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Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: a systematic review and meta-analysis

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Abstract

Aims This study aimed to assess by a meta-analysis the clinical characteristics, all-cause and cardiovascular mortality, and hospitalization of patients with heart failure (HF) with mid-range ejection fraction (HFmrEF) compared with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).

Methods and results Data from 12 eligible observational studies including 109 257 patients were pooled. HFmrEF patients were significantly different and occupied a mid-position between HFrEF and HFpEF: mean age 73.6 ± 9.8 vs. 72.6 ± 9.8 and 77.6 ± 7.2 years, male gender 59% vs. 68.5% and 40%, ischaemic heart disease 49% vs. 52.6% and 39.4%, hypertension 67.3% vs. 61.5% and 76.5%, atrial fibrillation 45.2% vs. 39.6% and 46%, chronic obstructive pulmonary disease 26.4% vs. 24.9% and 30.5%, estimated glomerular filtration rate 62 ± 30 vs. 63.3 ± 23 and 59 ± 22.5, use of renin–angiotensin system inhibitors 79.6% vs. 90.1% and 68.7%, beta-blockers 82% vs. 89% and 73.5%, and aldosterone antagonists 20.3 vs. 31.5% and 26%, P-values < 0.05. After a mean follow-up of 31 ± 5 months, all-cause mortality was significantly lower in HFmrEF than in HFrEF and HFpEF (26.8% vs. 29.5% and 31%): risk ratio (RR) 0.95 [0.93–0.98; 95% confidence interval (CI)], P < 0.001, and 0.97 (0.94–0.99; 95% CI), P = 0.014, respectively. Cardiovascular mortality was lowest in HFmrEF (9.7% vs. 13% and 12.8%): RR = 0.81 (0.73–0.91), P < 0.001, and 1.10 (0.97–1.24; 95% CI), P = 0.13, respectively. HF hospitalization in HFmrEF compared to that in HFrEF and HFpEF was 23.9% vs. 27.6% and 23.3% with RR = 0.89 (0.85–0.93), P < 0.001, and RR = 1.12 (1.07–1.17), P < 0.001, respectively.

Conclusions The results of this study support that HFmrEF is a distinct category characterized by a mid-position between HFrEF and HFpEF and with the lowest all-cause and cardiovascular mortality.

Keywords Heart failure; Ejection fraction; Mid-range; Borderline

Introduction

During the last three decades, left ventricular systolic ejection fraction (LVEF) has been used as the main diagnostic and prognostic parameters in management of patients with chronic heart failure (CHF). Reduced LVEF is generally associated with increased risk of overt heart failure (HF) and worse prognosis, but the majority of randomized controlled trials using therapeutic or mechanical interventions has been restricted to CHF patients with LVEF < 35%. Nonetheless, observational studies on patients with mildly reduced LVEF have shown poorer prognosis compared with those with HF and normal LVEF.

Until recently, CHF patients have been classified into two categories: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) based on LVEF estimation with cut-off limits of ≤ 40% and ≥ 50%, respectively. However, grey-area patients with moderately impaired LVEF...
have not been comprised in these traditional categories and have been poorly characterized. Recently, more attention has been given to patients with borderline low systolic LVEF, whereas both the European Society of Cardiology and American Society of Cardiology have introduced a new category of CHF with borderline reduced LVEF of 40–49%, called HF with mid-range ejection fraction (HFmrEF).\textsuperscript{3,4}

Despite publication of a considerable number of epidemiological studies and reviews on patients with HFmrEF compared with HFrEF and HFpEF, the clinical characteristics and prognosis of this newly suggested entity are still inadequately addressed and the results concerning mortality and hospitalization have varied considerably across the published studies.\textsuperscript{5–7} By means of a systematic review and meta-analysis of the current literature, we collected and pooled all available published data in order to shed more light on patient characteristics, mortality, and hospitalization of HFmrEF patients compared with the established categories HFrEF and HFpEF.

