The impact of heart rate on patients diagnosed with heart failure with mid-range ejection fraction

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Abstract

Objective: The relationship between prognosis and heart rate remains unclear among patients diagnosed with heart failure with mid-range ejection fraction (HFmrEF). The aim of the present study was to assess the effect of heart rate in this group of patients.
Methods: Of the 197 patients diagnosed with HFmrEF, 92 had a heart rate <70 beats/min (bpm), and 105 had a heart rate ≥70 bpm. We analyzed the outcomes including all-cause death and HF-related hospitalization and evaluated the quality of life.
Results: The outcome demonstrated a lower incidence in patients with heart rate <70 bpm. The outcome-free survival illustrated significant difference in survival rate (p=0.045). The Minnesota Living with Heart Failure Questionnaire total scores and physical subscale in the lower heart rate group decreased compared with the heart rate ≥70 bpm group (p=0.048 and p=0.03, respectively). In the following analysis of patients with sinus rhythm, beta blockers showed great positive effects on patients with heart rate <70 bpm (p=0.046), as for the quality of life in patients with beta blocker, heart rate <70 bpm showed lower total and physical scores (p=0.025 and p=0.017, respectively).
Conclusion: Our results showed that heart rate is an important prognostic factor in patients with HFmrEF. Patients with heart rate <70 bpm was related with a lower risk of outcomes and better quality of life. Beta blockers reduced the outcome rate in patients with sinus rhythm. *(Anatol J Cardiol 2019; 21: 68-74)*
Keywords: HFmrEF, heart rate, quality of life, beta blockers

Introduction

Heart failure (HF) is a clinical syndrome characterized by typical symptoms and signs caused by functional and/or structural cardiac defects (1). It is traditionally divided into two types as heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) based on the retention of left ventricular ejection fraction (LVEF <40% or ≥50%). However, in 2016, the European Society of Cardiology (ESC) defined a third type of HF with mid-range LVEF (40%–49%) as heart failure with mid-range ejection fraction (HFmrEF) in their newly updated diagnostic and treatment guidelines (1). Some trials showed that HFmrEF was a distinct clinical entity (2, 3), whereas others preferred a transitional status between HFpEF and HFrEF rather than its independence. Its clinical features are intermediate between HFpEF and HFrEF; however, alternative transitions from HFmrEF to HFpEF or HFrEF occur within the first year of the pathological processes, dynamically (4, 5). The ESC guideline recommends screening patients with HFmrEF for comorbidities, and if present, it should be treated with safe and effective interventions to improve symptoms (1).

Heart rate has been regarded as an independent predictor of outcome for patients with HFrEF, and therapeutic strategies aimed to lowering heart rate have been proven to improve the outcomes in patients with HF (6-9). There was no evidence that heart rate control improves symptoms in patients diagnosed with HFpEF (10, 11), and the management of atrial fibrillation (AF) in HFpEF has not been investigated to the same extent as in HFrEF. As such, the current guidelines recommend initial heart rate control via agents followed by a trial of rhythm control if symptoms of AF persist (12). Patients with HFmrEF have generally been included in trials of HFpEF, so there was less evidence evaluating the impact of heart rate on HFmrEF. It might be pos-

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sible to make separate recommendations for each phenotype as new data and analyses become available (13).

The health-related quality of life (HRQoL) of patients with HF is an important outcome as it reflects the impact of HF on their daily lives. Qualifying the patients' physical and emotional statuses is important and reliable for physicians to evaluate the effect of therapy. In addition, improving HRQoL is an important goal in HF treatment. There is less information on the comparisons of HRQoL in these three populations of patients with HF. Various specific HRQoL questionnaires for patients with HF have been regarded as crucial assessment tools for the assessment of how HF impacts their symptoms, function, and quality of life in recent decades (14-17). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is one of the most widely used and highly regarded HRQoL questionnaires for patients with HF (18, 19).

Therefore, in this retrospective study, we evaluated the associations of heart rate with outcomes in patients with HFmrEF, aiming to find out the relationship between heart rate control and prognosis in patients with HFmrEF.

Methods

Study design and patients

We retrospectively referred all patients admitted to the First Affiliated Hospital of China Medical University and diagnosed with HF from November 2014 to May 2015. Patients with LVEF were continuously enrolled and ranged from 40% to 49% according to their echocardiography result at admission; the definition criteria for HFmrEF was according to the ESC HF guideline (1). Exclusion criteria includes recent history of acute coronary syndrome, any organic and/or psychiatric disorder that might hinder the content completion of health-related questionnaire.

