The Traditional Japanese Medicine (Kampo) Boiogito has a Dual Benefit in Cardiorenal Syndrome : A Pilot Observational Study

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Background : Conventional treatment for cardiorenal syndrome (CRS) is frequently associated with drug resistance and limited clinical success. We aimed to explore a new approach utilizing Boiogito (TJ-20), a traditional Japanese medicine (Kampo), in combination with conventional treatment for patients with CRS.
Methods and Results : We enrolled 26 patients with CRS (18 men ; mean age, 77±8.4 years ; mean serum brain natriuretic peptide (BNP), 241.5±196.6 pg/mL ; mean estimated glomerular filtration rate (eGFR), 40.02±10.54 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$). Treatment with TJ-20 was started at an average dose of 4.6±1.5 g/day, which was increased to 5.2±1.2 g/day at 3.5 months and to 5.9±1.5 g/day at 9.4 months. TJ-20 treatment significantly increased mean eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) to 44.60±10.76 at 3.5 months (P=0.001), and to 45.93±11.57 at 9.4 months (P=0.0004). In addition, the New York Heart Association functional classification improved (P=0.019), and serum BNP levels decreased significantly to 195.5±145.7 pg/mL at 3.5 months (P=0.008) and to 163.3±130.2 pg/mL at 9.4 months (P=0.007). The increase in eGFR had no correlation with the decrease in BNP level, indicating independent effects on both renal function and heart failure status.
Conclusions : TJ-20 can benefit both renal function and heart failure status in patients with CRS. Alternative medicine utilizing TJ-20 may provide a novel and useful strategy for the difficult management of patients with CRS. *Shinshu Med J 62 : 89—97, 2014*

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Key words : chronic heart failure, renal insufficiency, renal function, brain natriuretic peptide

I Introduction

Cardiorenal syndrome (CRS) is characterized by a combination of cardiac and renal dysfunction. Its incidence is increasing, because of shared risk factors such as hypertension, diabetes mellitus, atherosclerosis, and renovascular disease[1)]. CRS has been identified in 30-60 % of patients with chronic heart failure (CHF) and is associated with adverse outcomes in these patients[2)-4)]. Ronco et al described the bidirectional pathophysiology of CRS as follows : "acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ"[5)]. Complex and poorly understood cardiorenal interactions in CRS make patient management a clinical challenge. In addition, most medications used in CHF may be either underused or understudied in patients with renal insufficiency, because patients with renal dysfunction are often excluded from clinical heart failure trials. The evidence base is, therefore, limited regarding the optimal management of patients with CRS[4)6)]. In

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addition, conventional treatment with diuretics and inotropes has not shown any benefit in relation to the long-term survival of patients with CRS ; therefore, alternative therapeutic approaches are of major clinical importance.

Kampo prescription, a variation of ancient Chinese medicine, comprises several elemental herbs[7]. These agents are available for ethical use and are included in the Japanese National Health Insurance Drug List[7]. The combination of herbs is thought to increase the effectiveness and decrease the adverse reactions of each individual herb[8]. In addition, Kampo prescription can be added to conventional medications in clinical practice as these agents have been shown to produce little inhibition on the activity of drug-metabolizing major cytochrome enzymes and the major drug transporter P-glycoprotein[9].

Boiogito (TJ-20, Tsumura & Co., Tokyo, Japan) elicits moderate diuretic effects and has been used to control imbalance of the distribution of body fluids in patients presenting with easy fatigability, lower limb edema, or renal dysfunction in rheumatoid arthritis[10)–12)]. An interesting fluid control effect of TJ-20 has been reported to decrease joint effusion in osteoarthritis of the knee[10)], whereas no study has investigated its efficacy in CRS. Based on these previous findings and reports, we hypothesized that the moderate diuretic effects of TJ-20 added to standard treatment for heart failure might benefit CRS patients, who require body fluid control. We here report the findings of a preliminary observational study that evaluated the effects of TJ-20 in combination with the standard therapy for CHF in patients with CRS.

