Original Paper

Efficacy of Sacubitril/Valsartan in Treating Hemodialysis Patients with Reduced Ejection Fraction Heart Failure: A Retrospective Study

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Introduction. Heart failure with reduced ejection fraction (HFrEF) is a prevalent and challenging complication among patients undergoing hemodialysis. Sacubitril/Valsartan (Sac-Val), an angiotensin receptor-neprilysin inhibitor, has shown promise in improving cardiac outcomes in HFrEF patients. This study aims to evaluate the efficacy and safety of Sac-Val in treating HFrEF in patients undergoing hemodialysis.
Methods. This retrospective analysis was conducted on 30 patients with HFrEF undergoing regular hemodialysis at Beijing Shijingshan Hospital between January 2019 and January 2023. The patients were divided into two groups: the Sac-Val group (14 patients) and the control group (16 patients). The Sac-Val group received an initial dose of 50 mg, titrated over four weeks to a maximum tolerated dose of 100 mg, while the control group received conventional heart failure treatment without Sac-Val. Both groups continued regular hemodialysis three times weekly. Statistical analysis included independent t-tests or Mann–Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. Heart failure improvements, blood pressure, NT-proBNP levels, biochemical markers, and echocardiographic changes were assessed after one year.
Results. The Sac-Val group showed significant improvements in systolic blood pressure ($P = .027$), NT-proBNP levels ($P < .05$), left ventricular ejection fraction (LVEF) ($P < .04$) compared to the control group. The Sac-Val group also had a higher total effective rate (85.71%) in alleviating heart failure symptoms compared to the control group (69%, $P = .023$).
Conclusion. Sac-Val is a safe and effective treatment for HFrEF patients undergoing hemodialysis, potentially improving their quality of life, heart function and clinical outcomes.

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INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF), is a condition occurring when the heart muscle is weakened and cannot pump blood effectively, is a prevalent and challenging complication in patients undergoing maintenance hemodialysis (MHD).[1] Cardiovascular disease is highly prevalent among dialysis patients, with a reported rate of 76.5% in hemodialysis and 65% in peritoneal dialysis; nearly half of these patients

suffer from heart failure, including 13% with HFrEF.[2] In China, cardiovascular events account for over 50% of deaths among dialysis patients.[3] Even though heart failure can be controlled with strategies like adequate dialysis, anemia correction, and management of bone-mineral disorders, a significant proportion of patients, particularly the elderly, remain resistant to these interventions, in part due to the challenges of fluid removal during dialysis sessions and blood pressure instability. While options such as extending dialysis duration, increasing the frequency of dialysis sessions,[4] or continuous renal replacement therapy[5] may help but are often impractical due to limited resources. These limitations highlight the urgent need for effective pharmacological strategies tailored to this high-risk population.

The angiotensin receptor-neprilysin inhibitor (ARNi) Sacubitril/Valsartan (Sac-Val) has shown promise in improving prognosis, reducing hospitalization rates, and decreasing mortality in chronic HFrEF. Sac-Val combines neprilysin inhibition with blockade of the renin-angiotensin-aldosterone system (RAAS), enhancing the natriuretic peptide system, inhibiting maladaptive cardiac remodeling, and promoting vascular relaxation.[6,7] Sacubitril inhibits neprilysin, resulting in elevated levels of natriuretic peptides such ANP and BNP, which promote vasodilation, natriuresis, and diuresis, countering the consequences of heart failure.[8] Valsartan, an angiotensin II receptor blocker, acts by preventing angiotensin II receptor, reducing vasoconstriction, salt retention, and adverse cardiac remodeling.[8] Together, these mechanisms offer potential benefits for patients with both heart failure and chronic kidney disease, including those on dialysis.[8]