Of the 208 patients enrolled, 11 were lost to follow-up or refused to complete the questionnaire. A total of 197 patients were included in the study. Informed consent was obtained from all patients. The detailed clinical data recorded at the time of the patients' inclusion were echocardiography, laboratory blood tests, and treatments. LV end-diastolic volumes and EF parameters were measured and calculated by echocardiography using the Simpson biplane method.

Admission and discharge heart rates (in beats/min, bpm) were identified by palpation, electrocardiogram, or Holter monitoring among patients with sinus rhythm. In order to minimize bias caused by possible measurement errors or acute inpatient clinical instability, we focused on patients with stable heart rates, which was defined as admission to discharge heart rate variation of <20 bpm. For those with AF, we adopted and identified their Holter results according to their mean heart rate for 24 h. According to previous evidence, in patients with left ventricular dysfunction and HF, heart rate >70 bpm with an increment in resting heart rate of 1 and 5 bpm has been linked to a higher cumulative risk of death for cardiovascular causes and to a higher rate of hospitalizations for HF, with 3% and 16%, respectively (9). Therefore, we identified the cut-off value of heart rate as 70 bpm.

Of the 197 patients, 92 (46.7%) had a discharge heart rate of <70 bpm. We identified the heart rate cut-off value as 70 bpm to define low heart rate because a heart rate <70 bpm has been shown to be associated with improved cardiovascular outcomes in patients with HFrEF.

Follow-up and endpoints

Patients were followed up by phone calls or clinical visits 1 year after discharge from the hospital. Eleven patients were excluded from the study, with nine of them lost to follow-up and the other two refused to complete their MLHFQ. Thus, all 11 patients were censored for survival analysis. The endpoints were defined as the presence of all-cause mortality or repeated HF-related hospitalization. All-cause death was defined as cardiac (HF or non-HF), non-cardiac, or unknown cause. HF-related hospitalization was defined as hospitalization due to the following reasons: unplanned hospitalization, leading to changes in HF treatment; emergency room visit or urgent care visit requiring intravenous drug treatment (diuretics or inotropic medication); invasive intervention (assist device); and initiation of any intravenous drug treatment (diuretics or inotropic medication) related to HF, without emergency room or urgent care visit. During the follow-up, all patients received the MLHFQ, which is one of the most widely used HRQoL questionnaires for patients with HF (18, 19). The MLHFQ is a self-administered disease-specific questionnaire for patients with HF, comprising 21 items representing different degrees of impact of HF on HRQoL, graded from 0 (none) to 5 (very much). It provides a total score (range 0–105), scores for two dimensions, physical limitations (questions 2–7 and 12–13 range 0–40), and emotional limitations (questions 17–21, range 0–25). Higher scores indicate worse HRQoL, and the questions cover symptoms and signs that are relevant to HF.

Statistical analysis

Quantitative variables are expressed as mean (standard deviation) or median [95% confidence interval (CI)], as appropriate, and categorical variables as frequency (percentage, %). Normality test was used to assess continuous variables for fitting of normal distribution, and for normally distributed continuous variables, the Student's t-test was used. Non-normally distributed variables were analyzed using the non-parametric Mann-Whitney U test. The chi-square or Fisher's exact test was used for comparison of categorical variables. Survival analysis was conducted by Kaplan–Meier analysis, and statistical differences between curves were assessed by log-rank test. The 1-year follow-up MLHFQ scores among three groups were also compared by Student's t-test. Cox proportional hazard model analysis was used to identify the potential prognostic factors. Hazard ratio (HR) and 95% CI were calculated. All p-values were two-sided. A p-value <0.05 was considered statistically significant. Data were analyzed using the SPSS 22.0 for Windows.

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Internal reliability of the MLHFQ

Cronbach's α was used to determine the internal consistency of the MLHFQ domains among patients in the three subgroups, separately. It evaluates the internal consistency of the items within a domain. Values ranged from 0 to 1, with larger values providing greater consistence (20). A value ≧0.70 was considered satisfactory for internal consistency.

Results

We continuously enrolled 197 patients diagnosed with HFmrEF in the First Affiliated Hospital of China Medical University between November 2014 and May 2015. Figure 1 shows the trial flowchart. The follow-up ended in June 2015, and complete follow-up was obtained for 94.7% of the patients. The median follow-up period was 362 (360–368) days. Among the 197 patients with intact follow-up information, the baseline and procedural characteristics were not statistically different among both groups, except effective glomerular filtration rate (eGFR), and U test of eGFR showed that p=0.214 (Table 1).