**Methods**

**Study design**

This is a systematic literature review and meta-analysis, which was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis.\textsuperscript{8}

**Search strategy**

The search was conducted in the electronic databases PubMed and Web of Science for all published clinical studies that examined baseline characteristics and mortality in patients with HFmrEF compared with HFrEF and HFpEF. The following keywords in different combinations were used: heart failure, left ventricle, ejection fraction combined with the terms mid-range and borderline. All electronically published papers were screened by titles and abstracts and by reviewing the full paper if deemed relevant. The literature search was restricted to papers published until 30 September 2017. The systematic search was supplemented by reviewing all references in retrieved eligible studies, as well as key review papers.

**Study eligibility**

Observational studies and randomized controlled trials were considered for inclusion if they reported key baseline characteristics and all-cause mortality in patients with HFmrEF (defined as LVEF of 40–49%) compared with HFrEF (defined as LVEF <40%) and HFpEF (defined as LVEF ≥50%). The diagnosis of HF categories should rely on the recent transthoracic echocardiographic findings and clinical judgement according to the guidelines. Eligible studies were also required to provide numbers of events for all-cause and cardiovascular mortality, and preferably HF-specific hospitalization with a follow-up period of at least 1 year. We excluded all studies with a follow-up period shorter than 1 year, small-sized studies including <100 participants, and studies with insufficiently reported data.

**Data extraction**

We extracted data on the demographic features and key baseline clinical variables reported as means or medians with standard deviations (SD) or ranges from each study. We extracted absolute numbers for all-cause and cardiovascular mortality and HF hospitalization. Values reported as medians with ranges were re-estimated to their corresponding means with SDs. Values presented as percentages were recalculated to absolute numbers. In one study,\textsuperscript{7} the death and hospitalization numbers were approximated from the Kaplan–Meier curve. In case of studies lacking key data in published reports, we contacted the corresponding authors to request the missing information. Two authors (J. A. and J. L.) conducted the search and data extraction independently. Any disagreement was resolved by consensus.

**Statistical methods**

Baseline characteristics were pooled and analysed as either weighted means or numbers. The weighted mean difference method was used for pooling of means and their SDs. The reported numbers of all-cause and cardiovascular mortality and HF hospitalization in eligible studies were pooled for the HFmrEF vs. HFrEF and HFpEF groups, followed by an estimation of a risk ratio (RR) with 95% confidence interval (CI). Despite the significant heterogeneity between studies, we used a fixed-effects model in order to maintain the real sizes of the larger studies but beside that presented the results of random-effects methods wherever reasonable. For the overall estimated RR, a P-value <0.05 was considered statistically significant. Heterogeneity among studies was tested using the χ\textsuperscript{2} method (P-values <0.05 were considered statistically significant) and the I\textsuperscript{2} statistic. The I\textsuperscript{2} ranging between 0% and 100% indicated the percentage of variation in the study results attributable to between-study heterogeneity rather than due to sampling error, and an I\textsuperscript{2} value >20% was considered statistically significant. All analyses were performed using the meta-analysis package of the statistic software program Stata Version 13 (Stata Corporation, Lakeway Drive, College Station, TX).
Results

Twelve eligible observational studies were included in this meta-analysis. The search process and outputs are shown in Figure 1.

Study and patient characteristics

Study characteristics are shown in Table 1. The included studies were either registry or retrospective data analyses of previously conducted prospective trials. Of a total population of 109,257 patients, 51,496 (47.1%) had HFrEF, 20,114 (18.4%) had HFmrEF, and 37,647 (34.4%) had HFrEF. Patients were followed up for at least 12 months with a mean period of 31 ± 5 months.