Reduced ejection fraction is a well-documented prognostic indicator in patients with heart failure;[9] however, data specific to end-stage kidney disease patients are sparse. Despite the theoretical advantages of Sac-Val, its clinical efficacy in the MHD population has not been well characterized, as these patients are often excluded from large heart failure trials.[10–15] Additionally, pivotal ARNI trials, such as PARADIGMHF systematically excluded patients on maintenance hemodialysis, leaving a critical evidence gap for this highrisk group.[16] Published data are limited to small, singlecenter series (≤54 participants) from Korea, Israel and China as well as shortterm pharmacokinetic studies. These reports offer inconclusive signals for mortality or hospitalization and no evaluation of nutritional or electrolyte endpoints.[10–12] Recent metaanalyses demonstrate a consistent improvement in left ventricular ejection fraction LVEF in dialysisdependent HFrEF. they highlight the complete lack of data on serum magnesium and the absence of evidence concerning the Chinese population.[17–19] Accordingly, we undertook a oneyear realworld study in a strictly defined Chinese HFrEFMHD cohort, incorporating metabolic markers to address these unmet needs. This work aims to fill the research gap by providing empirical data on the safety and efficacy of Sac-Val in MHD patients with HFrEF. By focusing on a population with limited treatment options, this study seeks to inform therapeutic strategies that could meaningfully affect both survival and quality of life. We assessed adverse events and treatment efficacy in addition to monitoring improvements in heart failure symptoms, changes in biochemical markers, and echocardiographic parameters. By addressing these questions, our findings could provide valuable insights into managing heart failure in hemodialysis patients, potentially improving their quality of life and clinical outcomes.

MATERIALS AND METHODS

Study participants

This retrospective analysis was conducted on 30 patients with HFrEF who underwent regular hemodialysis at the Hemodialysis Center of Beijing Shijingshan Hospital from January 2019 to January 2023. Participants were divided into two groups: The Sac-Val group, comprising 14 patients on regular hemodialysis treated with Sac-Val and control group, consist of 16 patients on regular hemodialysis but without Sac-Val. Both groups received the same conventional treatment. Inclusion criteria were age > 18 years, regular hemodialysis for ≥3 months, a clinical diagnosis of heart failure with reduced ejection fraction (LVEF < 40%), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 300 pg/ml. Exclusion criteria included patients with preserved ejection fraction (HFpEF), prior use of Sacubitril/Valsartan for less than six months, concurrent treatment with ACE inhibitors or ARBs, known intolerance

to ARNi therapy, active infection, malignancy, or recent cardiovascular events within the past three months. Patients with arrhythmias (e.g., atrial fibrillation) or vascular disorders (e.g., peripheral artery disease) were not excluded unless they had experienced a recent cardiovascular event within the past three months. Consequently, the study population included HFrEF patients both with and without rhythm or vascular abnormalities, reflecting the typical clinical spectrum seen in the dialysis population.

Treatment methods

The dialysis protocol consisted of hemodialysis three times a week, each session lasting four hours. The types of vascular access included autologous arteriovenous fistula, artificial arteriovenous fistula, or tunneled central venous catheter with a Dacron sleeve. The dialysate contained calcium (Ca^{2+}) at a concentration of 1.5 mmol/L and potassium (K^{+}) at a concentration of 2.5 mmol/L. The dialysate flow rate was set at 500 ml/min, and the blood flow rate ranged from 200 to 250 ml/min. The initial dose of Sac-Val was 50 mg once or twice daily, which was gradually titrated to a maximum tolerated dose of 100 mg once or twice daily within four weeks. In addition to Sac-Val, patients in both groups might have received erythropoietin, active vitamin D, calcium supplements, phosphate-lowering agents, or calcimimetics based on their laboratory test results.

Study Outcomes

Data collected included sex, age, dialysis duration, systolic and diastolic blood pressures, type of dialysis access, primary renal disease, antihypertensive medications, and NYHA classification.

Clinical efficacy was assessed before and after treatment using the NYHA classification standard.[20] Marked effectiveness was defined as the disappearance of heart failure symptoms, significant improvement in various monitoring indicators, and an improvement of two or more levels in the NYHA heart function classification. Partial effectiveness was defined as an improvement in heart failure symptoms, enhanced monitoring indicators, and an increase of one level in the NYHA classification. The condition was considered ineffective if heart failure symptoms did not improve, discomfort persisted at rest, and monitoring indicators either remained unchanged or worsened. Total effective rate was calculated as (marked effectiveness+ partial effectiveness) / total number of cases × 100%.

Blood pressure readings (systolic and diastolic), NT-proBNP, uric acid, corrected calcium, blood phosphorus, albumin, alkaline phosphatase, blood and serum magnesium, serum creatinine, urea, blood glucose, triglycerides, total cholesterol, and parathyroid hormone levels were monitored before and after treatment. The recorded echocardiographic parameters included left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), intraventricular septum wall thickness, end diastolic (IVSTd), left ventricular end-systolic diameter (LVSd), left atrial diameter (LAD), right ventricular end-diastolic diameter (RVDd), and pulmonary artery diameter (PAD). Additionally, the presence of pulmonary arterial hypertension (PAH), decreased left ventricular diastolic function (DLVDF), and pericardial effusion were noted.