II Methods

A Study design

This was a prospective, observational study. Twenty-six patients with CHF, New York Heart Association (NYHA) functional class I-III, Stage B (structural heart disease but without signs or symptoms of heart failure) or Stage C (structural heart disease with prior or current symptoms of heart failure)[13)], along with renal insufficiency (estimated glomerular filtration rate, eGFR $< 65\ \mathrm{mL \cdot min^{-1} \cdot 1.73\ m^{-2}}$) were enrolled in the study. Our enrolled patients fell under either CRS type 2 or CRS type 4 categories, as described by Ronco et al[14)]. Patients with intravascular volume depletion, indications for hemodialysis or acute kidney injury, sepsis or ongoing infection, alcohol and/or drug abuse, hepatic insufficiency, known allergy to the study medication or any of its components, or enrollment in other clinical trials involving medical or device-based interventions, were excluded from the study. Patients received standard medications including angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics (**Table 1**). TJ-20 treatment at a dose of 2.5 g, 5.0 g, or 7.5 g per day was added to the standard medications in each patient and the dose of TJ-20 was modified within the conventional dose according to the patient's acceptance and adherence.

The institutional ethics committee of Shinshu University School of Medicine approved the protocol. The protocol has been registered at the University Hospital Medical Information Network (UMIN000012762). All enrolled patients received a full explanation of the treatment agents and gave their informed written consent prior to the study. The study was performed in accordance with the Declaration of Helsinki and with Good Clinical Practice. Patients were managed based on the recommended guidelines from the Japanese Circulation Society, and in accordance with the 2013 American College of Cardiology Foundation/American Heart Association guidelines for the management of heart failure[13)].

B Laboratory analyses

During the follow-up period, levels of serum creatinine (sCr), eGFR, blood urea nitrogen (BUN), brain natriuretic peptide (BNP), and serum electrolytes including sodium (Na^+), potassium (K^+), and chloride (Cl^-) ions, were measured using routine laboratory tests. Levels of eGFR were calculated using the Modified Diet in Renal Disease (MDRD) study equation, modified for Japanese patients with

Table 1 Baseline characteristics of the study patients (n=26)

Characteristics	n (%)
Gender, male	18 (69)
Age, years (n±SD)	77±8.4
NYHA class I/II/III	5/17/4
Stage B/C	11/15
Etiology and risk factors	
Diabetes mellitus	7 (27)
Hypertension	22 (85)
Hypertensive heart disease	10 (39)
Cerebrovascular disease	5 (19)
Ischemic heart disease	7 (27)
Peripheral arterial disease	0
Arrhythmias	18 (69)
Cardiomyopathy	4 (15)
Valvular heart disease	6 (23)
Dyslipidemia	11 (42)
Medications	
ARBs	17 (65)
ACEIs	9 (35)
β-blockers	22 (85)
Diuretics	16 (62)

Abbreviations: NYHA, New York Heart Association; ARBs, angiotensin II receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors

chronic kidney disease (CKD): eGFR=194×Serum creatinine$^{-1.094}$×Age$^{-0.287}$ (×0.739 if female) mL·min^{-1}·1.73 m^{-2} [15]. Laboratory parameters were averaged from 2-3 outpatient visits for each of 3 points as follows: 1) before initiation of the treatment (3±1.8 months), and followed at mean intervals of 2) 3.5±1.8 and 3) 9.4±2.3 months after starting the treatment.

C Statistical analyses

Data were expressed as mean±standard deviation (SD) for continuous variables, such as age and laboratory parameters. Treatment efficacy at 3.5 months and 9.4 months from baseline was analyzed by comparing the means using the Wilcoxon matched-pairs signed-rank test. Spearman's correlation was used to show the association between continuous variables. One- or two-way ANOVA tests were used to determine changes in eGFR and BNP levels in the presence or absence of background treatment agents. All tests were two-sided and $P<0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 5.0f, GraphPad Software, San Diego, California.

Ⅲ Results

A Clinical characteristics

In total, 26 patients aged between 57 and 93 years were studied, with follow-up examinations after 3.5 and 9.4 months. The mean age of the patients was 77±8.4 years, and 18 patients (69%) were men. Treatment with TJ-20 was started at an average dose of 4.6±1.5 g/day, increasing to 5.2±1.2 g/day at 3.5 months and to 5.9±1.5 g/day at 9.4 months. No patient was lost during the follow-up period. The mean eGFR at baseline was 40.02±10.54 mL·min^{-1}·1.73 m^{-2}, corresponding to stage 3 CKD. The baseline characteristics are summarized in **Table 1**.

