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Research Article

Clinical Characteristics of Hospitalized Acute Decompensated Heart Failure with Preserved, Mid-Range and Reduced Ejection Fraction

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Abstract

Background: Hospitalization for acute decompensated heart failure is common in Chinese patients. However, characteristics and therapy strategy of HF with different ejection fraction has not been well elaborated. Therefore we conducted this study to observe the clinical characteristics of the acute decompensated heart failure patients with different ejection fraction values and to identify strategies of management.

Methods: A total of 834 hospitalized patients with acute decompensated heart failure who were admitted to the heart failure center of Sichuan provincial People's hospital from May 2015 to July 2017 were enrolled. According to the left ventricular ejection fraction (LVEF) measured by color Doppler echocardiography, the patients were divided into three groups: HFrEF group (LVEF ≤ 40%), HFmrEF group (40% < LVEF < 50%); HFpEF group (LVEF ≥ 50%). At admission, patients' characteristics including age and gender as well as the individual medical condition (systolic and diastolic blood pressure, prior complications, medication for heart failure) were gathered. Furthermore, admission-to-discharge changes of serum creatinine, uric acid, electrolytes, body weight and BNP were analyzed.

Results: 848 in-patients with acute decompensated heart failure were included. 314 (37.65%) of them belonged to HFrEF group, 63 (7.5%) to HFmrEF group, and 457 (54.80%) to HFpEF group. There was no significant difference in mean age, sex, nationality, resting heart rate and blood pressure among the three groups ($p > 0.05$). The incidence of anemia (47.62%), atrial fibrillation (34.92%) and diabetes mellitus (39.68%) was relatively common in HFmrEF patients ($p < 0.05$). The percentage of patients who were treated with ACEI/ARB (81.92%), β-blocker (90.96%), loop diuretic (81.92%), spironolactone (49.05%) and inotropes (32.17%) were significantly higher in the HFrEF group in comparison to the other two groups ($p < 0.01$). The usage of CCB (29.54%) was more common in the HFpEF group and intravenous nitrate (42.85%) was used more often in the HFmrEF ($p < 0.01$). The changes in body weight correlated significantly with EF ($p = 0.056$). The percentage of patients who lost more than 2 kg after admission to hospital was significantly higher in the HFpEF group ($p = 0.056$). The renal function (serum creatinine level (154.13 ± 214.16 μmol/L) was worst in the HFmrEF group at admission ($p < 0.01$), while there was no difference among the three groups before discharge ($p > 0.05$). The BNP level in HFrEF patients was highest compared to the other groups (1535.47 ± 1358.38 pg/mL vs 1440.48 ± 1246.99 pg/mL vs 454.370 ± 732.74 pg/mL, $p < 0.001$). From admission to discharge, the chance of reduction of the BNP level (more than 30%) was significantly greater in the HFrEF group (67.74%) than in the HFmrEF (55.36%) and HFpEF (34.34%) group ($p < 0.01$).

Conclusion: There are some clinical characteristics that vary among heart failure patients with different LVEF. HFmrEF has some characteristics of both HFpEF and HFrEF and the treatment strategy should be adjusted concretely. Relatively poor therapeutic effect was shown in HFpEF.

Keywords: *Heart Failure; Ejection Fraction; Therapy; Hospitalization*

Introduction

Advanced heart failure is hallmarked by refractory symptoms despite guideline-directed therapies and thus represents the end stage of cardiovascular disease. According to ESC guideline of heart failure 2016, one can distinguish three entities: heart failure with reduced ejection fraction (HFrEF, LVEF < 40%), heart failure with mid-range ejection fraction (HFmrEF, 40% < LVEF < 50%) and heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%) [1]. HFmrHF classification was newly introduced and refers to HF patients who belong to a borderline cohort. The clinic characteristics and the management strategies for the Chines population with acute decompensated HFmrEF are not quite clear; besides, there is still a lack of data concerning the characteristics and response to current therapy strategies of Chinese hospitalized acute decompensated heart failure patients with different ejection fraction. We analyzed our data in order to differentiate clinical characteristics and different responses to present therapy stratifies of our HF patients with different LVEF, providing more evidence for clinical management strategies.