Adverse events were tracked, including allergic reactions, hypotension, hyperkalemia, impaired liver function, and angioedema. Hard endpoints were defined as deaths caused by cardiovascular events such as myocardial infarction, arrhythmia, and heart failure.

Statistical Analysis

Statistical data were expressed as mean and standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. For comparisons between and within groups, continuous variables meeting normal distribution were tested using the unpaired two-samples t-test, while those not meeting normal distribution were tested using the rank-sum test. Categorical variables were tested using the chi-square test. A P value < .05 was considered statistically significant. Statistical analysis was performed using SPSS 26.0 software. We tested normality using the Shapiro-Wilk test. For continuous variables, parametric (independent sample t-test) or non-parametric (Mann-Whitney U test) tests were applied as appropriate. Paired t-tests or Wilcoxon signed-rank tests were used for within-group comparisons. Categorical data were analyzed using chi-square or Fisher's exact test. No adjustments for multiple comparisons were made due to the exploratory nature of the

study. Missing data were minimal and handled by complete-case analysis.

RESULTS

Demographic and Clinical Characteristics of the Study Population

This study included 30 patients with HFrEF undergoing regular hemodialysis, who were divided into a Sac-Val group (14 patients) and a control group (16 patients). In the Sac-Val group comprised 11 males (78.57%) and three females (21.43%), with a mean age of 62.63 ± 8.24 years. The dialysis duration ranged from 4 to 132 months, with an average of 64.14 ± 43.08 months. Dialysis access types were predominantly autologous arteriovenous fistula (nine cases), with fewer cases of artificial arteriovenous fistula (one case) and tunneled central venous catheter with Dacron sleeve (four cases). Primary renal diseases included diabetic nephropathy (10 cases, 71.43%), chronic glomerulonephritis (two cases, 14.29%), hypertensive nephropathy (one case, 7.14%), and polycystic kidney disease (one case, 7.14%). In the control group, there were 12 males (75%) and four females (25%), with a mean age of 63.51 ± 7.64 years. Dialysis duration varied from 6 to 108 months, averaging 58.69 ± 40.18 months. Dialysis access types included autologous arteriovenous fistula (eight cases), artificial arteriovenous fistula three cases), and tunneled central venous catheter with Dacron sleeve (five cases). Primary renal diseases in this group were diabetic nephropathy (11 cases, 68.75%), chronic glomerulonephritis (three cases, 18.75%), and hypertensive nephropathy (two cases,12.5%).

Sac-Val Treatment Significantly Alleviates Heart Failure Symptoms in Hemodialysis Patients

The New York Heart Association (NYHA) classification is a functional classification system that categorizes patients based on the severity of their heart failure symptoms and physical limitations, providing a standardized measure to assess and compare the clinical status of patients before and after treatment.[21] The distribution of NYHA categories in the Sac-Val group changed significantly after treatment, as detailed in Table 1. Initially, the group comprised two patients with NYHA class II (14.29%), ten with NYHA class III (71.42%), and two with NYHA class IV (14.29%). Post-treatment, the group showed a significant improvement: nine patients were classified as NYHA class I (64.29%), four as class II (28.57%), one as class III (7.14%), and none remained at class IV. The chi-square test confirmed statistically significant changes in NYHA classification of the Sac-Val group (P = .00027). The control group, however, did not show such a dramatic shift in NYHA classifications. In terms of therapeutic efficacy, in the Sac-Val group, seven patients (50%)

Table 1. NYHA classification of patients in the Sac-Val and control groups before and after treatment

NYHA Class	Before Treatment (n, %)	After Treatment (n, %)	
	Sac-Val Group	Sac-Val Group	*P*
Class I	0 (0%)	9 (64.29%)	.00027
Class II	2 (14.29%)	4 (28.57%)	
Class III	10 (71.42%)	1 (7.14%)	
Class IV	2 (14.29%)	0 (0%)	
	Control Group	Control Group	
Class I	0 (0%)	0 (0%)	> .05
Class II	3 (18.75%)	3 (18.75%)	
Class III	11 (68.75%)	10 (62.5%)	
Class IV	2 (12.5%)	3 (18.75%)	

Note: *P*-values were calculated using Chi-square test.

