.32 ± 8.16	54.83 ± 5.08	70.257	< 0.001**
	Control group	132	48.31 ± 9.88	51.58 ± 7.83	28.996	< 0.001**
	Totals	264	48.81 ± 9.05	53.21 ± 6.79	96.272	< 0.001**
	F	–	0.817	16.036	–	–
	P	–	0.367△	< 0.001**	–	–
PPS	Treatment group	120	49.00 ± 8.13	54.83 ± 5.33	73.283	< 0.001**
	Control group	122	48.40 ± 9.86	51.59 ± 8.15	28.007	< 0.001**
	Totals	242	48.70 ± 9.03	53.20 ± 7.07	98.568	< 0.001**
	F	–	0.265	13.379	–	–
	P	–	0.607△	< 0.001**	–	–

△ Represents $P > 0.05$, **Represents $P \leq 0.001$

retrosternal pain (XGHTT), regurgitation, belching (FWAQ), pharyngeal obstruction sensation (YBGZG), and abdominal distension (FZ) were clustered together. In contrast, female patients exhibited a different pattern, with heartburn (SX), pantothenic acid (FS), pharyngeal obstruction sensation (YBGZG), dry pharynx, sore throat (YGYT), fatigue (SPFL), and distraction-induced insomnia (XFSM) forming a distinct symptom cluster. These

Table 35 Repeated measurement ANOVA of psychiatric mental health scores

Dataset	Source of variation	*SS*	*df*	*MS*	*F*	*P*
FAS	Time	2546.113	1	2546.113	96.272	< 0.001**
	Time*group	166.456	1	166.456	6.294	0.013*
	Intra-group error	6929.118	262	26.447	–	–
	group	599.169	1	599.169	6.042	0.015*
	Inter-group error	25,982.140	262	99.168	–	–
PPS	Time	2461.998	1	2461.998	98.568	< 0.001**
	Time*group	211.585	1	211.585	8.471	0.013*
	Intra-group error	5994.665	240	24.978	–	–
	group	446.379	1	446.379	4.278	0.040*
	Inter-group error	25,044.829	240	104.353	–	–

*Represents $P < 0.05$, **Represents $P \leq 0.001$

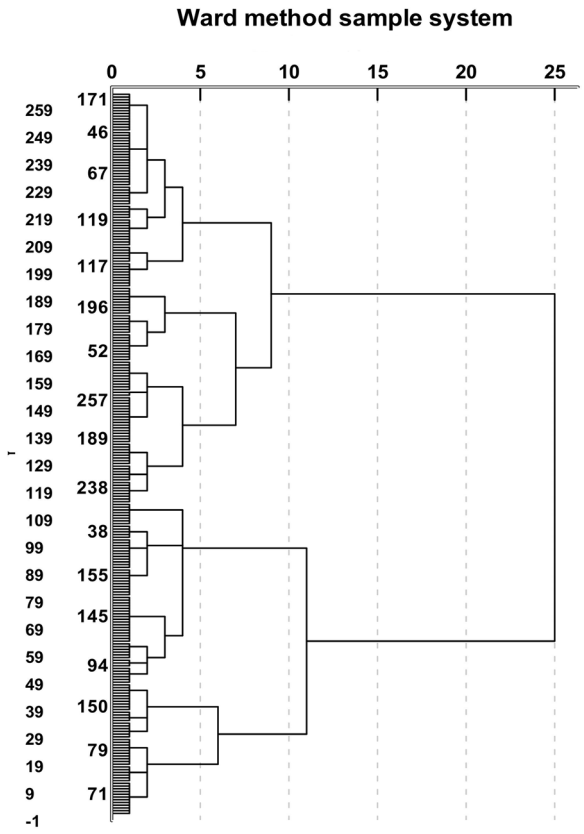

Fig. 5 Cluster diagram of Ward method sample system for all rGERD patients

findings indicated some variation in symptom grouping between the two genders (Fig. 8).

