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ORIGINAL ARTICLE

Efficacy of guideline-directed medical treatment in heart failure with mildly reduced ejection fraction

Xinxin Zhang[1], Yuxi Sun[1,2], Yunlong Zhang[3], Ning Wang[1], Qiuyan Sha[1], Songqi Yu[1], Xin Lv[1], Zijie Ding[1], Yanli Zhang[1], Gary Tse[1,4]* and Ying Liu[1]*

[1]*Heart Failure and Structural Cardiology Ward, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning Province 116021, China;* [2]*Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province 610041, China;* [3]*Department of Emergency Medicine, Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Beijing ChaoYang Hospital, Capital Medical University, Beijing, 100020, China; and* [4]*Kent and Medway Medical School, Canterbury, Kent CT2 7NT, UK*

Abstract

Aims Heart failure with mildly reduced ejection fraction (HFmrEF) has received increasing attention following the publication of the latest ESC guidelines in 2021. However, it remains unclear whether patients with HFmrEF could benefit from guideline-directed medical treatment (GDMT), referring the combination of ACEI/ARB/ARNI, β-blockers, and MRAs, which are recommended for those with reduced ejection fraction. This study explored the efficacy of GDMT in HFmrEF patients.

Methods This was a retrospective cohort study of HFmrEF patients admitted to The First Affiliated Hospital of Dalian Medical University between 1 September 2015 and 30 November 2019. Propensity score matching (1:2) between patients receiving triple-drug therapy (TT) and non-triple therapy (NTT) based on age and sex was performed. The primary outcome was all cause death, cardiac death, rehospitalization from any cause, and rehospitalization due to worsening heart failure.

Results Of the 906 patients enrolled in the matched cohort (TT group, n = 302; NTT group, N = 604), 653 (72.08%) were male, and mean age was 61.1 ± 11.92. Survival analysis suggested that TT group experienced a significantly lower incidence of prespecified primary endpoints than NTT group. Multivariable Cox regression showed that TT group had a lower risk of all-cause mortality (HR 0.656, 95% CI 0.447–0.961, P = 0.030), cardiac death (HR 0.599, 95% CI 0.380–0.946, P = 0.028), any-cause rehospitalization (HR 0.687, 95% CI 0.541–0.872, P = 0.002), and heart failure rehospitalization (HR 0.732, 95% CI 0.565–0.948, P = 0.018).

Conclusions In patients with HFmrEF, combined use of neurohormonal antagonists produces remarkable effects in reducing the occurrence of the primary outcome of rehospitalization and death. Thus, the treatment of HFmrEF should be categorized as HFrEF due to the similar benefit of neurohormonal blocking therapy in HFrEF and HFmrEF.

Keywords Heart failure with mildly reduced ejection fraction; Neurohormonal blocking therapy; Triple therapy; Guideline-directed medical treatment

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**Correspondence to: Ying Liu, Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, 193 United Road, Dalian, Liaoning Province, 116021, China. Email: yingliu.med@gmail.com*
Gary Tse, Kent and Medway Medical School, University of Kent, Canterbury, UK. Email: garytse86@gmail.com; gary.tse@kmms.ac.uk
Xinxin Zhang and Yuxi Sun contribute equally to this article and are considered co-first authors.

Introduction

Heart failure (HF), a major public health issue in most countries, is categorized based on the left ventricular ejection fraction (LVEF). In 2021, the European Society of Cardiology (ESC) Heart Failure guidelines defined the HF subgroup as heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 40–49%) between HF with reduced (HFrEF; <40%) and preserved (HFpEF; ≥50%) LVEF.[1] At present, HFrEF and HFpEF populations have been extensively studied; however, it is not clear whether HF patients with LVEF in the intermediate zone of 40–49% share characteristics with HFrEF or HFpEF or have to be treated as a separate additional phenotype.[2] To date, no prospective studies have specifically evaluated the effects of pharmacological therapy on patients with HFmrEF. The existing evidence for pharmacological

treatment of HFmrEF is based on post hoc analysis of studies that partially or fully included HF patients with LVEF of 40–49%.