Table 2. Comparison of treatment effects between the two groups of patients

Group	Number of cases	Marked effect (n)	Effective (n)	Ineffective (n)	Total Effective Rate (%)
Sac-Val	14	7	5	2	85.71%
Control	16	6	5	5	69%
P					0.023

Note: *P*-value was calculated using Chi-square test.

had a significant effect, while five patients (35.71%) showed partial effectiveness, and a total effective rate of 85.71%, as shown in Table 2. In contrast, the control group comprised six patients (37.5%) with a significant effect and five patients (31.25%) with effective results, for a total effective rate of 69%. The comparison of the two groups indicated a statistically significant difference ($P = .023$). These findings demonstrate the efficacy of Sac-Val in improving heart failure symptoms in patients on regular HD compared to standard treatment, supporting its use in clinical practice.

Significant Reduction in Systolic Blood Pressure and Dry Weight Following Sac-Val Treatment

The differences in systolic blood pressure and dry weight between the two groups before and after treatment were statistically significant ($P < .05$), as illustrated in Table 3. Specifically, the systolic blood pressure in the Sac-Val group decreased from 120.96 ± 15.95 mmHg to 114.03 ± 14.70 mmHg ($P < .05$), while in the control group it did not change significantly. Thus, Sac-Val treatment significantly lowered systolic blood pressure compared to the control group. ($P = .027$) In addition, both groups exhibited a significant decrease in dry weight: the Sac-Val group decreased from 65.99 ± 9.09 kg to 63.35 ± 10.47 kg ($P < .05$), and the control group decreased from 67.12 ± 7.68 kg to 64.01 ± 9.89 kg ($P < .05$). No differences were observed in diastolic blood pressure or heart rate between the two groups. These findings indicate that Sac-Val effectively reduces systolic blood pressure and dry weight, which are critical factors in managing heart failure in hemodialysis patients.

Sac-Val Significantly Improves Markers Associated with Heart Failure in Hemodialysis Patients

Key laboratory indicators, including uric acid, calcium, phosphorus, albumin, alkaline phosphatase, magnesium, and NT-proBNP are crucial for assessing the metabolic and cardiac health of heart failure patients, providing insights into the disease's biochemical and physiological changes and its management. Before treatment, no differences were observed between the two groups in several laboratory indicators, as detailed in Table 4. Following treatment, the Sac-Val group

Table 3. Changes of blood pressure, heart rate and dry weight in the two groups before and after treatment

Group	SBP (mmHg)		DBP (mmHg)		Heart rate (beats/min)		Weight (kg)	
	Before	After	Before	After	Before	After	Before	After
Sac-Val	120.96 ± 15.95	114.03 ± 14.70*	69.28 ± 14.49	61.63 ± 10.77	74.60 ± 10.88	73.24 ± 11.34	65.99 ± 9.09	63.35 ± 10.47*
Control	121.79 ± 15.41	120.28 ± 15.18	69.03 ± 17.56	62.74 ± 11.49	73.38 ± 11.69	74.07 ± 10.57	67.12 ± 7.68	64.01 ± 9.89*
P	0.205	0.027	0.124	0.216	0.48	0.54	0.27	0.32

Note: DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure.
P-values were calculated using t-test (two-tailed).
*The withing group comparison before/after treatment is significant, $P < 0.05$.

Table 4. Laboratory test results of the two groups of patients before and after treatment