The grading of symptom severity during the patient's initial visit

The primary symptoms observed during the initial visit of patients with rGERD, ranked in descending order based on the severity composition ratio (Table 36), were as follows: regurgitation and belching (25.4%), retrosternal pain (20.8%), acid reflux (14.4%), and heartburn (13.6%). When considering the composition ratio of moderate and severe cases, the order of prevalence was as follows: regurgitation and belching (59.9%), acid reflux (46.2%), heartburn (44.3%), and retrosternal pain (40.5%).

Among the other symptoms in patients with rGERD, the top five in terms of severity included dry mouth and bitterness (26.9%), pharyngeal obstruction (25.0%), insomnia and heartburn (16.7%), abdominal distension (15.9%), and fatigue (14.4%). When considering the component ratios of moderate and severe cases, the top five included dry mouth (53.0%), pharyngeal obstruction (48.9%), bloating (41.7%), insomnia (38.7%), and fatigue (35.5%).

Safety assessment

Research has demonstrated that certain Chinese herbal medicines may have adverse effects on liver and kidney function. In this study, we assessed the incidence of abnormalities in ALT, AST, BUN, Cr, WBC, urinalysis, fecal routine, electrocardiogram in both groups. The results indicated that there was no statistically significant difference in the incidence of abnormalities in these parameters before treatment and after 8 weeks of treatment within each group ($P > 0.05$). Furthermore, when comparing the treatment group to the control group, there was no statistically significant difference in the incidence of abnormalities before treatment and after 8 weeks of treatment ($P > 0.05$).

Adverse events

Among the 264 subjects, adverse events were reported in 9 cases at Yueyang Hospital, with 3 cases in the treatment group and 5 cases in the control group. At Shuguang Hospital, there was 1 case in the treatment group. Out of