Baseline characteristics of the three HF categories are reported in Table 2. There were statistically significant differences between HFmrEF and HFrEF and between HFmrEF and HFrEF. Patients with HFmrEF were older than those with HFrEF but younger than those with HFrEF. The proportion of males and prevalence of ischaemic heart disease (IHD) among HFmrEF were lower than those among HFrEF, but higher than those among HFrEF. Hypertension was more frequent in patients with HFmrEF than in those with HFrEF, but less frequent than in those with HFrEF. Diabetes was significantly less frequent in both HFmrEF and HFrEF than in HFrEF. Atrial fibrillation was more frequently present among HFmrEF than among HFrEF but less frequent than among HFrEF. The prevalence of chronic obstructive pulmonary disease (COPD) was highest in HFrEF relative to both HFmrEF and HFpEF. HFpEF patients had also significantly worse renal function than patients with HFrEF and HFmrEF. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers were more frequently used in HFrEF than in both HFmrEF and HFpEF. Aldosterone antagonists were used more frequently in patients with HFpEF than in both those with HFrEF and HFmrEF.

Meta-analysis of risk of all-cause mortality

At the end of follow-up, patients with HFmrEF had lower all-cause mortality 5,402/20,114 (26.8%) than those with HFrEF 15,222/51,496 (29.5%) and those with HFpEF 11,681/37,647 (31.0%). Pooled data of the 12 studies using the fixed-effects model showed that the risk of all-cause death was significantly lower in patients with HFmrEF than in those with HFrEF with RR = 0.95 (0.93–0.98; 95%CI), P < 0.001, and HFpEF with RR = 0.97 (0.94–0.99; 95%CI), P = 0.020 (Figure 2). There was significant heterogeneity between the included studies, P < 0.001 and I² > 20%. Running the analysis using the
### Table 1 Characteristics of the included studies

| Author and publication year | Study type | Number of patients | Mean follow-up (months ± SD) |
|-----------------------------|------------|--------------------|-----------------------------|
| Cheng et al., 2014          | Hospital registry data retrospective analysis | 40.239 | 18.897 | 12 ± NA |
| Junior et al., 2016         | Patients referred for exercise testing; retrospective analysis | 774 | 620 | 52 ± 9.5 |
| Delepaul et al., 2017       | HF unit care registry; retrospective analysis | 482 | 258 | 32 ± 14.5 |
| Gomez-Otero et al., 2017    | Prospective registry data | 1.420 | 227 | 12 ± NA |
| Chioncel et al., 2017       | Prospective registry data | 9.134 | 2.212 | 12 ± NA |
| Rickenbacher et al., 2017   | Prospective randomized trial; retrospective analysis | 622 | 108 | 27 ± 8 |
| Pascual-Figal et al., 2014  | Prospective cohorts of ambulatory patients | 3.446 | 460 | 41.5 ± 3.5 |
| Koh et al., 2017            | Swedish National Registry; retrospective analysis | 42.061 | 9.019 | 36 ± 12 |
| Coles et al., 2017          | Hospitals registry; retrospective analysis | 4.025 | 521 | 12 ± NA |
| Bonsu et al., 2017          | Hospitals registry; retrospective analysis | 1.488 | 265 | 60 ± NA |
| Margolis et al., 2017       | Patients admitted with STEMI and underwent PCI | 2.086 | 858 | 42 ± 30 |
| Tsuji et al., 2017          | Multicentre prospective observational study | 3480 | 2154 | 36 ± 12 |

HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction.