The sympathetic nervous system and renin–angiotensin–aldosterone (RAAS) system are activated, producing progressive left ventricular dilatation and reduced contractility, leading to worsening HF and potentially mortality.[3] Therefore, the purpose of drug therapy for chronic HF is to inhibit the hyperactivated neuroendocrine system, thereby reducing left ventricular remodelling and improving long-term prognosis.[4,5] The inhibition of RAAS and sympathetic nervous systems are recommended as the cornerstone therapy for patients with HFrEF, unless patients have contraindications or develop intolerance to these drugs.[1,6] Sacubitril/valsartan is the only currently available angiotensin receptor neprilysin inhibitor (ARNI) and is recommended for HFrEF patients remaining symptomatic despite treated with ACEI and ARB.[7,8] β-Blockers and RAAS inhibitors have shown remarkable improvements in death and hospitalization in different clinical trials.[9,10] Spironolactone has also been proven to prevent myocardial and vascular fibrosis and left ventricular remodelling in patients with HFrEF.[11,12] Based on the positive results achieved in HFrEF, the latest ESC HF guidelines historically recommended the application of ACEI/ARB/ARNI, β-blockers, and spironolactone in the treatment of HFmrEF (Class IIb, evidence level C).[1]

Currently, the evidence that the triple-drug combination therapy of neurohormonal antagonist improves the prognosis of patients with HFmrEF remains absent, and the effect is also unclear. In this retrospective study, we explored the therapeutic efficacy of guideline-directed medical treatment (GDMT) for HFmrEF, providing novel evidence for such a treatment strategy.

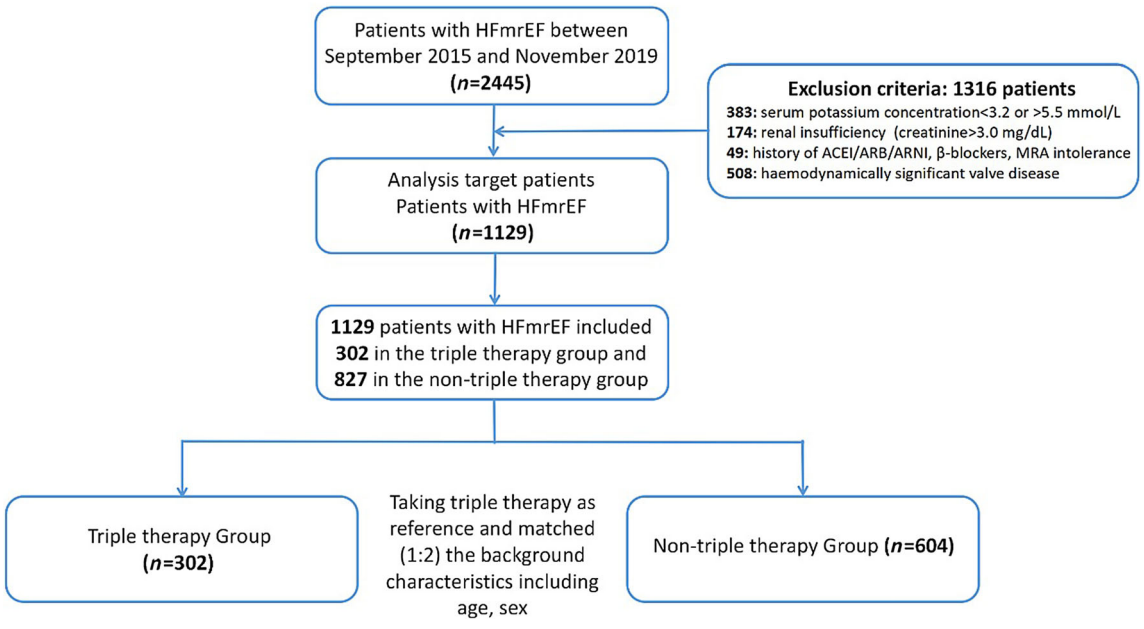
Material and Methods

Study design and population

The flow chart indicating the identification of patients and inclusion and exclusion criteria was shown in *Figure 1*. Patients diagnosed with HFmrEF between September 2015 and November 2019 at The First Affiliated Hospital of Dalian Medical University were identified. HFmrEF was defined according to the ESC HF Guidelines 2021. The exclusion criteria were serum potassium concentration >5.5 mmol/L, significant renal insufficiency (creatinine >3.0 mg/dL), haemodynamically significant valvular disease, and history of ACEI/ARB/ARNI, β-blockers, MRA intolerance. Notably, those in TT group consecutively received more than 90 days of ACEI/ARB/ARNI, β-blockers, and MRAs at a dose of at least 50% of the maximum GDMT dose, and the remaining cohort were classified into the non-triple therapy (NTT) group. To reduce the impact of confounding, propensity score matching (1:2) based on age and sex was conducted.