	Sac-Val Group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Serum creatinine (umol /L)	819.36 ± 208.89	831.49 ± 204.05	857.32 ± 291.08	829.45 ± 276.13
Uric acid (umol /L)	344.49 ± 61.12	330.68 ± 58.33*	343.22 ± 99.04	331.49 ± 67.03*
Urea (mmol/L)	21.79 ± 5.03	21.76 ± 6.14	21.39 ± 6.18	21.41 ± 6.01
Serum potassium (mmol/L)	4.52 ± 0.61	4.61 ± 0.60	4.58 ± 0.58	4.66 ± 0.59
Corrected calcium (mmol/L)	8.81 ± 0.52	9.09 ± 0.59*	8.98 ± 0.75	9.07 ± 0.55*
Phosphorus (mmol/L)	1.74 ± 0.50	1.58 ± 0.43*	1.84 ± 0.48	1.60 ± 0.39*
Albumin (g/L)	40.09 ± 2.98	41.26 ± 3.16*	40.16 ± 3.07	40.53 ± 4.78
Triglycerides (mmol/L)	2.13 ± 1.55	1.94 ± 1.18	2.07 ± 1.66	1.89 ± 1.97
Total cholesterol (mmol/L)	3.75 ± 0.89	3.74 ± 0.89	3.62 ± 1.02	3.63 ± 0.98
Alkaline phosphate (U/L)	85.44 ± 22.92	100.96 ± 35.63*	87.04 ± 24.18	102.34 ± 32.54*
Magnesium (mmol/L)	1.06 ± 0.12	1.12 ± 0.14*	1.08 ± 0.16	1.09 ± 0.13
β_2 – microglobulin (µg/ml)	32.31 ± 10.34	34.08 ± 8.90	33.45 ± 11.26	34.97 ± 9.22
NT-proBNP (ng /ml)	4561.4 (1255.4, 10572.5)	1644.9 (864.9, 7079.8)*	4708.4 (1367.4, 10725.8)	5914.6 (1884.6, 14907.1)#
PTH (ng /ml)	230.63 ± 187.86	256.87 ± 208.57	228.36 ± 176.57	232.91 ± 203.64

Note: *P*-values were calculated using t-test (two-tailed) /Chi-square test.
*The withing group comparison before/after treatment is significant, $P < 0.05$.
#The comparison between the groups after treatment is significant, $P < 0.05$.

exhibited significant changes in blood levels of uric acid, calcium, phosphorus, albumin, alkaline phosphatase, and magnesium ($P < .05$). Of note, magnesium levels significantly increased from 1.06 ± 0.12 mmol/L to 1.12 ± 0.14 mmol/L ($P < .05$), indicating improved metabolic stability, which is crucial as higher serum magnesium levels are associated with reduced heart failure incidence and mortality.[22] In contrast, the control group showed significant changes in blood levels of uric acid, calcium, phosphorus, and alkaline phosphatase, but not in albumin or magnesium levels. This lack of change in magnesium levels in the control group highlights a distinct benefit of Sac-Val treatment, as the increase in magnesium in the Sac-Val group suggests better overall metabolic management. NT-proBNP levels, an important marker for heart failure, showed no significant difference between the two groups before treatment. Although improvements in various markers were observed in both groups, the situation is distinct for NT-proBNP. Its levels significantly decreased in the Sac-Val group compared to their baseline levels after treatment ($P < .05$), whereas an increase was noted in the control group ($P < .05$).

Echocardiographic Improvements in Hemodialysis Patients Treated with Sac-Val

Echocardiographic parameters were assessed to evaluate cardiac structure and function. As shown in Table 5, no significant differences were observed between the Sac-Val and control groups at baseline. However, after one year of treatment, the Sac-Val group showed significant improvements in LVEF, LVSd, LAD, and RVDd exhibited statistically significant changes ($P < .05$). The control group, also showed a significant difference were found in LVEF, LVSd, and LAD ($P < .050$) except in RVDd parameter ($P > .05$). Although both groups showed improvement in LVEF, the increase was significantly greater in the Sac-Val group compared to the control group ($P = 0,04$).

Regarding pericardial effusion, before treatment, 57.14% of patients in the Sac-Val group had pericardial effusion, as shown in Table 5. After treatment, the number of patients with pericardial effusion (PEff) significantly decreased to 14.29% (2 patients), and the proportion of patients without PEff increased to 85.71% (12 patients). In the control group, PEff was present in 56.25% of

Table 5. Echocardiographic data of the two groups of patients before and after treatment