Events during follow-up

When evaluating the impact of heart rate on the prognosis, we compared patients with heart rate <70 bpm and ≥70 bpm. The results showed that lower heart rate was associated with reducing the incidence of total outcomes (19.5% vs. 32.3%, HR: 0.508, 95% CI 0.263–0.980, p=0.042) (Table 2). The incidence of all-cause death and HF hospitalization was not significantly different between the two groups.

Quality of life

All patients' quality of life was measured by the MLHFQ at the end of a 1-year follow-up. In patients in the <70 bpm group, the degree of inter-item correlation that was evaluated by the Cronbach's α in each MLHFQ domain was large (α>0.80); Cronbach's α coefficients ranged from a low of 0.82 (physical subscale) to a high of 0.92 (total score) in the MLHFQ. Similar conditions could be found in patients with heart rate >70 bpm, α=0.90 of total score, 0.88 of physical score, and 0.85 of emotional score. As shown in Figure 2, we found that the difference for total scores was significant between the two groups (30.7 vs. 33.2, p=0.048), and the comparison of both emotional and physical components was also performed. We found that patients with <70 bpm had lower physical scores (13.9 vs. 15.3, p=0.030); however, there

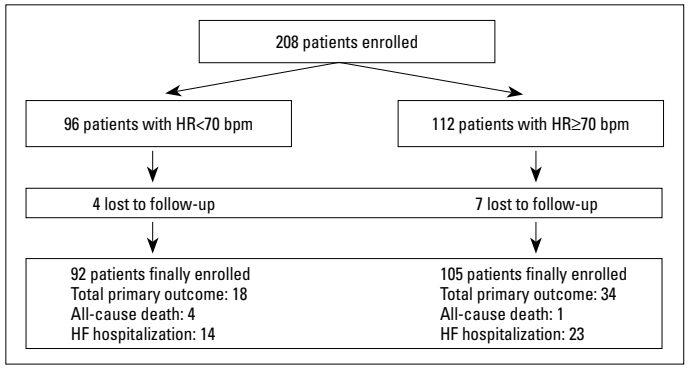

Figure 1. Trial flowchart

Table 1. Baseline characteristics

	Group 1	Group 2	*P*-value
Age, years	65.1±1.33	63.0±1.29	0.301
Female sex, n (%)	50 (54.3)	61 (58.1)	0.597
Clinical history, n (%)			
Hypertension	55 (59.7)	71 (67.6)	0.253
Diabetes mellitus	38 (41.3)	46 (42.8)	0.723
Ischemic etiology	25 (27.2)	30 (28.5)	0.827
Prior MI	17 (18.4)	18 (17.1)	0.807
Stroke	50 (54.3)	46 (43.8)	0.140
Atrial fibrillation	21 (22.8)	23 (21.9)	0.877
Heart rate	66.8±10.6	78.4±13.1	0.068
NYHA class, n (%)			0.994
I	17 (18.5)	20 (19.1)	
II	51 (55.4)	58 (55.2)	
III	24 (26.1)	27 (25.7)	
LVDd, mm	51.4±7.5	55.2±9.2	0.168
LVDs, mm	42.1±5.5	45.6±6.6	0.098
Laboratory data			
Hemoglobin, g/L	112.26±15.45	112.77±16.09	0.245
Creatinine, μmol/L	91.82±7.02	83.84±3.23	0.356
Albumin, g/L	38.38±5.08	37.85±4.25	0.551
eGFR, mL/min	80.57±32.86	84.74±41.33	0.324
HDL-C, mmol/L	0.95±0.311	0.96±0.27	0.884
LDL-C, mmol/L	2.88±1.05	2.95±1.14	0.204
BNP, pg/mL	858.1±693.83	747.2±616.56	0.196
Discharge medication (%)			
Beta blockers	54 (58.6)	63 (60)	0.852
ACEI/ARB	49 (53.2)	60 (57.1)	0.585
Diuretics	73 (79.3)	79 (75.2)	0.493
Digoxin	18 (19.6)	33 (31.4)	0.058
Spironolactone	37 (40.2)	43 (40.9)	0.917
Aspirin	32 (34.7)	36 (34.3)	0.942
Nitrates	25 (27.2)	30 (28.6)	0.827
Discharge clinical findings			
Systolic blood pressure, mm Hg	123.09±15.74	118.22±22.17	0.079
Diastolic blood pressure, mm Hg	69.46±8.40	69.03±9.47	0.589