Details of clinical characteristics, co-morbidities, drug therapies, laboratory values, and echocardiography findings of the subjects were obtained from Yidu Cloud Database. This study was conducted in accordance with the Declaration of

Figure 1 Flow chart of enrolled patients.



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Helsinki and was approved by the Institutional Review Board of Dalian Medical University. The committee waived the need for informed consent owing to its retrospective and observational nature.

Follow-up and event ascertainment

The primary endpoints were all-cause mortality, cardiovascular mortality, all-cause rehospitalization, and heart failure rehospitalization. Data on mortality and cause of death were acquired from Yidu Cloud or telephone follow-up. The deadline for follow-up was 30 November 2020.

Data analysis

Standardized difference was used to assess the balance of covariates after matching, with a difference of no more than 10% considered acceptable. Categorical data were expressed as percentages (%), and chi-squared test was used for comparison between the groups. Continuous data with non-normal distribution were expressed as median (interquartile range), and the Kruskal–Wallis test was used. Kaplan–Meier curves were conducted to calculate time-dependent occurrences of events. Cox proportional hazards regression was performed to compare the risk of outcomes between the groups in the propensity-matched cohort. A P value of <0.05 was considered significant. Data analysis was performed with SPSS statistical software, Version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the study participants

A total of 2445 HFmrEF patients who were hospitalized at The First Affiliated Hospital of Dalian Medical University between September 2015 and November 2019 were initially identified. Of these, 1316 patients were excluded due to reaching exclusion criteria. After matching, a total of 906 patients were finally included in our analysis, with 302 patients in TT group and 604 in NTT group.

The baseline characteristics were presented in *Table 1*. In short, most of the clinical, laboratory, and echocardiographic findings were comparable between the TT and NTT groups. However, patients in NTT group were more likely to have a history of coronary artery disease and atrial fibrillation, more often took medications, such as aspirin and nitrates, and had higher value of interventricular septal thickness. In contrast, those in TT group received more digoxin and loop diuretics, had higher concentrations of BNP and uric acid, and showed greater diameters of left atrial and ventricular.

Clinical Outcomes

Over a mean follow-up of 38.0 months, 40 (13.2%) in TT group and 139 (23.0%) NTT group died, and the rates of cardiovascular death were 24 (7.9%) and 89 (14.7%), respectively. Whereas for rehospitalization, 106 (35.10%) and 319 (52.81%) were rehospitalized, with the proportion of HF 77 (25.4%) and 226 (37.4%) for the TT and NTT groups, respectively. Kaplan–Meier analysis showed that the prespecified primary outcome in TT group was significantly lower than that in NTT group (*Figures 2*).

Multivariable Cox regression showed that age, diabetes mellitus, cerebrovascular disease, and creatinine were significant predictors of higher all-cause mortality, with systolic blood pressure and haemoglobin identified as protective factors after adjusting for significant variables (*Table S1*). Compared with NTT group, the TT group showed a significantly lower risk of mortality both before (HR 0.619, 95% CI 0.435–0.880, P = 0.008 for all-cause death; HR 0.577, 95% CI 0.368–0.906, P = 0.017 for cardiovascular death) and after adjustment (HR 0.656, 95% CI 0.447–0.961, P = 0.030 for all-cause death; HR 0.599, 95% CI 0.380–0.946, P = 0.028 for cardiovascular death). Similar to mortality, the TT group tended to present a lower rehospitalization with a statistical difference (HR 0.673, 95% CI 0.540–0.838, P = 0.000 for any-cause rehospitalization; HR 0.714, 95% CI 0.553–0.922, P = 0.010 for HF rehospitalization). These associations persisted without appreciable attenuation (HR 0.687, 95% CI, 0.541–0.872, P = 0.002 for any-cause rehospitalization; HR 0.732, 95% CI 0.565–0.948, P = 0.018 for HF rehospitalization) (*Table 2*), even after adjusting for age, coronary artery disease, hypertension, diabetes mellitus, cerebrovascular disease, haemoglobin, BNP, ICD, CRT, creatinine, and serum sodium, which were significantly associated with readmission on univariable Cox regression (Table *S2*).