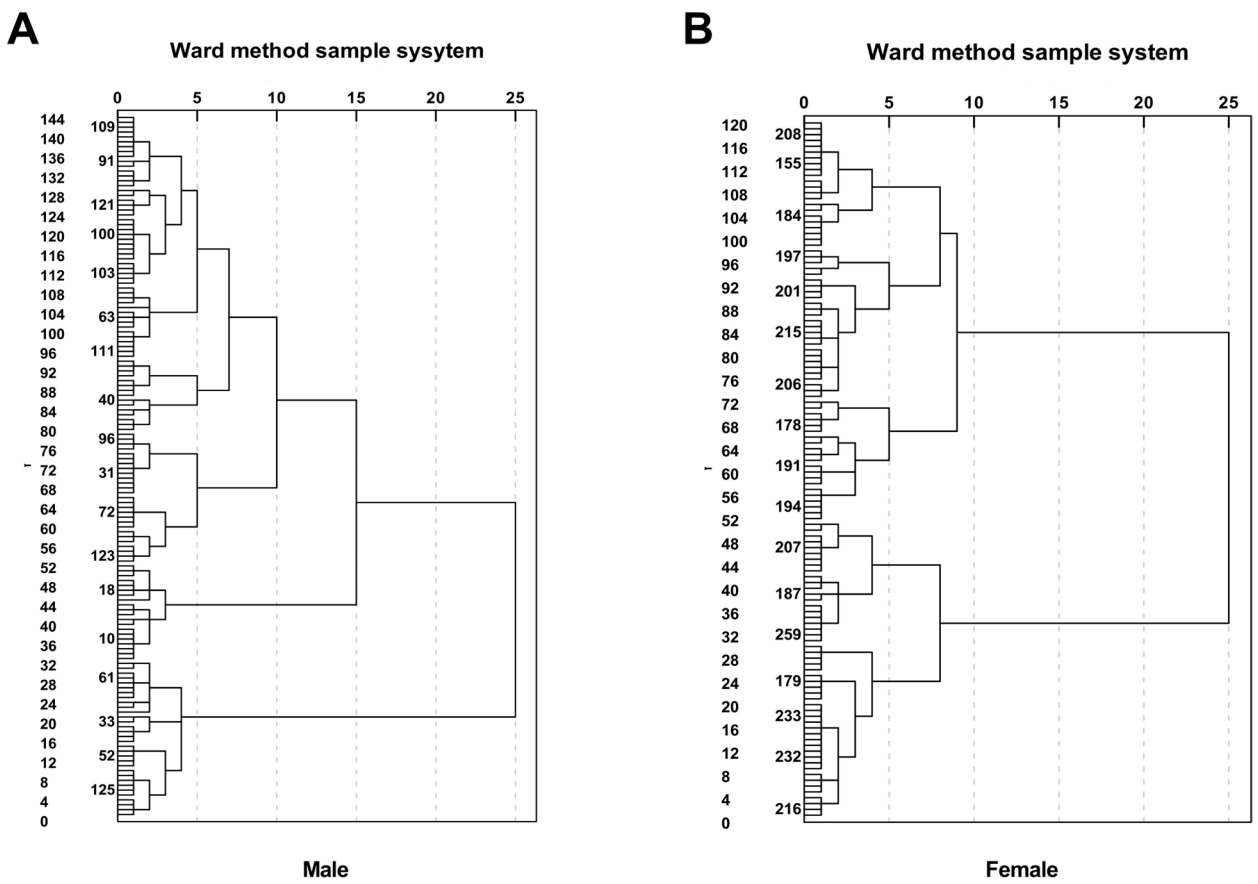

Fig. 6 Cluster diagram of Ward method sample system for rGERD patients of different genders

these 9 patients, 1 patient was removed from the clinical trial due to a suspected drug-related adverse reaction, while the other 2 were removed from the trial due to other medical conditions necessitating treatment.

Discussion

GERD is a condition that is characterized by symptoms and complications resulting from the backward flow of stomach contents into the esophagus, mouth (including the larynx), or even the lungs [18]. Its clinical presentation varies, mostly characterized by heartburn, acid reflux, and retrosternal burning pain, along with the presence of a variety of symptoms related to extraesophageal reflux [19]. PPIs are the preferred medication for treating GERD. However, many patients do not respond effectively to PPIs [20]. This subset of patients is referred to as having rGERD. Hence, it was imperative to investigate adjunctive approaches to PPI therapy for rGERD. In recent years, more researchers have recognized the distinct advantages of TCM in treating GERD [21]. In this study, we demonstrated that the combination of SHF and rabeprazole was superior to rabeprazole monotherapy in the treatment of rGERD. This superiority was evident in various aspects, including symptom scores, clinical main symptom scores (heartburn, retrosternal pain, regurgitation and belching, acid regurgitation, reflux esophagitis), and SF-36 scale. Then, a systematic clustering analysis using Ward's method and Euclidean distance was conducted on a sample of 264 patients with rGERD, based on their first Chinese medicine evidence. This analysis clustered the patients according to the degree of symptom similarity, resulting in the categorization of patients into five distinct groups. Subsequently, an index systematic clustering analysis was carried out.

The rGERD is characterized by an incomplete or lack of response to PPI therapy, often accompanied by severe and recurrent reflux symptoms [22]. Currently, research has identified multiple factors contributing to rGERD. The weakening of the physiological antireflux barrier, whether caused by a weak resting lower esophageal sphincter or the displacement of the lower esophageal sphincter and crural diaphragm (hiatal hernia), can lead to heightened reflux and an increased exposure to stomach acid [20, 23]. Reduced esophageal clearance can have an impact on esophageal peristalsis, salivary secretion, and the basal rates of esophageal clearance, thereby