Group 1: heart rate <70 bpm; Group 2: heart rate ≥70 bpm; ACEI - angiotensin converting enzyme inhibitors; ARB - angiotensin II receptor blocker; BNP - brain natriuretic peptide; eGFR - effective glomerular filtration rate; HDL-C - high-density lipoprotein cholesterol; MI - myocardial infarction; NYHA - New York Heart Association; LDL-C - low-density lipoprotein cholesterol

Table 2. Outcome of a 1-year follow-up for patients with different heart rate regimens

	Group 1	Group 2	Hazard ratio (95% CI)	*P*-value
Total primary outcome	18 (19.5%)	34 (32.3%)	0.508 (0.263-0.980)	0.042
All-cause death	4 (4.3%)	1 (0.9%)	0.491 (0.164-1.470)	0.196
HF hospitalization	14 (15.2%)	23 (21.9%)	0.640 (0.307-1.332)	0.231

Group 1: heart rate <70 beats/min; Group 2: heart rate ≥70 beats/min; HF - heart failure

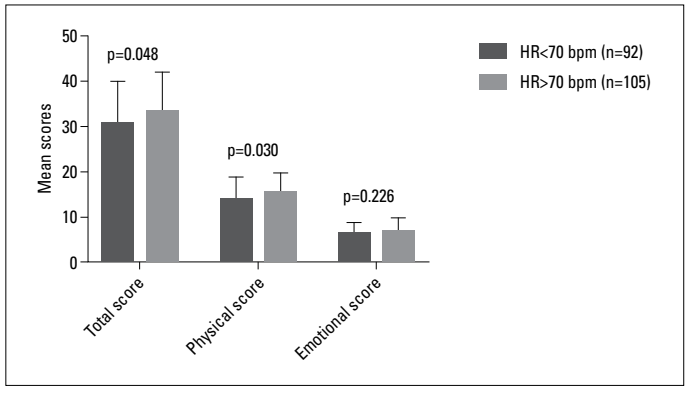

Figure 2. Kaplan–Meier cumulative survival at a 1-year follow-up

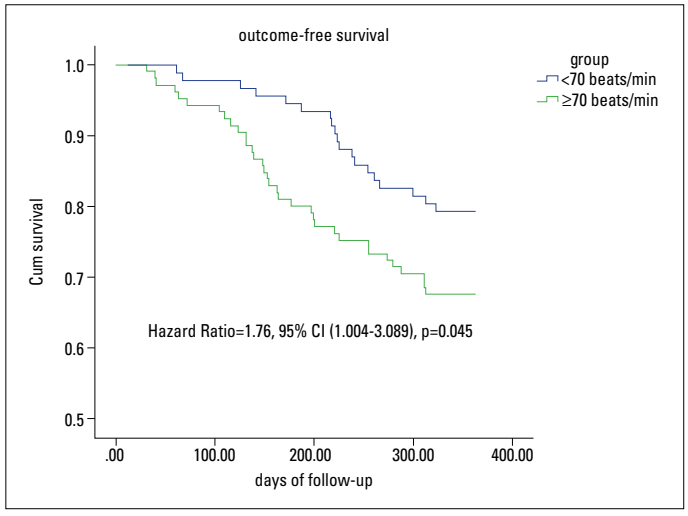

Figure 3. Kaplan–Meier cumulative survival at a 1-year follow-up among patients with sinus rhythm

was no significant difference for the emotional subscale (6.2 vs. 6.7, p=0.226).

Survival analysis

Kaplan–Meier analysis was conducted for survival analysis. First, we compared the overall outcome-free survival ignoring the influence of AF. Outcome-free prognosis was significantly better in the <70 bpm than in the ≥70 bpm group (HR=1.76, 95% CI 1.004–3.089, p=0.045) (Fig. 3). In the following comparison, we focused on patients diagnosed with AF or sinus rhythm, and patients received beta blocker or not.