Discussion

The main findings of this study were that GDMT provided significant benefits both in terms of survival and rehospitalization in patients with HFmrEF. Our results supported that the response to medical treatment in HFmrEF was more similar to patients with reduced LVEF and complement our previous analysis in different HF subpopulations.[13–17]

Interestingly, in our study, the baseline left ventricular diameter and brain natriuretic peptide level in TT group were higher than that of NTT group, indicating more severe HF in the TT group. It was possible that cardiologists considered patients with greater severity of illness, where the GDMT may be more appropriate. In general, LVEF is the most commonly assessed parameter used for HF classification and risk stratification, but it is not static and could change with time.

Table 1 Baseline demographics and clinical characteristics

Characteristics	All patients	TT group	NTT group	*P* value	Matched patients	TT group (Matched)	NTT group (Matched)	*P* value
Number of patients	1129	302	827	-	906	302	604	-
Age, years	63.60 ± 12.24	60.04 ± 13.20	64.90 ± 11.61	<0.01	61.12 ± 11.92	60.04 ± 13.20	61.66 ± 11.19	-
Male (*n*, %)	753 (66.70%)	219 (72.52%)	534 (64.57%)	0.01	653 (72.08%)	219 (72.52%)	434 (71.85%)	-
Systolic blood pressure, mmHg	135.9 ± 23.19	132.9 ± 21.98	136.9 ± 23.54	0.01	135.0 ± 23.11	132.9 ± 21.98	136.1 ± 23.61	0.05
Diastolic blood pressure, mmHg	80.41 ± 13.66	81.86 ± 14.04	79.88 ± 13.49	0.03	80.72 ± 13.86	81.86 ± 14.04	80.15 ± 13.75	0.08
NYHA class III–IV (*n*, %)	302 (26.75%)	79 (26.16%)	223 (26.96%)	0.82	251 (27.70%)	79 (26.16%)	172 (28.48%)	0.47
Coronary artery disease (*n*, %)	614 (54.38%)	146 (48.34%)	468 (56.59%)	0.01	485 (53.53%)	146 (48.34%)	339 (56.13%)	0.02
Atrial fibrillation (*n*, %)	303 (26.84%)	65 (21.52%)	238 (28.78%)	0.01	234 (25.83%)	65 (21.52%)	169 (27.98%)	0.03
Cancer (*n*, %)	62 (54.92%)	10 (3.31%)	52 (6.29%)	0.05	48 (5.30%)	10 (3.31%)	38 (6.29%)	0.06
Cerebrovascular disease (*n*, %)	171 (15.15%)	34 (11.26%)	137 (16.57%)	0.03	121 (13.36%)	34 (11.26%)	87 (14.40%)	0.21
Diabetes mellitus (*n*, %)	398 (35.25%)	97 (32.12%)	301 (36.40%)	0.20	314 (34.66%)	97 (32.12%)	217 (35.93%)	0.26
Hypertension (*n*, %)	689 (61.03%)	163 (53.97%)	589 (71.22%)	<0.01	527 (58.17%)	163 (53.97%)	364 (60.26%)	0.07
Aspirin (*n*, %)	663 (58.72%)	156 (51.66%)	507 (61.31%)	<0.01	514 (56.73%)	156 (51.66%)	358 (59.27%)	0.03
Digoxin (*n*, %)	147 (13.02%)	66 (21.85%)	81 (9.79%)	<0.01	128 (14.13%)	66 (21.85%)	62 (10.26%)	<0.01