### Table 2 Comparison of baseline characterizes of heart failure with mid-range left ventricular ejection fraction with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

| Characteristics | Number of studies providing data | Values shown as weighted means ± SD or numbers (%) | P-values |
|-----------------|---------------------------------|----------------------------------------------------|----------|
| Age (years)     | 12                              | HFrEF 72.3 ± 9.3 HFrEF 73.6 ± 9.8 HFrEF 77.6 ± 7.2 | <0.001 <0.001 |
| Male gender     | 12                              | 35 259/51 496 (68.5%) 11 950/20 114 (59%) 15 211/37 647 (40%) | <0.001 <0.001 |
| Ischaemic heart disease | 12                              | 5918/20 114 (49%) 14 842/37 647 (39.4%) | 0.034 <0.001 |
| History of hypertension | 12                              | 13 536/20 114 (67.3%) 28 824/37 647 (76.5%) | <0.001 <0.001 |
| History of diabetes | 11                              | 6079/20 114 (26.4%) 10 322/33 845 (30.5%) | 0.001 <0.001 |
| History of atrial fibrillation | 6                               | 8709/20 114 (45.2%) 16 857/36 634 (46%) | <0.001 <0.001 |
| Chronic obstructive pulmonary disease | 9                               | 4810/18 200 24.9% 10 322/33 845 30.5% | 0.001 <0.001 |
| Estimated glomerular filtration rate | 6                               | 63.3 ± 23 62.0 ± 30.0 59.0 ± 22.5 | <0.001 <0.001 |
| Mean baseline LVEF | 8                                | 26.3 ± 4.2 43.1 ± 2.7 59.8 ± 3.6 | <0.001 <0.001 |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; SD, standard deviation.
random-effects model showed that the risk of all-cause death was still significantly lower in patients with HFmrEF than in those with HFrEF with RR = 0.90 (0.83–0.98; 95% CI), \( P = 0.010 \), but not significant when compared with those with HfPEF with RR = 1.01 (0.96–1.10; 95%CI), \( P = 0.59 \).

Data from five large size studies\(^5,6,9-11\) including 94 981 patients were also pooled to estimate 1 year all-cause mortality. There were 14 078/46 126 (30.5%) deaths in HFrEF, 4876/16 936 (28.8%) in HFmrEF, and 10 740/31 919 (33.6%) in HFpEF. Using the fixed-effects model, the risk of all-cause mortality in the first year of follow-up was RR = 0.96 (0.94–0.99; 95% CI), \( P = 0.013 \), and RR = 0.94 (0.91–0.97; 95%CI), \( P < 0.001 \), comparing HFmrEF with HFrEF and HfPEF, respectively.

A sensitivity analysis was performed by excluding the relatively small study by Margolis \(^{12}\) due its larger effect in order to exclude the small-study effect. The results were unchanged when comparing HFmrEF with HFrEF and HfPEF.

**Meta-analysis of risk of cardiovascular death**

Five studies provided data for cardiovascular death.\(^6,7,11,13,14\) There were 1229/9469 (13%) deaths among HFrEF patients, 365/3760 (9.7%) among HFmrEF patients, and 735/5739 (12.8%) among HfPEF patients. Meta-analysis using the fixed-effects model showed a significant lower risk of death in patients with HFmrEF than in those with HFrEF, RR = 0.81 (0.73–0.91; 95% CI), but no significant difference when compared with HfPEF, RR = 1.10 (0.97–1.24; 95% CI) (Figure 3). The results were unchanged using the random-effects model.

**Meta-analysis of risk of heart failure hospitalizations**

Five studies provided data for HF hospitalization.\(^5-7,11,15\) There were 6319/22 891 (27.6%) hospitalizations among HFrEF patients, 2094/8769 (23.9%) among HFmrEF patients, and 5445/2323 (23.3%) among HfPEF patients. When data are pooled using the fixed-effects model, the risk of hospitalization was significantly lower in HFmrEF than in HFrEF but higher in HfPEF, RR = 0.89 (0.85–0.93; 95% CI), \( P < 0.001 \), and 1.12 (1.07–1.17; 95% CI), \( P < 0.001 \), respectively (Figure 4). It was not relevant to repeat the analysis using the random-effects model due to the large study effect.