Material and Methods

Data sources and study population

This is a retrospective, single center, and observational study. A total of 834 patients with acute decompensated heart failure hospitalized in our heart failure center from November 2015 to July 2017 were enrolled in our study. At baseline, transthoracic echocardiography was performed in all patients and left ventricular ejection fraction was determined by modified Simpson's method. According to the estimated EF, patients were divided into three groups: HFrEF (LVEF < 40%), HFmrEF (40% ≤ LVEF < 50%); HFpEF, LVEF ≥ 50%. The clinical characteristics included age, gender, blood pressure, comorbidities as diabetes mellitus, atrial fibrillation (AF), and anemia (hemoglobin < 120 g/L). Heart failure medication consisted of Renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitor, ACEI; angiotensin receptor blocker, ARB), spironolactone, beta blocker, diuretics, nitrate and inotropes. Admission-to-discharge changes of the renal function (serum creatinine level), serum potassium, serum sodium, body weight and brain natriuretic peptide (BNP) were analyzed and compared among the three groups retrospectively.

Statistical Analysis

All analyses were performed using Empower (R) (www.empowerstats.com, X and Y solutions, inc. Boston MA) and R (http://www.R-project.org). Bivariate comparisons were performed using the t-test for normally distributed continuous variables or the Kruskal-Wallis rank sum test for variables that were not normally distributed. Bivariate comparisons of categorical variables were done with the $\chi 2$ test. If $p < 0.05$, the null hypothesis was rejected.

Results

General clinical characteristics at baseline

In total, 834 patients with acute decompensated heart failure were enrolled in this study. 314 of them (37.65%) belonged to the HFrEF group with a mean age of 66.49 ± 14.76 years, and 63 (7.55%) to the HFmrEF group with a mean age of 65.79 ± 15.08 years. The largest group (HFpEF) consisted of 457 (54.80%) patients with a mean age of 66.07 ± 14.27 years. At admission, there was no significant difference in mean age, sex and nationality, resting heart rate and blood pressure (systolic and diastolic pressure) among the three groups ($p > 0.05$). However, the incidence of anemia differed significantly (HFrEF: 31.67%, HFmrEF: 47.62%; HFpEF: 44.12%) ($p < 0.01$). The incidence of hypertension was highest in the HFpEF group (45.51%). 34.92% and 39.68% of HFmrEF patients suffered atrial fibrillation (AF) and diabetes, respectively ($p < 0.01$) (Table 1).

EF	HFrEF	HFmrEF	HFpEF	P-value
n	314 (37.65%)	63 (7.55%)	457 (54.80%)	
Age	66.49 ± 14.76	65.79 ± 15.08	66.07 ± 14.27	0.901
Han nationality	295 (94.86%)	60 (95.24%)	415 (91.21%)	0.117
Gender				0.281
Male	169 (53.82%)	27 (42.86%)	236 (51.64%)	
Female	145 (46.18%)	36 (57.14%)	221 (48.36%)	
HR (bpm)	79.56 ± 17.65	81.90 ± 20.14	81.35 ± 19.64	0.390
SBP	126.01 ± 23.03	127.48 ± 22.11	126.33 ± 23.95	0.903
DBP	73.69 ± 31.28	75.381 ± 14.82	74.51 ± 32.27	0.895
Anemia	89 (31.67%)	30 (47.62%)	199 (44.12%)	0.002
HTN	94 (29.94%)	24 (38.10%)	208 (45.51%)	< 0.001
DM	66 (21.02%)	22 (34.92%)	122 (26.70%)	0.037
AF	60 (19.17%)	25 (39.68%)	138 (30.20%)	< 0.001

Table 1: *Baseline characteristics of HF with different ejection fraction.*

HR: Rest Heart Rate; bpm: Beats Per Minute; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HTN: Hypertension; DM: Diabetes Mellitus; AF: Atrial Fibrillation.

Medications used to treat heart failure

Heart failure with reduced EF was treated with ACEI/ARB (81.92% of patients), beta blockers (90.96%), oral loop diuretics (81.92%), spironolactone (49.05%) and inotropes (32.17%); additionally, 29.54% of HFpEF patients received calcium channel blockers (CCB) and 42.86% of HFmrEF patients were medicated with nitrate drips. Treatment with thiazide and intravenous diuretics was equivalent in all groups ($p > 0.05$) (Table 2 and Figure 1).