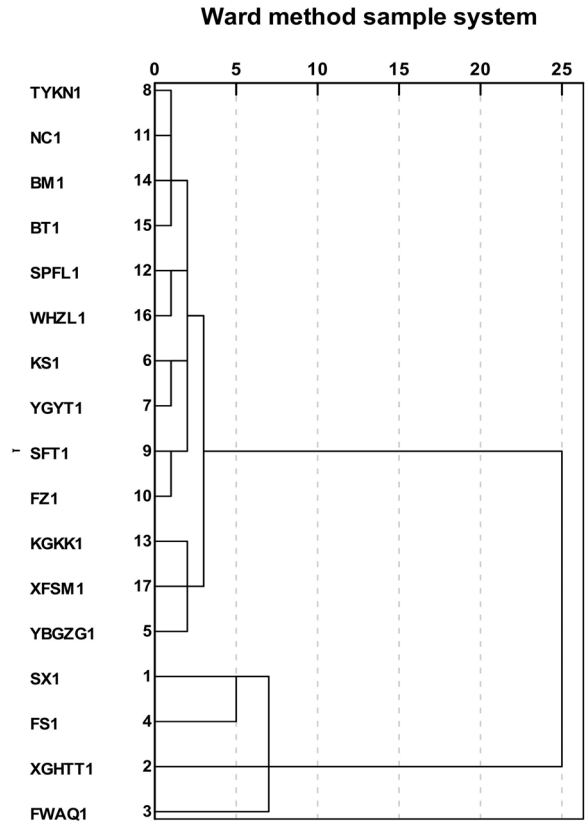

Fig. 7 Systematic clustering of Ward's method indicators for all rGERD patients

worsening reflux symptoms [24–26]. Moreover, delayed gastric emptying potentially play a role in PPI-refractory GERD by causing increased gastric distension and triggering reflux events through transient lower esophageal sphincter relaxations [27]. In addition, esophageal hypersensitivity, hypervigilance, and lower baseline mucosal impedance lead to rGERD [28–30]. Therefore, it is best to personalize the care of PPI-refractory GERD to the mechanism, patient profile, and patient desire.

Current research has identified a variety of modified regimens of PPIs for the treatment of rGERD. The modified PPI formulation, dexlansoprazole extended-release (MR), is a recently introduced medication for managing individuals with erosive esophagitis or nighttime symptoms of GERD. However, it is costly and may be effective in individuals who do not truly have GERD [31]. Splitting PPI-dose can also improve the therapeutic effect of PPIs on rGERD [32]. Intravenous PPI formulations act more quickly to suppress gastric acid secretion compared to oral PPI preparations. This leads to a rapid elevation in intragastric pH, effectively alleviating the patient's symptoms associated with reflux [33]. In addition, combining specific anxiolytic medications with PPI treatments and gastric stimulant drugs has shown promise in ameliorating both the physiological and psychological aspects of rGERD in patients [34]. However, these improvement methods are still limited in improving the efficacy of PPIs in the treatment of rGERD.

In China, TCM formulas have a well-established history of providing benefits for GERD [35], and clinical studies have consistently demonstrated the efficacy and safety of these TCM formulas in the treatment of GERD [36, 37]. TCM focuses on clearing the liver and stomach, resolving phlegm and resolving depression in the treatment of rGERD. Research has suggested that Wendan decoction associated with Ligan Hewei therapy may address issues related to phlegm and restore gastrointestinal homeostasis by affecting both acid and bile secretion [38]. Furthermore, acupuncture aimed at regulating qi based on the compatibility of the five meridians (affiliated with Ligan Hewei therapy) may also play a significant role in treating GERD with liver and stomach disharmony syndrome. Its mechanisms could be related to the regulation of the neuro-endocrine-immune system, which may help alleviate transient lower esophageal sphincter relaxations, enhance gastrointestinal motility, reduce acid secretion, and protect the gastric mucosa [39]. In recent years, a promising approach has emerged in the treatment of GERD, involving the combination of TCM formula and Western medicine. This combined therapy has demonstrated notable advantages, including substantial improvements in treatment effectiveness, reduced recurrence rates, minimized side effects associated with western medicine, and the potential to decrease the required dosage and treatment duration of western medications [40].

Most PPI drugs (e.g., omeprazole, cimetidine, etc.) are metabolized by P450 enzymes, 12% of which are dependent on CYP2C19, and Asians are a high-frequency population in which CYP2C19 occurs [41]. Rabeprazole, as a new generation of PPI preparation, does not rely on P450 enzyme system for metabolism, thus avoiding individual differences in acid inhibition caused by polymorphisms in the CYP2C19 gene, and has a strong inhibitory effect on gastric acid secretion [42]. A growing number of investigations suggest that multiple TCM formulas combined with Rabeprazole may be a promising new strategy for rGERD treatment. A prospective, randomized, multicenter trial in Japan revealed a significant reduction in Frequency Scale for the Symptoms of GERD (FSSG) score after 4 weeks of treatment with rikkunshito combined