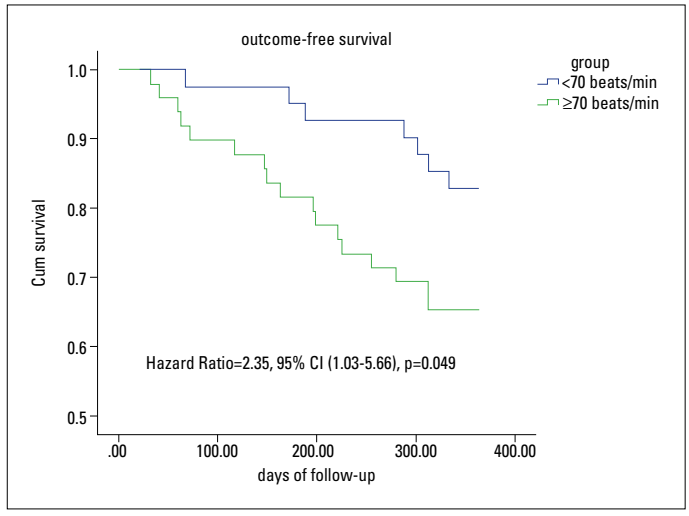

Figure 4. Kaplan–Meier cumulative survival at a 1-year follow-up for patients in sinus rhythm with or without beta blockers

Table 3. Quality of life in patients with beta blockers

	Group 1	Group 2	*P*-value
Patients without beta blockers			
Total scores	31.4±9.62	32.0±7.38	0.76
Physical scores	14.3±5.08	14.6±3.66	0.76
Emotional scores	6.4±2.51	6.6±1.65	0.70
Patients with agents			
Total scores	29.7±8.64	34.0±9.01	0.025
Physical scores	13.3±4.60	15.7±4.59	0.017
Emotional scores	6.14±2.61	6.7±2.33	0.279

Group 1: heart rate <70 beats/min; Group 2: heart rate ≥70 beats/min.

For the previous comparison, we compared patients diagnosed with sinus rhythm and did not enroll patients with AF; the results showed that patients in the <70 bpm had better prognosis than those in the ≥70 bpm group (HR=2.35, 95% CI 1.03–5.66, p=0.049) (Fig. 4). Owing to the relatively low rate of AF diagnosis, there was no significant statistical analysis among patients with AF. Then, we analyze the impact of beta blockers on patients' survival among patients diagnosed with sinus rhythm, but there was no difference between the two heart rate groups who did

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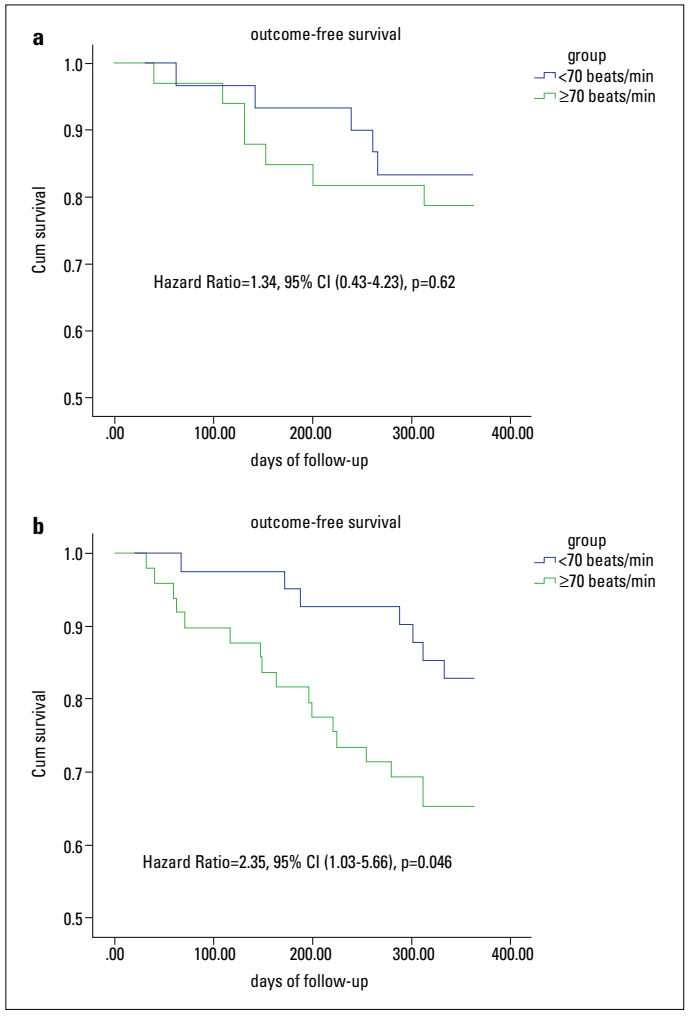

Figure 5. The impact of beta blockers on patients' survival at a 1 year follow-up

not receive beta blocker (HR=1.34, 95% CI 0.43–4.23, p=0.62) (Fig. 5a), and for those given beta blocker, patients in the <70 bpm had better prognosis than those in the ≥70 bpm group (HR=2.35, 95% CI 1.03–5.66, p=0.046) (Fig. 5b). In the following analysis of the quality of life, we also offered similar evidence (Table 3).