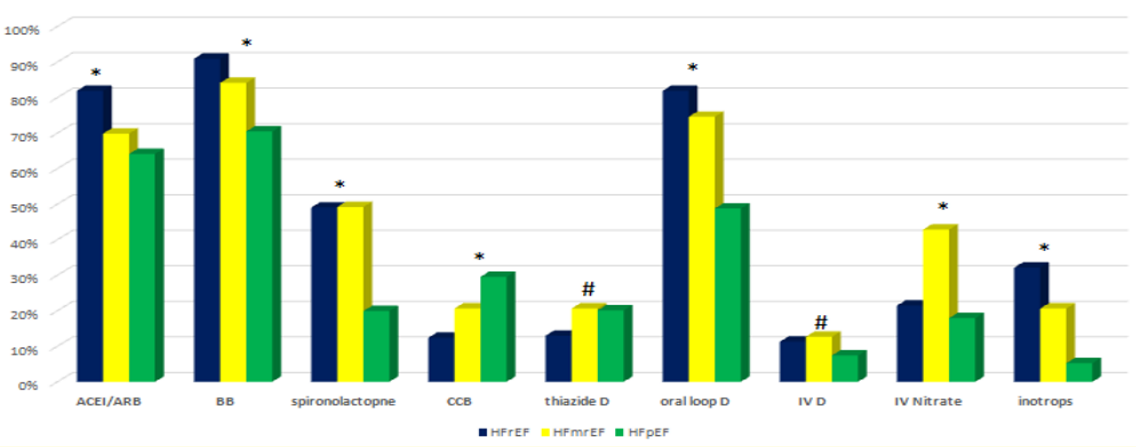


Figure 1: *HF medication for patients with HF and different ejection fraction.*
**: $p < 0.001$; #: $p > 0.05$*

Groups	HFrEF	HFmrEF	HFpEF	P-value
ACEI/ARB	145 (81.92%)	44 (69.84%)	293 (64.11%)	< 0.001
BB	161 (90.96%)	53 (84.13%)	322 (70.46%)	< 0.001
Spiro	154 (49.05%)	31 (49.21%)	91 (19.91%)	< 0.001
CCB	22 (12.43%)	13 (20.64%)	135 (29.54%)	< 0.001
Thiazide	23 (12.994%)	13 (20.635%)	92 (20.131%)	0.102
Oral loop D	145 (81.92%)	47 (74.60%)	223 (48.80%)	< 0.001
IV D	20 (11.30%)	8 (12.70%)	34 (7.44%)	0.167
IV nitrate	38 (21.47%)	27 (42.86%)	82 (17.94%)	< 0.001
Inotropes	101 (32.17%)	13 (20.64%)	24 (5.25%)	< 0.001

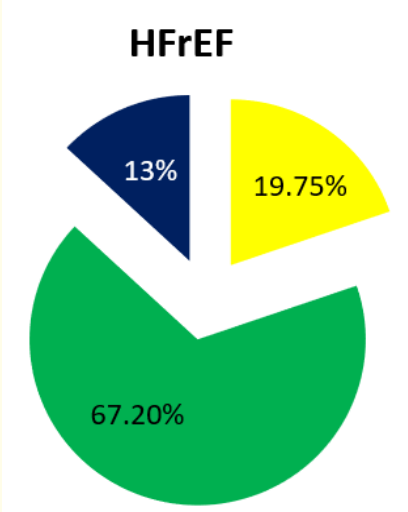
Table 2: *HF medication.*

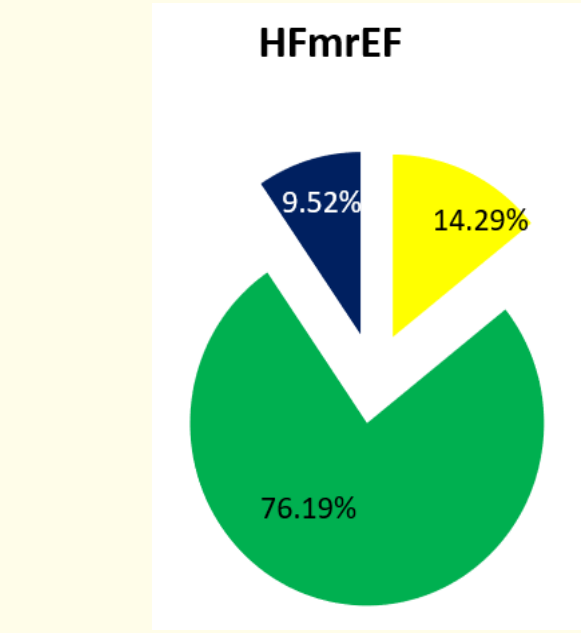
ACEI/ARB: ACE-Inhibitor, Angiotensin II Receptor Blocker; BB: Beta Blocker; Spiro: Spironolactone; CCB: Calcium Channel Blocker; IV: Intravenous; Oral loop D: Oral Loop Diauretics.