Group	Time	LVEF (%)	LVDd (mm)	LVSd (mm)	IVSTs (mm)	LAD (mm)	RVDd (mm)	PAD (mm)	PAH	PEff, n (%)		DLVD, n (%)
										PEff	No PEff	
Sac-Val	Before	36.50 ± 3.01	60.40 ± 7.41	49.11 ± 8.22	8.57 ± 1.59	44.33 ± 3.37	26.00 ± 6.41	23.71 ± 2.31	5 (35.71%)	8 (57.14%)	6 (42.86%)	14 (100%)
	After	50.80 ± 8.23	53.50 ± 7.51	39.88 ± 5.93	10.14 ± 1.25	39.75 ± 4.63	19.57 ± 4.10	23.14 ± 3.36	4 (28.57%)	2 (14.29%)	12 (85.71%)	13 (92.86%)
Control	Before	35.38 ± 3.59	58.38 ± 5.71	49.23 ± 9.21	10.39 ± 2.35	45.33 ± 5.65	24.80 ± 5.32	23.56 ± 3.00	6 (37.5%)	9 (56.25%)	7 (43.75%)	16 (100%)
	After	45.25 ± 7.88	55.35 ± 5.02	40.02 ± 7.70	11.15 ± 1.86	41.30 ± 6.27	24.48 ± 5.23	23.75 ± 3.07	4 (25%)	4 (25%)	12 (75%)	16 (100%)
t/ P-value Sac-Val (before and after treatment)		-7.46/0.0001	8.74/0.06	2.86/0.02	1.93/0.08	2.54/0.04	1.97/0.047	1.67/0.74	0.18	0.045		0.5
t/ P-value control (before and after treatment)		-4.24/0.04	6.36/0.07	1.87/0.04	3.54/0.12	1.79/0.04	3.65/0.48	4.27/0.62	0.21	0.049		-
t/ P-value between groups (after treatment)		7.68/0.04	7.21/0.06	2.15/0.06	2.71/0.14	1.92/0.06	2.01/0.07	3.14/0.71	0.23	0.19		0.6

Note: PEff = pericardial effusion; DLVDF = Decreased Left Ventricular Diastolic Function; PAH = Pulmonary arterial hypertension; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; IVSTd = intraventricular septum wall thickness; LVSd = left ventricular end-systolic diameter; LAD = left atrial diameter; RVDd = right ventricular end-diastolic diameter; PAD = pulmonary artery diameter.
P-values were calculated using t-test (two-tailed).

patients before treatment and 25% after treatment ($P < .05$), with the proportion of patients without PEff increasing from 43.75% to 75% ($P < .05$). These results underscore the effectiveness of Sac-Val in improving key echocardiographic parameters, highlighting its potential to enhance cardiac function and reduce complications in patients with heart failure undergoing hemodialysis.

During the one-year treatment period, no adverse reactions such as hypotension, severe hyperkalemia, or neurogenic edema were observed in the Sac-Val group, and there were no cardiovascular-related deaths in either group.

DISCUSSION

Heart failure is a significant issue in hemodialysis patients, accounting for over 50% of deaths in China.[2,3] Some patients, particularly the elderly, remain refractory to treatments such as adequate dialysis and anemia correction for heart failure, facing challenges such as rapid blood pressure drops during ultrafiltration. Angiotensin receptor-neprilysin inhibitors (ARNi), specifically Sac-Val, can induce natriuresis and reverse cardiovascular remodeling, improving prognosis, reducing hospitalization rates, and lowering mortality in chronic heart failure.[6,7] This study aims to evaluate the efficacy and safety of Sac-Val in the treatment of HFrEF in patients undergoing hemodialysis.

Pharmacokinetic data provide a mechanistic basis for the conservative dosing used in our cohort. Following a single 100 mg dose in patients with endstage kidney disease, the areaunderthecurve (AUC) of sacubitril almost doubles compared to individuals with normal renal function, whereas valsartan exposure remains relatively unchanged; because both moieties are > 97% proteinbound, < 5% of the administered dose is removed during a 4hour hemodialysis session [21–23]. Current labelling recommends starting at 24/26 mg twice daily (total 50 mg) in severe renal impairment and titrating upward slowly as tolerated.[23] Consistent with this guidance, each patient in our study started the treatment with 50 mg once daily following the mid-week dialysis session, and none exceeded 100 mg per day; with no occurrence of symptomatic hypotension, severe hyperkalemia or angiooedema occurred, supporting the safety of this regimen.

Our findings contribute to the body of literature on Sacubitril/Valsartan in dialysisdependent

HFrEF. Compared to previous East Asian reports that enrolled heterogeneous EF groups or followed ≤54 patients for < 6 months,[10–12] our cohort of 30 patients was confined to those with LVEF < 40 % and followed them for 12 months, thereby strengthening external validity. The 11 % absolute LVEF rise and marked NYHA downgrading align with the pooled +11–14 % LVEF change seen in recent metaanalyses,[17] while our realworld design complements the survival signal reported in the USRDS registry.[19] Importantly, we newly demonstrate concurrent increases in serum albumin and magnesium, biomarkers previously unreported (Mg) or sporadically described (albumin) in this setting,[24,25] suggesting a potential nutritional and antiarrhythmic benefit that merits prospective confirmation.