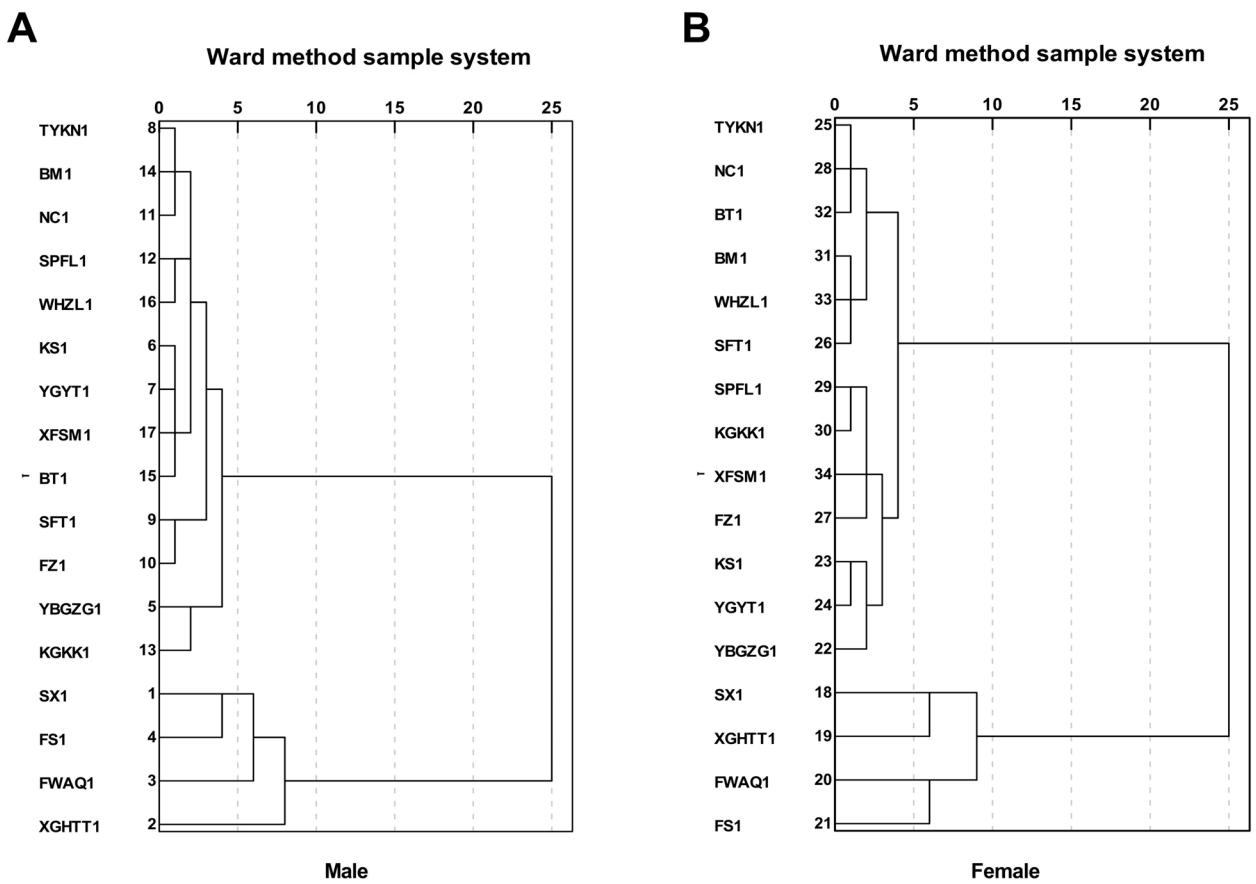

Fig. 8 Clustering diagram of the Ward method indicator system for patients of different genders