All findings of the baseline characteristics, all-cause and cardiovascular mortality, and hospitalization are summarized in Figures 5 and 6.
Figure 3  Meta-analysis of cardiovascular death comparing heart failure (HF) with mid-range ejection fraction (HFmrEF) with HF with reduced ejection fraction (HFrEF) and HF preserved ejection fraction (HFpEF). CI, confidence interval; RR, risk ratio.

| Study          | Death | Total | In favour of HFmrEF | RR (95% CI) | Weight % |
|----------------|-------|-------|---------------------|-------------|----------|
| HFmrEF vs. HFrEF |       |       |                      |             |          |
| Chioncel       | 85    | 2212  | 257                 | 0.82 (0.65, 1.05) | 14.21    |
| Pascual-Fidal  | 93    | 460   | 621                 | 0.80 (0.66, 0.99) | 18.80    |
| Gomez-Otero    | 36    | 227   | 94                  | 1.03 (0.72, 1.48) | 4.83     |
| Bonus          | 86    | 265   | 116                 | 0.97 (0.76, 1.24) | 9.67     |
| Tsuji          | 65    | 596   | 146                 | 0.59 (0.45, 0.78) | 12.11    |
| Test of RR=1; p=0.001  |        |       |                      | 0.81 (0.73, 0.91) | 59.63    |
| Heterogeneity: F=56.2%, p=0.058 |

Figure 4  Meta-analysis of heart failure (HF) hospitalization comparing heart failure with mid-range ejection fraction (HFmrEF) with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). CI, confidence interval; RR, risk ratio.

| Study          | Event | Total | In favour of HFmrEF | RR (95% CI) | Weight % |
|----------------|-------|-------|---------------------|-------------|----------|
| HFmrEF vs. HFpEF |       |       |                      |             |          |
| Chioncel       | 1597  | 5626  | 4856                | 1.30 (1.09, 1.55) | 5.03     |
| Pascual-Fidal  | 178   | 596   | 292                 | 1.14 (0.88, 1.47) | 9.04     |
| Gomez-Otero    | 192   | 2212  | 797                 | 1.03 (0.72, 1.47) | 4.93     |
| Bonus          | 178   | 596   | 292                 | 1.10 (0.89, 1.36) | 11.52    |
| Tsuji          | 108   | 196   | 106                 | 1.00 (0.77, 1.29) | 9.86     |
| Test of RR=1; p=0.13  |        |       |                      | 1.10 (0.97, 1.24) | 40.37    |
| Heterogeneity: F=0.9%, p=0.815 |

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Discussion

Including recently published studies with substantial numbers of patients in each CHF category, the results of this meta-analysis demonstrated marked differences in key baseline characteristics, all-cause and cardiovascular mortality, and HF hospitalization between the three categories. Patients with HFmrEF were older, less often male, and less frequently had IHD compared with HFrEF patients. In contrast, HFmrEF patients were younger, more often of male gender, and with IHD compared with HFpEF patients. Baseline co-morbidities such as hypertension, diabetes, and atrial fibrillation were more frequent in patients with HFmrEF than in those with HFrEF but markedly less frequent in patients with HFpEF. Importantly, renal function was worse, and there were more COPD cases among patients with HFpEF than among those with HFmrEF and HFrEF. As expected, use of the recommended medications such as renin–angiotensin system inhibitors and beta-blockers was higher in patients with HFrEF and in those with HFmrEF than in those with HFpEF. All-cause mortality in the first year and after approximately 3 years of follow-up was lowest in HFmrEF. Similarly, cardiovascular mortality was lower in HFmrEF than in both HFrEF and HFpEF patients, while HF hospitalization was markedly lower in HFmrEF than in HFrEF and slightly higher in HFmrEF than in HFpEF. Overall, these epidemiological findings demonstrate that the HFmrEF category occupies an intermediate position between the two established categories concerning clinical profile and burden of co-morbidities, but meanwhile HFmrEF is associated with the lowest mortality. These findings

Figure 5 Summary of the study findings illustrating the mid-positioning of heart failure (HF) with mid-range ejection fraction (HFmrEF) between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) concerning the key baseline characteristics. AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease.