Admission-to-discharge changes

Body weight loss

The body weight change from admission to discharge of all groups correlated significantly with LVEF (p = 0.056). The overall percentage of body weight change from admission to discharge ranged between -2 to +1kg (HFrEF: 67.20%, HFmrEF: 76.19%, HFpEF: 56.10%). Besides, the percentage of patients who lost more than 2 kg of weight during hospitalization was significantly higher in the HFpEF group compared to the others (p = 0.056) (Table 3 and Figure 2).





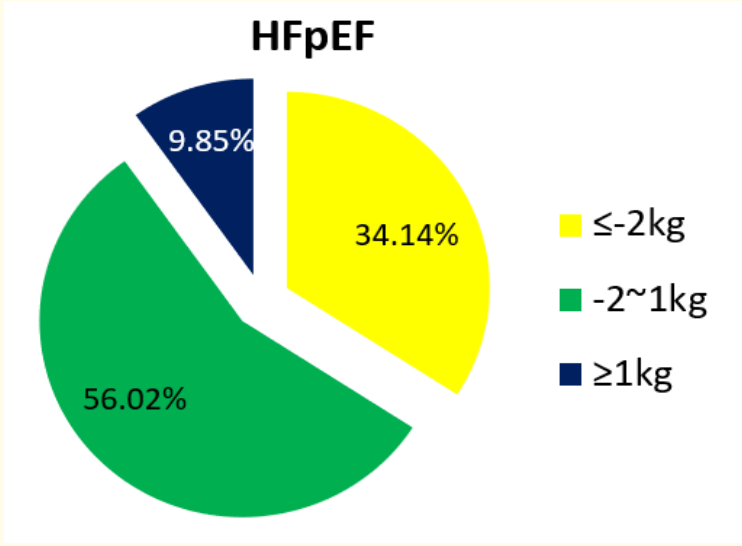


Figure 2: *Body weight change during hospitalization.*
P = 0.056

Groups	HFrEF	HFmrEF	HFpEF	P-value
N	314	63	457	
Weigh t(I)	60.57 ± 11.86	58.47 ± 11.94	61.79 ± 13.73	0.129
Weight (O)	60.38 ± 11.35	60.25 ± 11.34	60.70 ± 12.52	0.969
≤-2 kg	62 (19.75%)	9 (14.29%)	156 (34.14%)	0.056
-2~1 kg	211 (67.20%)	48 (76.19%)	256 (56.10%)	
≥1 kg	41 (13.06%)	6 (9.52%)	45 (9.84%)	

Table 3: *Body weight change during hospitalization.*

I: Admission; O: Discharge

≤-2 kg body weight loss 2 kg or/and more

-2~1 kg body weight change range from -2 kg to 1 kg

> 1 kg body weight increased 1 kg or/and more

Parameters and biomarker changes

In this cohort, patients of the HFmrEF group had the worst renal function at admission, the creatinine level of the three groups was 107.036 ± 82.94 μmol/L (HFrEF), 154.13 ± 214.16 μmol/L (HFmrEF), and 99.792 ± 93.47 μmol/L (HFpEF), respectively ($p < 0.01$). Before discharge, these differences could not be detected any more. Serum potassium and sodium levels did not differ significantly at either testing time ($p > 0.05$).The BNP level of HFrEF patients was significantly higher than that of the other two groups (1535.47 ± 1358.38 pg/mL vs 1440.48 ± 1246.99 pg/mL vs 454.37 ± 732.74 pg/mL ($p < 0.001$). A admission-to-discharge reduction of BNP levels of more than 30% was evident in 67.74% of HFrEF patients – in comparison to 55.36% of HFmrEF patients and 34.34% of HFpEF patients ($p < 0.01$). The BNP level before discharge was slightly increased compared with the baseline in the HFpEF group but without significant difference (454.37 pg/mL ± 732.74 pg/mL vs 504.03 pg/mL ± 726.06 pg/mL) ($p > 0.05$) (Table 4).