with rabeprazole, which is similar to the effect of double-dose rabeprazole in rGERD [43]. Another study has shown that there is no significant difference in FSSG scores between Hangeshashinto combined with rabeprazole therapy and double-dose rabeprazole therapy, and that Hangeshashinto combined with Rabeprazole therapy showed superiority in the treatment of non-obese and non-elderly rGERD patients with dyspeptic symptoms [44]. Moreover, the combined Yukgunja-tang and Rabeprazole has demonstrated both effectiveness and safety in the treatment of rGERD [45]. In this study, based on detoxification of the liver, harmonization of the stomach and reduction of rebelliousness, and regulation of qi throughout the body, we constructed SHF formula with 12 herbs and combined it with rabeprazole for the treatment of rGERD. The results showed that compared with rabeprazole alone, SHF combined with rabeprazole treatments significantly improved clinical outcomes, reduced total clinical symptom score, major symptom score, as well as improved quality of life in patients with rGERD. Based on the composition ratio of symptom severity during the first Chinese medicine consultation, regurgitation and belching were the most prevalent main symptoms. Dry mouth and bitter mouth, along with the sensation of pharyngeal obstruction, were the top two among other symptoms. In conclusion, the combination of SHF formula with rabeprazole demonstrates significant efficacy and safety in treating rGERD, suggesting its potential as a combined Chinese and Western medicine approach for rGERD treatment.

When SHF was used with rabeprazole, it greatly improved the overall effectiveness of treatment for symptoms and lowered total symptom scores more than rabeprazole alone. Combined LHF and rabeprazole treatment was also more effective at lowering rGERD major symptom scores, such as heartburn, retrosternal pain, regurgitation and coughing, acid reflux, and reflux esophagitis. Also, SHF treatment along with rabeprazole was better at improving quality of life than rabeprazole treatment alone. In this study, we found that SHF treatment with rabeprazole treatment significantly improved the therapeutic efficacy of rGERD, providing new treatment options and insights for TCM

Table 36 Grading of the severity of Chinese medicine symptoms in the first consultation of patients in the three centers

Symptom		None		Slight		Moderate		Severe		Totals	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Main symptoms	Heartburn	87	33.0	60	22.7	81	30.7	36	13.6	264	100.0
	Retrosternal pain	102	38.6	55	20.8	52	19.7	55	20.8	264	100.0
	Regurgitation and belching	42	15.9	64	24.2	91	34.5	67	25.4	264	100.0
	Acid reflux	79	29.9	63	23.9	84	31.8	38	14.4	264	100.0
Other symptoms	Pharyngeal obstruction	103	39.0	32	12.1	63	23.9	66	25.0	264	100.0
	Cough	166	62.9	37	14.0	37	14.0	24	9.1	264	100.0
	Dry throat and sore throat	126	47.7	47	17.8	64	24.2	27	10.2	264	100.0
	Dysphagia	221	83.7	24	9.1	18	6.8	1	0.4	264	100.0
	Epigastric pain	139	52.7	45	17.0	51	19.3	29	11.0	264	100.0
	Bloating	117	44.3	37	14.0	68	25.8	42	15.9	264	100.0
	Poor appetite	193	73.1	41	15.5	23	8.7	7	2.7	264	100.0
	Fatigue	130	49.2	43	16.3	53	20.1	38	14.4	264	100.0
	Dry mouth and bitterness	67	25.4	57	21.6	69	26.1	71	26.9	264	100.0
	Constipation	201	76.1	27	10.2	22	8.3	14	5.3	264	100.0
	Loose stools	193	73.1	25	9.5	34	12.9	12	4.5	264	100.0
	Chilly limbs	152	57.6	57	21.6	28	10.6	27	10.2	264	100.0
	Anxiety and insomnia	113	42.8	49	18.6	58	22.0	44	16.7	264	100.0
	Other	0	0.0	0	0.0	0	0.0	0	0.0	264	100.0

combined with Western medicine in the treatment of rGERD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02030-z.

Supplementary Material 1. Fig 1. The DeMeester score was used to calculate the distal pH variables for rGERD patients with grades A-D.

Supplementary Material 2. Table 1. Symptom severity scale. Table 2. Observation period and follow-up nodes

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Author contributions
Xiulian Zhang, Zhongfu Wang and Tingting Xu: Substantial contributions to conception and design, data acquisition, drafting the article; Lei Wei, Fangying Liu and Chunfang Liu: data acquisition, drafting the article; Li Li, Wei Zhang and Shengliang Zhu: data acquisition; reviewing the article; All the authors took part in the experiment. All the authors read and approval the manuscript.

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Availability of data and materials
All data in the manuscript are available through the responsible corresponding author.