B Laboratory evaluations before and after treatment

The eGFR levels improved significantly from 40.02±10.54 mL·min^{-1}·1.73 m^{-2} to 44.60±10.76 mL·min^{-1}·1.73 m^{-2} at 3.5 months ($P=0.001$), and to 45.93±11.57 mL·min^{-1}·1.73 m^{-2} at 9.4 months ($P=0.0004$, **Fig. 1**). As shown in **Fig. 1**, mean sCr levels decreased significantly from 1.40±0.67 mg/dL to 1.23±0.50 mg/dL at 3.5 months ($P<0.0001$), and to 1.21±0.51 mg/dL at 9.4 months ($P=0.0002$). The mean BUN levels also decreased significantly from 25.67±6.68 mg/dL to 24.20±6.48 mg/dL at 3.5 months ($P=0.047$), and to 23.96±6.83 mg/dL at 9.4 months ($P=0.029$, **Fig. 1**). There were no significant changes in the levels of serum sodium (141.4±1.93 meq/L vs. 141.6±1.67 meq/L, and 141.2±1.59 meq/L; $P>0.05$; **Fig. 2**), serum chloride (106±2.43 meq/L vs. 106.2±2.84 meq/L, and 105.8±2.45 meq/L; $P>0.05$; **Fig. 2**) or serum potassium (4.54±0.35 meq/L vs. 4.52±0.36 meq/L, and 4.42±0.38 meq/L; $P>0.05$; **Fig. 2**) from baseline to 3.5 and 9.4 months, respectively. Mean BNP levels decreased progressively from 241.5±196.6 pg/mL to 195.5±145.7 pg/mL at 3.5 months ($P=0.008$), and to 163.3±130.2 pg/mL at 9.4 months ($P=0.007$; **Fig. 3**). No significant changes in eGFR,

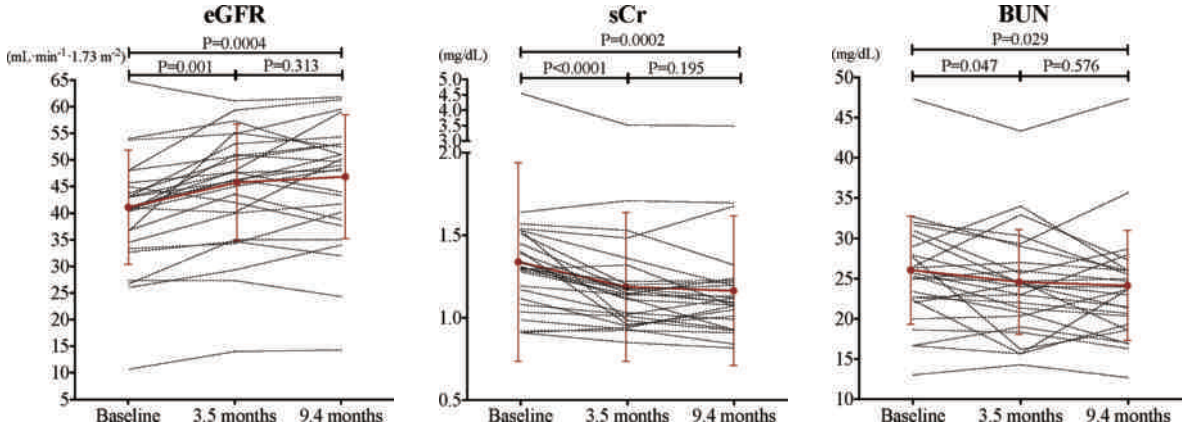

Fig. 1 Significant improvements in serum estimated glomerular filtration rate (eGFR), creatinine (sCr), and blood urea nitrogen (BUN) in patients with cardiorenal syndrome treated with TJ-20 (n=26). Data are expressed as mean ± SD.