Groups	HFrEF	HFmrEF	HFpEF	P-value
N	314	63	457	
Crea (I) umol/L	107.036 ± 82.94	154.128 ± 214.16	99.79 ± 93.47	< 0.001
Crea (O) umol/L	101.28 ± 100.49	108.48 ± 132.61	110.59 ± 129.44	0.749
UA (I) umol/L	495.12 ± 165.50	484.14 ± 154.11	399.48 ± 157.16	< 0.001
UA (O) umol/L	436.67 ± 169.96	448.545 ± 130.35	443.38 ± 164.76	0.873
K (I) mmol/L	4.118 ± 0.52	4.043 ± 0.57	4.015 ± 0.57	0.113
K (O) mmol/L	4.11 ± 0.52	4.07 ± 0.60	4.25 ± 2.16	0.612
Na (I) mmol/L	137.93 ± 11.31	137.90 ± 5.90	138.68 ± 8.24	0.566
Na (O) mmol/L	136.83 ± 13.83	136.93 ± 16.95	138.15 ± 9.67	0.453
BNP. (I) pg/mL	1535.47 ± 1358.38	1440.478 ± 1246.99	454.37 ± 732.74	< 0.001
BNP (O) pg/mL	785.68 ± 892.48	962.367 ± 960.11	504.03 ± 726.06	< 0.001
BNP %[#]	105 (67.74%)	31 (55.36%)	125 (34.34%)	< 0.001

Table 4: *Laboratory parameters.*

[#]: Admission-to-discharge BNP reduction more than 30%.

Discussion

Heart failure, the end-stage of cardiovascular diseases, remains the most common diagnosis of patients treated in hospital. Due to different etiologies, heart failure underlies various patho-mechanisms and requires specific treatment strategies. Currently, heart failure guidelines recommend the classification of heart failure based on left ventricular ejection fraction measured by cardiac color Doppler ultrasound. The ESC heart failure guideline from 2016 recommends a division of the HF spectrum into three entities: HFrEF, HFmrEF and HFpEF [1,2]. There is still a lack of data from Chinese HFmrEF patients. We enrolled acutely decompensated heart failure patients who were admitted to our center and analyzed the individual patients' characteristics, medications and therapy effects according to the different ejection fractions.

838 patients with acute decompensated heart failure were included in this cohort for observation, in which HFrEF, HFmrEF and HFpEF accounted for 37.65%, 7.50% and 54.80%, respectively. More than 50% of the hospitalized patients belonged to the HFpEF group [3]. Although it was reported that HFpEF was more common in old and/or female patients [4,5], we could not identify any significant difference in age and gender among our three groups. this might be due to the majority subjects were patients with acute decompensated heart failure. Usually, It was reported that faster heart rate and higher blood pressure were correlated to the 180-day mortality in patients of HFpEF [1]. However, in this cohort there was no significant difference of rest heart rate and blood pressure at admission compared to the clinical parameters of the patients at discharge. were detected in the three groups which means there was no correlation between LVEF with blood pressure and heart rate at admission of acute decompensated heart failure.

Patients of the HFpEF group were at higher risk for hypertension which is consistent with other reports [6]. Anemia (47.62%), diabetes mellitus (34.92%) and atrial fibrillation (39.68%) were more common in HFmrEF patients than in the other groups ($p < 0.5$). While an impaired renal function is typically associated with HFrEF, the creatinine level at admission was significantly higher in the HFmrEF group ($p < 0.5$). One of the reasons for this finding might be that some patients with HFmrEF recovered from HFrEF, but renal function did not recover simultaneously. HFmrEF patients can have characteristics of both the HFpEF and the HFrEF group.

According to the recommended ESC guidelines, ACEI, ß-blockers and spironolactone were routinely dispensed to the patients in order to decrease the mortality and re-hospitalization rate of HFrEF patients [7]. Especially, HFrEF patients received multiple drug treatment ($p < 0.01$). In particular, spironolactone is closely related to a better prognosis in HFmrEF patients [8-10]. In our cohort, the percentage of patients under spironolactone treatment was about the same in the HFrEF and HFmrEF group. The percentage of oral loop diuretics was highest in HFrEF patients (81.92%) while the amount of patients who received intravenous loop diuretics was the same in all three groups. Since most of the patients suffered from severe edema and thus were treated with intravenous diuretics, the severity of edema was not significantly different among the three groups.