Declarations

Ethical approval and consent to participate
The study protocol received approval from the Ethics Committee of Yueyang Hospital of Integrative Medicine affiliated with Shanghai University of Traditional Chinese Medicine (Ethics No. 2013-060). The written informed consent was obtained from all participating patients. This clinical trial was conducted in strict accordance with the Declaration of Helsinki (Edinburgh 2000 version) and relevant Chinese clinical trial research norms and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Clarrett DM, Hachem C. Gastroesophageal reflux disease (GERD). Mo Med. 2018;115(3):214–8.
2. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. Gastroenterology. 2018;154(2):267–76.
3. Chen J, Brady P. Gastroesophageal reflux disease: pathophysiology, diagnosis, and treatment. Gastroenterol Nurs. 2019;42(1):20–8.
4. Delshad SD, et al. Prevalence of gastroesophageal reflux disease and proton pump inhibitor-refractory symptoms. Gastroenterology. 2020;158(5):1250-1261.e2.
5. Talley NJ, Zand Irani M. Optimal management of severe symptomatic gastroesophageal reflux disease. J Intern Med. 2021;289(2):162–78.
6. Cheng Y, et al. Direct comparison of the efficacy and safety of vonoprazan versus proton-pump inhibitors for gastroesophageal reflux disease: a systematic review and meta-analysis. Dig Dis Sci. 2021;66(1):19–28.
7. Kunsch S, et al. Prospective evaluation of duodenogastroesophageal reflux in gastroesophageal reflux disease patients refractory to proton pump inhibitor therapy. Digestion. 2012;86(4):315–22.
8. Zerbib F, et al. Modern medical and surgical management of difficult-to-treat GORD. United Eur Gastroenterol J. 2013;1(1):21–31.
9. Sigterman KE, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2013;2013(5):CD002095.
10. Dellon ES, Shaheen NJ. Persistent reflux symptoms in the proton pump inhibitor era: the changing face of gastroesophageal reflux disease. Gastroenterology. 2010;139(1):7-13.e3.
11. Dai YK, et al. Different traditional herbal medicines for the treatment of gastroesophageal reflux disease in adults. Front Pharmacol. 2020;11:884.
12. Li Z, et al. Modified Xiaochaihu Decoction for gastroesophageal reflux disease: a randomized double-simulation controlled trial. World J Gastroenterol. 2021;27(28):4710–21.
13. Liu J, et al. Treatment of the gastroesophageal reflux disease with chinese herbal medicine (BanxiaXiexin Decoction): evidence from meta-analysis. Evid Based Complement Alternat Med. 2022;2022:1500660.
14. Li F, et al. Herbal Medicine Hewei Jiangni decoction is noninferior to oral omeprazole for the treatment of nonerosive gastroesophageal reflux disease: a randomized double-blind, and double-dummy controlled trail. Evid Based Complement Alternat Med. 2022;2022:9647003.
15. Tominaga K, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. J Gastroenterol. 2014;49(10):1392–405.
16. Li S, et al. Efficacy of Chinese herbal formula Sini Zuojin decoction in treating gastroesophageal reflux disease: clinical evidence and potential mechanisms. Front Pharmacol. 2020;11:76.
17. Ge Z, et al. Using deep learning and explainable artificial intelligence to assess the severity of gastroesophageal reflux disease according to the Los Angeles classification system. Scand J Gastroenterol. 2023;58(6):596–604.
18. Herdiana Y. Chitosan nanoparticles for gastroesophageal reflux disease treatment. Polymers (Basel). 2023;15(16):3485.
19. Zhang C, et al. A preliminary investigation of laparoscopic fundoplication treatment on gastroesophageal reflux disease-related respiratory symptoms. Surg Laparosc Endosc Percutan Tech. 2012;22(5):406–9.
20. Zerbib F, et al. ESNM/ANMS consensus paper: diagnosis and management of refractory gastro-esophageal reflux disease. Neurogastroenterol Motil. 2021;33(4): e14075.
21. Ho CE, et al. GERD: an alternative perspective. Psychosomatics. 2016;57(2):142–51.
22. Scarpellini E, et al. Management of refractory typical GERD symptoms. Nat Rev Gastroenterol Hepatol. 2016;13(5):281–94.