Discussion

Findings from our study showed that among patients with HFmrEF, a discharge heart rate of <70 bpm was associated with lower risk of the combined endpoint of HF readmission or all-cause mortality. However, lower heart rate had no significant association with HF readmission or all-cause death. In addition, our analysis confirmed a reduction in mortality with beta blockers for patients with HFmrEF in sinus rhythm. In the past, few trials analyzed the features and prognosis in patients with HFmrEF who have generally been included in the HFpEF trials.

Approximately half of the hospitalizations for the deterioration and continuing unmitigated syndrome of HF occurred in patients with preserved or mid-range ejection. Unfortunately, no treatment options have been proven to improve the prognosis in HFmrEF (21).

Heart rate represents an important factor of myocardial oxygen consumption and of coronary blood flow playing an important role in the adaptation of cardiac output to the metabolic requirements of the organism. It has been found that heart rate is associated with higher mortality in various conditions (22). The Framingham study showed a 14% increase in all-cause death for every 10 bpm increase. In addition, it demonstrated that basal heart rate higher than 80 bpm was associated with significantly increased risk of developing HF (23). In the CHARM trial, an increase in heart rate during follow-up was a significant predictor of events; therefore, heart rate can be identified as an important biological marker of prognosis and could represent an important therapeutic target (24).

Unlike HF with reduced EF, no treatment strategies have been proven to improve the outcomes in patients with HFmrEF among patients with chronic HF, and nearly half had normal or near normal LVEF; HFmrEF (40%–49%) is receiving increasing attention. Prior studies have investigated the features, triggers, prognosis, and response to therapy in patients with HFmrEF (25, 26). The HRQoL, which reflects the impact of HF on their daily life, is an important outcome for patients with HF who suffer from not only physical but also emotional pains in their end status of various cardiovascular diseases. It is extremely important for the physician to evaluate both the psychosomatic state and the efficacy of therapy. In the present study, we surveyed the quality of life among all patients enrolled through a commonly used questionnaire, MLHFQ. The results showed that the quality of life assessment of patients with HFmrEF demonstrated that a discharge heart rate of <70 bpm was associated with better quality of life according to the total scores and physical subscale, but not for emotional one.

Our study also focused on the impact of beta blocker and AF on patients with HFmrEF. HF and AF are common conditions increasing in prevalence and reducing the quality of life. AF is both a cause and consequence of HF. It is associated with a threefold increased risk of incident HF (27). Owing to our limited data, we excluded patients diagnosed with AF and analyzed the prognosis of patients with sinus rhythm; we separately analyzed the prognosis of patients with or without beta blocker. The results showed that patients receiving beta blocker have better prognosis and higher quality of life; this may provide reasonable therapy strategy for patients with HFmrEF in the future.

There are several interesting points that we need to take note. First, the rate of AF in the <70 bpm group was higher than that in the ≥70 bpm group, whereas the usage rate of digoxin was lower as shown in Table 1. Therefore, we reviewed all patients' medical records and found that patients with a heart rate ≥70 bpm complained about fatigue and had shortness of breath more frequently. Many of them (36.7%) presented with a high heart rate (>100 bpm); for these patients, beta blocker alone could not

effectively control their heart rate, so many of them received digoxin. Second, some trials identified that HFmrEF was a transitional stage from HFpEF to HFrEF, indicating that there may be some similarities to HFpEF, patients with HFpEF were older, more commonly female, and more likely to be hypertensive, but less likely to have coronary artery disease (28). This may explain that in our cohort, it is almost 50% female and very rarely ischemic. We reviewed the medical records of our patients and found that patients with HFpEF were older, more commonly female, and more likely to be hypertensive, but less likely to have coronary artery disease.

Study limitations

Our study has several limitations. First, the sample size was relatively small, and we could not obtain sufficient data to analyze the impact of AF on patients. Second, this was a retrospective analysis and background therapy. In addition, patients enrolled in our trial used different beta blockers, which may cause bias on the prognosis. Finally, we did not have data on heart rate before hospital admission.

Conclusion

In conclusion, we believe heart rate is an important prognostic factor in patients with HFmrEF. Patients with a discharge heart rate <70 bpm was associated with a lower risk of outcomes and better quality of life. Beta blockers reduced the outcome rate in patients with HFmrEF in sinus rhythm.

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