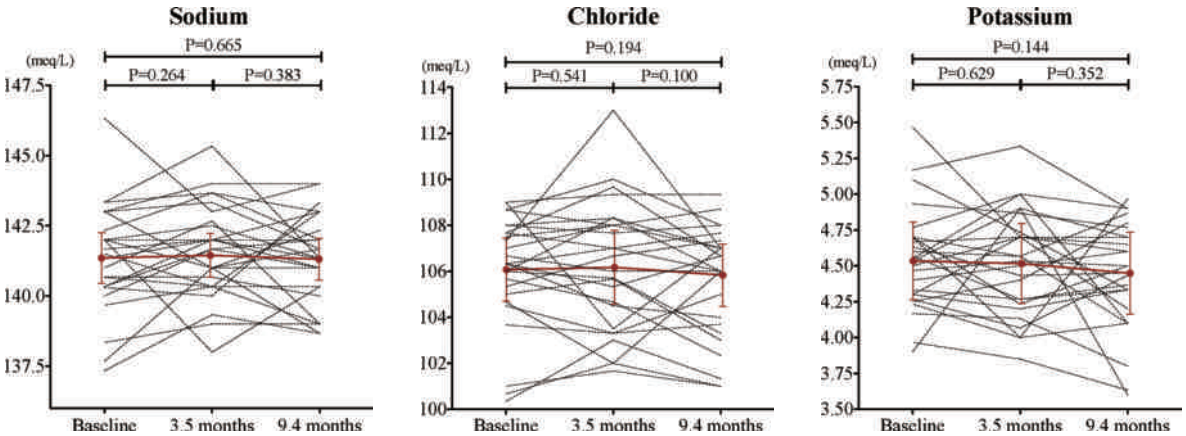

Fig. 2 No significant interval changes were observed in levels of serum sodium, chloride, or potassium in patients treated with TJ-20 (n=26).

BUN, sCr, and BNP levels were observed between the 3.5-month and 9.4-month follow-up examinations (P>0.05). The effects were observed consistently in all patients followed up at 9.4 months (**Fig. 1** and **Fig. 3**). To evaluate effects of background treatment agents, we calculated the changes in eGFR and BNP levels at baseline, 3.5 and 9.4 months between patents with and without receiving angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, β-blockers, or diuretics (**Table 2**). No significant changes in eGFR and BNP levels in the presence or absence of these background treatment agents were observed (P>0.05).

C Changes in NYHA functional class

The NYHA classification of the patients is shown in **Fig. 3**. Six out of 26 patients (23 %) treated with TJ-20 demonstrated an improvement in NYHA functional class at 3.5 months from baseline (mean from 2.0±0.63 to 1.76±0.58; P=0.019). This improvement was maintained in all patients who were followed up at 9.4 months (1.76±0.58; P=0.019).

D Correlations between changes in eGFR and BNP levels

No significant correlations were found between the increase in eGFR and the decrease in BNP levels at either 3.5 or 9.4 months (Spearman r=0.033, P=0.876 and r=0.061, P=0.766, respectively; **Fig. 3**).