Loop diuretics (*n*, %)	415 (36.76%)	165 (54.64%)	250 (30.23%)	<0.01	352 (38.85%)	165 (54.64%)	187 (30.96%)	<0.01
Nitrates (*n*, %)	425 (37.64%)	92 (30.46%)	333 (40.27%)	<0.01	330 (36.42%)	92 (30.46%)	238 (39.40%)	<0.01
Statins (*n*, %)	739 (65.46%)	185 (61.26%)	554 (66.99%)	0.07	581 (64.13%)	185 (61.26%)	396(65.56%)	0.21
Warfarin (*n*, %)	215 (19.04%)	65 (21.52%)	150 (18.14%)	0.20	183(20.20%)	65 (21.52%)	118 (19.54%)	0.48
Pacemaker (*n*, %)	74 (6.56%)	14 (4.64%)	60 (7.26%)	0.13	46 (5.08%)	14 (4.64%)	32 (5.30%)	0.74
ICD (*n*, %)	18 (1.59%)	8 (2.65%)	10 (1.21%)	0.10	17 (1.88%)	8 (2.65%)	9 (1.49%)	0.29
CRT (*n*, %)	22 (1.95%)	13 (4.30%)	9 (1.09%)	<0.01	20 (2.21%)	13 (4.30%)	7 (1.16%)	<0.01
White blood cell, ×10 ^ 9/L	7.62 ± 3.00	7.84 ± 3.13	7.44 ± 2.81	0.01	7.78 ± 3.10	7.84 ± 3.13	7.62 ± 2.92	0.23
Haemoglobin level, g/L	137.7 ± 20.80	141.9 ± 20.50	136.2 ± 20.72	<0.01	139.4 ± 20.98	141.9 ± 20.50	138.2 ± 21.13	0.01
Platelet count, × 10 ^ 9/L	209.2 ± 66.71	223.2 ± 80.54	204.1 ± 60.13	<0.01	211.2 ± 69.64	223.2 ± 80.54	205.2 ± 62.70	<0.01
Creatinine, umol/L	75 (62.00, 94.00)	78 (63.00, 97.00)	74.00 (61.00, 93.00)	0.24	0.2465 (62.00, 93.00)	78 (63.00, 97.00)	73.5 (62.00, 91.00)	0.27
UA, umol/L	406.5 ± 131.7	433.3 ± 142.0	397.5 ± 126.8	<0.01	412.1 ± 131.0	433.3 ± 142.0	402.3 ± 124.5	<0.01
Serum sodium, umol/L	141.7 ± 3.12	141.6 ± 3.18	141.7 ± 3.10	0.62	141.6 ± 3.00	141.6 ± 3.18	141.6 ± 2.91	0.84
Glucose, umol/L	6.38 ± 2.64	6.41 ± 2.88	6.37 ± 2.55	0.84	6.39 ± 2.72	6.41 ± 2.88	6.38 ± 2.64	0.90
D-Dimer, umol/L	420 (210.0, 960.0)	400 (200.0, 970.0)	430.0 (210.0, 935.0)	0.30	400 (190.0, 860.0)	400 (200.0, 970.0)	395 (181.5, 840.0)	0.11
BNP level, ng/L	312.4 (119.0, 772.5)	508.2 (184.6, 1178)	257.4 (105.4, 643.2)	<0.01	317.5 (119.2, 807.1)	508.2 (184.6, 1178)	244.8 (98.09, 630.6)	<0.01
Left ventricular diameter, mm	53.59 ± 7.88	59.53 ± 7.11	51.53 ± 7.06	<0.01	54.69 ± 7.85	59.53 ± 7.11	52.40 ± 7.11	<0.01
Left atrial diameter, mm	42.48 ± 7.26	43.92 ± 6.29	41.98 ± 7.51	<0.01	42.78 ± 7.31	43.92 ± 6.29	42.23 ± 7.69	<0.01
Interventricular septal thickness, mm	10.65 ± 1.91	10.37 ± 1.65	10.75 ± 1.990	<0.01	10.63 ± 1.97	10.37 ± 1.65	10.75 ± 2.09	<0.01
E/e′	12.97 ± 5.63	13.45 ± 5.41	12.78 ± 5.71	0.18	12.89 ± 5.63	13.45 ± 5.41	12.57 ± 5.73	0.09

BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; E/e′, mitral Doppler early velocity/mitral annular early velocity; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; UA, uric acid.

Figure 2 Kaplan–Meier curves for primary outcome between the two groups.