23. Tolone S, et al. Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value? Neurogastroenterol Motil. 2015;27(10):1423–31.
24. Kahrilas PJ, et al. The Chicago classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27(2):160–74.
25. Reddy CA, Patel A, Gyawali CP. Impact of symptom burden and health-related quality of life (HRQOL) on esophageal motor diagnoses. Neurogastroenterol Motil. 2017. https://doi.org/10.1111/nmo.12970.
26. Zentilin P, et al. An evaluation of the antireflux properties of sodium alginate by means of combined multichannel intraluminal impedance and pH-metry. Aliment Pharmacol Ther. 2005;21(1):29–34.
27. Emerenziani S, Sifrim D. Gastroesophageal reflux and gastric emptying, revisited. Curr Gastroenterol Rep. 2005;7(3):190–5.
28. Boecxstaens V, et al. Tu2125 refractory GERD patients display increased visceral hypersensitivity for thermal chemical and mechanical esophageal stimulation. Gastroenterology. 2013. https://doi.org/10.1016/S0016-5085(13)63480-0.
29. Rohof WO, et al. Increased proximal reflux in a hypersensitive esophagus might explain symptoms resistant to proton pump inhibitors in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2014;12(10):1647–55.
30. Ates F, et al. Mucosal impedance discriminates GERD from non-GERD conditions. Gastroenterology. 2015;148(2):334–43.
31. Fass R, Frazier R. The role of dexlansoprazole modified-release in the management of gastroesophageal reflux disease. Therap Adv Gastroenterol. 2017;10(2):243–51.
32. Hammer J, Schmidt B. Effect of splitting the dose of esomeprazole on gastric acidity and nocturnal acid breakthrough. Aliment Pharmacol Ther. 2004;19(10):1105–10.
33. Devlin JW. Proton pump inhibitors for acid suppression in the intensive care unit: formulary considerations. Am J Health Syst Pharm. 2005;62(10 Suppl 2):S24-30.
34. Riehl ME, Chen JW. The proton pump inhibitor nonresponder: a behavioral approach to improvement and wellness. Curr Gastroenterol Rep. 2018;20(7):34.
35. Ling W, et al. Common mechanism of pathogenesis in gastrointestinal diseases implied by consistent efficacy of single chinese medicine formula: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2015;94(27): e1111.
36. Cheng Y, et al. Network pharmacology analysis of Hewei Jiangni granule for gastroesophageal reflux disease and experimental verification of its anti-neurogenic inflammation mechanism. Drug Des Devel Ther. 2022;16:1349–63.
37. Zhang X, et al. Efficacy and safety of the Chinese herbal formula Hewei Jiangni recipe for NERD with cold-heat complex syndrome: study protocol for a double-blinded randomized controlled trial. Trials. 2021;22(1):545.
38. Ling W, et al. Consistent efficacy of Wendan decoction for the treatment of digestive reflux disorders. Am J Chin Med. 2015;43(5):893–913.
39. Li X et al. Acupuncture for gastrointestinal diseases. Anat Rec (Hoboken), 2022.
40. Lin W, et al. Efficacy and safety of traditional Chinese herbal formula combined with western medicine for gastroesophageal reflux disease: a protocol for systematic review and meta-analysis. Medicine (Baltimore). 2020;99(41): e22454.
41. Furuta T, et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther. 1999;65(5):552–61.
42. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors–emphasis on rabeprazole. Aliment Pharmacol Ther. 1999;13(Suppl 3):27–36.
43. Tominaga K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. J Gastroenterol. 2012;47(3):284–92.
44. Takeuchi T, et al. Efficacy and safety of hangeshashinto for treatment of GERD refractory to proton pump inhibitors: usual dose proton pump inhibitors plus hangeshashinto versus double-dose proton pump inhibitors: randomized, multicenter open label exploratory study. J Gastroenterol. 2019;54(11):972–83.
45. Ha NY, Kim JW, Kim J. Clinical efficacy of Yukgunja-tang combined with a proton pump inhibitor for refractory gastroesophageal reflux disease: study protocol for randomized, double-blind, double-dummy clinical trial. BMC Complement Med Ther. 2023;23(1):444.

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