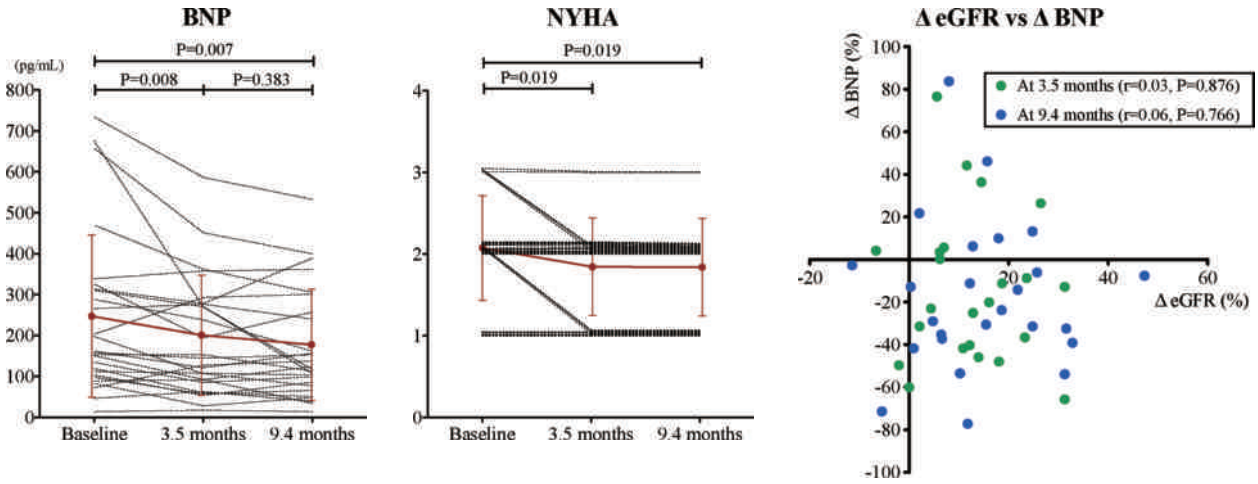

Fig. 3 Time courses of brain natriuretic peptide (BNP) levels and New York Heart Association (NYHA) functional class in patients with cardiorenal syndrome treated with TJ-20 (n=26). No correlations were observed between the changes in estimated glomerular filtration rate (ΔeGFR) and BNP (ΔBNP) at 3.5 months (green circles) or at 9.4 months (blue circles).

Table 2 Changes in eGFR and BNP levels in the presence or absence of background treatment agents

Laboratory parameters	Treatment agents	Number of patients	Baseline	3.5 months	9.4 months	P value*	P value#
eGFR							
	ARB+	17	42.25±8.59	46.71±9.09	48.33±10.69	0.187	0.964
	ARB−	9	35.42±12.77	40.63±13.02	40.60±11.61	0.601	
	ACEI+	9	39.07±14.71	43.93±14.48	46.27±14.07	0.565	0.925
	ACEI−	17	40.52±8.03	44.96±8.70	45.33±10.22	0.235	
	β-blockers+	22	40.64±11.02	45.13±11.22	46.68±12.04	0.199	0.920
	β-blockers−	4	36.59±7.52	41.72±8.43	40.03±4.63	0.595	
	Diuretics+	16	41.21±10.73	45.23±10.32	46.27±10.99	0.375	0.964
	Diuretics−	10	38.12±10.49	43.61±11.93	44.66±12.62	0.418	
BNP							
	ARB+	17	232.5±189.3	183.5±123.1	166.1±120.8	0.413	0.989
	ARB−	9	258.7±221.3	215.6±182.6	184.0±166.1	0.711	
	ACEI+	9	205.2±130.5	186.7±118.0	147.3±97.39	0.566	0.908
	ACEI−	17	260.8±225.7	199.9±161.2	185.5±152.4	0.452	
	β-blockers+	22	250.4±210.8	206.4±153.3	172.3±136.0	0.319	0.853
	β-blockers−	4	193.0±90.55	141.0±95.76	172.3±150.3	0.818	
	Diuretics+	16	289.4±233.7	213.8±162.8	201.6±154.6	0.363	0.745
	Diuretics−	10	164.9±77.88	158.9±103.4	125.4±82.63	0.565	

Results are expressed as mean±SD; *One-way ANOVA and #Two-way ANOVA. Abbreviations: eGFR, estimated glomerular filtration rate; ARBs, angiotensin II receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors; BNP, brain natriuretic peptide

E Safety

There were no significant adverse events resulting in discontinuation of TJ-20 treatment at the end of our study. No cardiovascular events were observed; however, 2 patients (8 %) developed pseudoaldosteronism with hypokalemia. The TJ-20 administration was discontinued when their serum potassium levels decreased to 2.4 meq/L and 2.6 meq/L, at 16 and 17 months, respectively.

Ⅳ Discussion

This is the first report that clearly demonstrates the beneficial effects of Japanese Kampo medicine (TJ-20), in combination with conventional treatment, for CHF patients with renal insufficiency. The administration of TJ-20 significantly ameliorated renal function, decreased BNP levels, and improved NYHA functional class from baseline. In the general population, GFR decreases at a constant rate of 3.73 and 7.53 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ per decade in people aged under 45 years and over 45 years, respectively[16]; therefore, the improvement in eGFR demonstrated in this study for up to 9.4 months was remarkable. Although the study had no control group, we can compare the results with the natural history of patients with CRS[16].