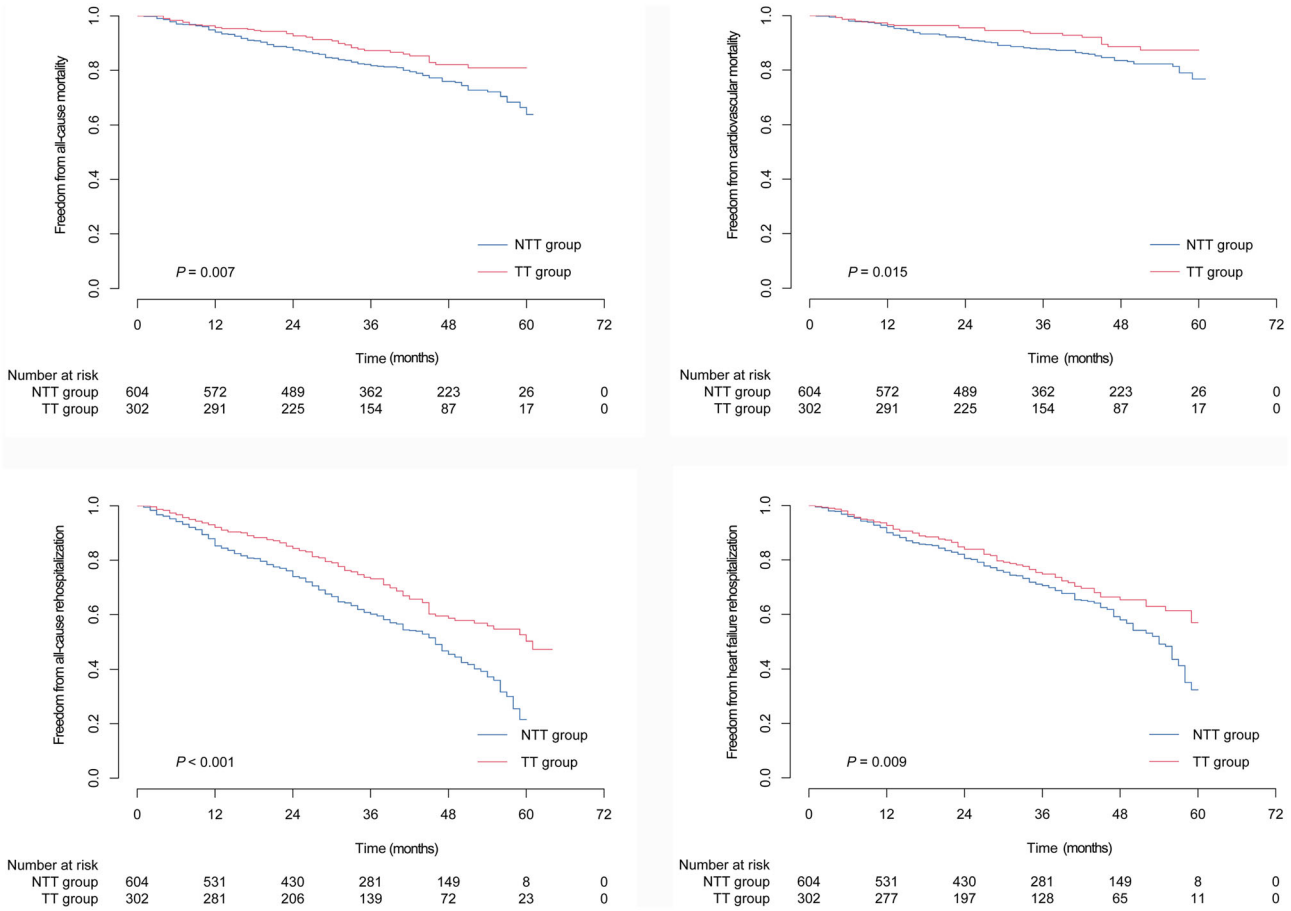

Table 2 Risk of death or hospitalization in HFmrEF subgroups

	Unadjusted		Fully adjusted	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
All-cause death				
Triple therapy vs. non-triple therapy	0.619 (0.435–0.880)	0.008	0.656 (0.447–0.961)	0.030
Cardiovascular death				
Triple therapy vs. non-triple therapy	0.577 (0.368–0.906)	0.017	0.599 (0.380–0.946)	0.028
All-cause hospitalization				
Triple therapy vs. non-triple therapy	0.673 (0.540–0.838)	<0.0001	0.687 (0.541–0.872)	0.002
Heart failure hospitalization				
Triple therapy vs. non-triple therapy	0.714 (0.553–0.922)	0.010	0.732 (0.565–0.948)	0.018

Previous study demonstrated that dynamic transitions from HFmrEF to HFpEF or HFrEF usually occurs within the first year after diagnosis,[18,19] and a reduction in LVEF is usually associated with a poor prognosis. Our study found that, compared with the NTT group, the TT group had a relatively lower risk of adverse outcome during the follow-up. A possible explanation is that the application of GDMT shifts LVEF values in a favourable direction, which needs to be confirmed in future studies.