The findings of our study also revealed that the Sac-Val group experienced a significant reduction in severity of heart failure symptoms and physical limitations, in fact NYHA class III patients decreased from 10 (71.42%) to one (7.14%), and patients with NYHA class IV improved post-treatment. This statistically significant change in NYHA class proportions before and after treatment ($P < .05$) in the Sac-Val group underscores the efficacy of ARNi in ameliorating heart failure symptoms in this patient population, consistent with previous reports.[10–15]

The NT-proBNP hormone, produced in heart ventricles, is a well-established biomarker for diagnosing and monitoring heart failure, particularly HFrEF. It is formed when proBNP splits into BNP and NT-proBNP.[26] Although Sacubitril inhibits neprilysin, an enzyme that degrades natriuretic peptides such as BPN, NT-proBNP levels remain unaffected, making it a reliable biomarker.[27,28] A notable finding was the significant decrease in NT-proBNP levels in the Sac-Val group ($P < .05$), indicating a substantial reduction in heart failure severity. Echocardiographic parameters showed a significant enhancement in the Sac-Val group, with increased LVEF and decreased LVSd and LAD, indicating improved cardiac function and reduced ventricular remodeling ($P < .05$). These findings align with previous studies by Niu *et al.* and Raphael *et al.*, which reported similar improvements in LVEF and clinical outcomes with ARNi treatment in dialysis patients.[10,13]

In addition to cardiac benefits, the study observed significant increases in plasma albumin and serum magnesium levels following treatment ($P < .05$), The rise in plasma albumin is likely due to improved cardiac function, leading to better appetite and nutritional status.[24] Similarly, the increase in serum magnesium can be attributed to the resolution of hypoalbuminemia and enhanced magnesium retention. Elevated serum magnesium levels are associated with reduced heart failure incidence and mortality, underscoring its prognostic significance.[25,29]

The limitations of our study include its retrospective, single-center design, and small sample size. These factors limit the generalizability of the findings. Additionally, due to the non-randomized nature of the study, there is a potential for selection bias, as treatment allocation may have been influenced by clinical judgment or unmeasured patient characteristics. Confounding variables, such as comorbidities, variations in dialysis regimens, or concurrent medications, could also have impacted outcomes and were not fully controlled. Importantly, this study did not include hard clinical endpoints such as cardiovascular mortality or re-hospitalization, which limits the ability to draw definitive conclusions about long-term prognosis. We acknowledge these potential sources of bias and emphasize that the findings should be considered exploratory and hypothesis-generating. The potential for bias and the limited generalizability of the findings necessitates further large-scale, multi-center randomized controlled trials to confirm these results. While baseline characteristics were generally comparable between groups, we acknowledge that residual confounding may remain due to the retrospective design. Factors such as dialysis adequacy (e.g., Kt/V), severity of comorbidities (e.g., diabetes mellitus, hypertension), medication adherence, and volume status were not fully assessed, which could influence the outcomes. Future prospective studies with multivariable adjustment or propensity score matching are warranted. Finally, although our sample is larger than prior Chinese series, multicenter trials powered for hard endpoints and mechanistic biomarkers are required to validate these hypothesisgenerating observations.

CONCLUSION

In conclusion, our findings provide preliminary

evidence suggesting the potential efficacy and safety of Sac-Val in improving cardiac function in hemodialysis patients with HFrEF. This study provides novel insights into the clinical advantages of Sac-Val for a population that has not received enough attention in previous research. However, given the retrospective nature, small sample size, absence of hard clinical endpoints, and possibility of residual confounding, these findings should be interpreted with caution. Further large-scale, prospective studies are warranted to confirm these findings and better establish Sac-Val's role in the management of heart failure in hemodialysis patients.

Author Contributions

Y.G. contributed to the study design, and W.L. contributed to data collection and data analysis. Y.G. contributed to manuscript writing and review. Z.D. critically revised the manuscript. All authors read and approved of the final manuscript.

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ETHICS APPROVAL

This study was approved by the ethical committee of Beijing Shijingshan Hospital (2024-20).

CONFLICT OF INTEREST

All authors declare no conflict of interests.

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