An intravenous loop diuretic is recommended as the first-line choice in patients with acute pulmonary congestion or edema without shock (class I recommendation, level of evidence B)[13]. Despite their ubiquitous use in acute settings, the safety and efficacy of loop diuretics are limited, and many concerns have been raised. First, the use of loop diuretics may decrease GFR by impairing renal perfusion and glomerular filtration pressure, and by activating both the renin-angiotensin-aldosterone system and the sympathetic nervous system[17]. Second, possible adverse effects of loop diuretics are hypokalemia, hyponatremia, and hypomagnesemia, which may lead to cardiac arrhythmias and increase the risk of sudden cardiac death[18][19]. Third, diuretic resistance can be seen in CRS patients, because the dose-response curve may shift to the lower right as a result of the CRS status[20]. Importantly, high-dose loop diuretics have been associated with sudden death or death from pump failure[20][21]. Moreover, CHF patients are likely to have a delicate balance between dehydration and overhydration, i.e., a narrow therapeutic window for optimal fluid balance[22]. Therefore, the use of diuretics can be a double-edged sword, and the dose should be kept to the minimum needed to achieve and maintain euvolemia[23].

Hydrostatic modulating effects of Saireito (TJ-114)[24], Goreisan (TJ-17)[25], and of TJ-20[26] have been reported to control body fluid imbalances in patients suffering from edema, thirst, spontaneous sweating, or oliguria. These agents elicit moderate diuretic effects in patients with excess body water but not in euvolemic patients; therefore, Kampo medicine may prevent dehydration and/or renal insufficiency. Although changes in diuretic agents (loop, thiazide, and potassium sparing) during the course of treatment were not significant in this study (data not shown), we speculate that the addition of TJ-20 has the potential to optimize diuresis and prevent renal dysfunction.

Although the mechanisms of action of individual components of TJ-20 are beyond the scope of this study, the following potential mechanisms derived from various studies suggest the beneficial effects of TJ-20. Oral treatment with TJ-20 in rats with puromycin aminonucleoside-induced nephrosis significantly suppressed proteinuria and urinary excretion of thromboxane B_2 (TXB_2), and increased the 6-keto-prostaglandin $F_{1\alpha}$/TXB_2 ratio in the kidney[27]. This indicates a renal release of vasodilatory prostaglandins. Treatment with TXA_2 (the precursor of TXB_2) synthase inhibitor in rats with subtotal nephrectomy prevented renal insufficiency and increased the renal synthesis of vasodilatory prostacyclin[28]. Astragalus, one of the components of TJ-20, induces natriuresis, partly by enhancing the response to endogenous atrial natriuretic peptide in rats with experimental CHF[29] and in healthy humans[30]. Astragalus also attenuated myocardial inflammation and fibrosis in a rat model of experimental autoimmune myocarditis[31]. These

reports are consistent with the beneficial effects of TJ-20 in improving renal function and CHF status in our study.

A post hoc analysis from the Scandinavian Simvastatin Survival Study has demonstrated renal protective effects of simvastatin in patients with coronary heart disease[32]. Similarly, atorvastatin treatment for patients with metabolic syndrome increased eGFR levels, especially in patients with stage 3 CKD[33]. Based on these reports, statins have been proposed as an option to treat patients with CKD and cardiovascular disease. In this study, there was no change in statin therapy during the study period.

Serum BNP levels can be partly dependent on the patient's renal function[34]. However, we found no correlation between the changes in eGFR and BNP levels after TJ-20 treatment, suggesting that the decrease in BNP levels could be distinct from the increase in eGFR levels. Although we could not clearly separate the beneficial effects of TJ-20 on renal function and the status of heart failure, our results suggest that these effects could have a dual benefit for cardiorenal protection.

A Study limitations

There were several limitations to this study. First, this hospital-based observational study cannot prove the mechanisms of action of TJ-20 or the roles of each component of the agent. Second, this study was a preliminary observational study and had only 26 patients with no controls. Third, eGFR calculation may involve inaccurate estimation, because the MDRD formula was derived from a cohort of relatively young patients with established CKD. Fourth, neither echocardiography nor any other means of assessing cardiac function was available. Finally, the follow-up period of 9.4 months was not sufficient to draw conclusions regarding the long-term effects of TJ-20. Further research will be required to understand the precise role of each component of TJ-20, and the potential mechanisms underlying the beneficial effects on CRS.

B Conclusion

The addition of TJ-20, the Japanese Kampo Boiogito, to standard heart failure treatment clearly demonstrated beneficial effects on the status of renal function and heart failure. The observations in this study may suggest new strategies for utilizing traditional Japanese medicine in the management of CRS.

Ⅴ Conflict of Interest : None declared

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