Currently, most studies about HF focused on HFrEF and HFpEF, with less attention paid to HFmrEF, resulting in limited evidence on which to base recommendation for therapy.[20] The current experience for HFmrEF therapy is mostly based on the results of subgroup analysis in clinical trials. The PARAGON-HF trial revealed that neurohormonal drugs may lead to a significant reduction of deaths or hospitalizations in patients with LVEF between 40 and 49%.[21] This favourable data implied that patients with HFmrEF

characterized by a mildly reduced LVEF would also benefit from neurohormonal treatments. In the OPTIMIZE-HF Registry, ACEI/ARB treatment showed no significant beneficial effects on HF patients with LVEF ≥40%.[22] In this study, ACEI/ARB did not significantly reduce mortality and rehospitalization rates, possibly because the cohort was not specifically classified as HFmrEF or HFpEF. In contrast, several studies using data from the SwedeHF Registry showed that ACEIs/ARBs reduced all-cause mortality both in patients with HFmrEF and HFpEF.[23] In a further analysis of the same registry, ACEIs/ARBs significantly reduced the mortality, regardless of coronary heart disease.[24]

In the CHART-2 study, β-blockers improved clinical outcomes and reduced mortality in both HFmrEF and HFrEF patients.[18] Cleland *et al*. conducted a meta-analysis of randomized controlled trials and found that, compared with placebo, β-receptor blockers reduced cardiovascular deaths in HFmrEF with sinus rhythm and markedly improve left ventricular systolic function.[25] Other studies suggested that for HF patients with sinus rhythm, the effect of β-blockers on mortality in patients with LVEF 40–49% was similar to that of patients with LVEF <40%. Another research also indicated that LVEF increased with β-blockers except for those with LVEF≥50%.[25]

To date, the most important study evaluating the effect of spironolactone on HF patients with LVEF ≥45% is the TOPCAT trial.[26] In a post hoc analysis, a greater potential benefit of spironolactone was observed in patients with a relatively lower LVEF (45–49%) in terms of the primary composite outcome, indicating that patients with HFmrEF may benefit from spironolactone therapy.[27] In a real-world study, it was found that only a minority of HFrEF patients who were eligible for MRA received the drugs following HF hospitalization, but those who did receive them showed better outcomes.[28] Future real-world studies are needed to determine the mortality-reducing effects of MRA in patients with HFmrEF.

Santiago *et al*. reported that the association between high norepinephrine (NE) levels and cardiovascular death was strongest in HFmrEF and weakest in HFpEF patients. Therefore, the response of HFmrEF patients to neurohormonal therapy is similar to that of HFrEF rather than HFpEF.[29] Other studies also confirmed that patients with LVEF between 40 and 49% respond to drug therapy more similarly to patients with reduced LVEF rather than those with preserved LVEF, not only for β-blockers, but also for RAAS inhibitors.[25,27]

These observations were consistent with the findings of our real-world study and reinforce an important role for increasing neurohormonal blockade treatment intensity in improving clinical outcomes in patients with HFmrEF. In the era of precision medicine, the future management of HF may involve accurately evaluating cardiac function and identification characteristics of each patient. This would provide valuable information on improving risk stratification and select the appropriate therapies.

Limitations

Some limitations of this study should be recognized. Firstly, this study was designed as a retrospective observational one to investigate all consecutive hospitalized HF patients. Thus, the resultant studied cohort may limit the generalization of the results to other HF populations. Secondly, the purpose was to detect whether standard treatment for HFrEF could be introduced to HFmrEF. Patients in NTT group were also treated with dual or single agents but were not further subdivided.

Conclusions

This study revealed the response to medical treatment in HFmrEF was more similar to patients with reduced LVEF, and GDMT may also have potential cardiovascular benefits for those with HFmrEF. Future randomized trials and prospective cohort studies are needed to explore in-depth understanding this special phenotype and determine the optimal strategies for this easily overlooked population.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cox proportional hazard regression for death.
Table S2. Cox proportional hazard regression for rehospitalization.

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