Inotropes were given more frequently to HFrEF patients (32.17%), but some patients of the HFpEF group (5.25%) also benefited from inotropic support, most of the subjects were COPD with pulmonary heart disease, right ventricular insufficiency or hypotensive shock. Intravenous nitrates were the most frequently given to HFmrEF patients (42.86%). It was reported that some HFmrEF patients may convert into HFrEF or HFpEF after follow-up for several years but this was not evident in our study [1]. Although a meta-analysis suggested that nitrates fail to reduce mortality in acute heart failure, it could improve dyspnea and is still widely used in clinical practice. Given the stable hemodynamic condition, nitrates combined with diuretics can improve the volume overload symptoms of acute HF patients [11,12]. We could demonstrate that there was no obvious hypotension episode in the HFmrEF group, even though 74.60% of the patients received oral and 12.07% intravenous loop diuretics.

Fluid retention is very common in acutely decompensated heart failure patients, diuretics are used to reduce water-sodium retention while increasing of the uric output. The patients are supposed to loss some body weight, and so the body weight change can partly reflect the different response to diuretics. Heart failure patients with poor response to diuretics have poor prognosis [13]. Changes in body weight during hospitalization were associated with mortality after discharge [14]. In the three groups most of the weight changes ranged from -2 kg to 1 kg, which means although the use of diuretics occurred more frequently during hospitalization, the overall weight loss of the patients was not significant. Currently, the recommended treatment strategy for HFpEF included application of diuretics and specific treatment of associated complications. In comparison, HFpEF patients lost more than 2kg of weight during hospitalization, which implied that HFpEF had a more sensitive response to diuretics than the other two groups in this cohort (34.14% vs 19.75% vs 14.29%).

The creatinine level of HFmrEF patients was the highest at admission, suggesting that the renal function damage of HFmrEF was more obvious in acutely decompensated heart failure [12,13]. Serum uric acid level was negatively correlated with ejection fraction [15] and also an independent risk factor for poor prognosis of heart failure [16]. However, there was no difference of creatinine and uric acid levels among the three groups before discharge in this cohort, which means the renal function of some heart failure patients, especially HFmrEF, recovered after effective and reasonable treatment. As patients with acute heart failure often have significant water and sodium retention, diuretics can help to reduce the volume overload and improve congestive symptoms. Meanwhile, the uric acid level can decrease in varying degrees with a reduced dosage of diuretics [17]. Therefore, hyperuricemia at admission was not a contradiction to diuretics. The serum potassium level before discharge decreased from baseline in all groups. It may be due to the use of diuretics, that the serum potassium level should be monitored closely during hospitalization in case of hypokalaemia.

BNP levels before discharge are regarded as strong predictors of 6-month mortality in patients with acute heart failure in HFrEF and HFpEF patients [18]. The BNP level in the HFrEF group was significantly higher than that in HFpEF and HFmrEF patients at admission and before discharge which indicated that HFrEF patients had the worst prognosis. Admission-to-discharge percentage BNP reduction of more than 30% is considered an indicator of effective treatment [19]. The percentage BNP reduction in the three groups was 67.74%, 55.36%, and 34.34% ($p < 0.05$), respectively. HFrEF patients had a better response to treatment strategy based on the current protocol recommended by the ESC heart failure guidelines. Nevertheless, there is still lack of evidence of effective treatment of HFpEF patients. Although the response to diuretics could be measured clinically, the levels of BNP, creatinine and uric acid increased slightly before discharge in the HFpEF group without any statistical significance ($p > 0.05$). Whether the therapeutic effect can be of long-term benefit for the patients is not completely understood yet.

Conclusion

HFmrEF has some special clinical characteristics of both HFpEF and HFrEF. Anemia, atrial fibrillation and diabetes mellitus occurred more often in the HFmrEF group compared to the other two groups. Better therapy effect was gained in HFrEF under the guidance of the recommended treatment strategy by the available evidence. Further evidences are needed for the strategies for HFmrEF and HFpEF patients.

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