Figure 6 Summary of the study findings illustrating the mid-positioning of heart failure (HF) with mid-range ejection fraction (HFmrEF) between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) concerning the lower all-cause (AC) mortality at 1 year and at the end of follow-up (mean 31 months), cardiovascular (CV) mortality, and HF hospitalization.

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strongly support that HFmrEF constitutes a distinct HF category and with distinguished favourable prognosis.

It is well known that IHD is one of the major contributing causes of death in CHF populations.\textsuperscript{6,17} The modifying role of IHD in addition to the associated increased use of beta-blockers on LVEF and mortality was well demonstrated in the Swedish registry by Koh et al., included in this review.\textsuperscript{18} Accordingly, the improved survival and lower HF hospitalizations in the HFmrEF category, as compared with HFrEF, may be explained by the lower prevalence of IHD. Compared with HFrEF, the lower all-cause mortality can be explained by the association of the markedly lower burden of co-morbidities, younger age, and possibly excessive use of beta-blockers and renin–angiotensin system blockers. Most likely, the worse renal function and higher prevalence of COPD contributed considerably to the poorer prognosis of HFpEF patients, despite the lower prevalence of IHD.\textsuperscript{19} The role of renal dysfunction as an independent predictor of mortality and the effect of its markedly high prevalence in HFpEF patients have been previously described and currently demonstrated in the Swedish registry.\textsuperscript{9} The higher prevalence of IHD and low LVEF in HFrEF and the higher prevalence of hypertension, diabetes, and atrial fibrillation in HFpEF patients may also explain the higher cardiovascular mortality in these two categories as compared with HFmrEF.

Prognosis of CHF patients has been primarily linked with the differences in LVEF as the traditional surrogate of prognosis despite the complex relationship between LVEF and CHF.\textsuperscript{20} LVEF has been therefore used as a classification tool to categorize CHF patients. It has been also confirmed that the evidence-based management of these patients, particularly of HFrEF, can reverse the unfavourable remodelling and improve both LVEF and prognosis markedly.\textsuperscript{4} Thus, the adverse effect of the remodelling process counteracted by the improving effect of the contemporary therapies has presumably a decisive impact on LVEF dynamics and transition of patients from one into another category.\textsuperscript{21} In this context, the suggested concepts of whether HFmrEF constitutes a distinct mid-position phenotype or whether HFmrEF is a transitional phase between HFrEF and HFpEF are worth a debate and further research. In the study by Tsuji et al.,\textsuperscript{7} the authors examined the dynamic transition between the three CHF categories over 3 years of follow-up and concluded that HFrEF and HFmrEF change categories during follow-up and concluded that HFmrEF represented a transitional status between HFrEF and HFpEF rather than an independent entity. However, a substantial part of HFmrEF patients maintained their position. In contrast, HFpEF seemed to be a more stable category in this study. Lacking similar data from the other included studies on this issue makes it difficult and too early to determine which of the aforementioned concepts is more plausible.

There is increasing evidence that a considerable number of patients with HFrEF recover and improve their LVEF following evidence-based treatment. This group of patients with improved LVEF has been suggested to constitute a distinct category called HF with improved EF (HFIEF).\textsuperscript{3} Patients with HFIEF share in fact some key characteristics with HFmrEF patients as they are more often younger females and of non-IHD origin unlike HFrEF patients, and this was pointed out in the study by Junior et al.\textsuperscript{22} Thus, HFIEF patients, most likely after a category transition, constitute a substantial part of patients with HFmrEF beside those who have been stable and maintained their LVEF between 40% and 50% without deterioration.\textsuperscript{23} This LVEF improvement and category change may explain the improved lower all-cause and cardiovascular mortality in patients with HFmrEF compared with patients in the other categories. On the other hand, HFpEF patients whose LVEF deteriorates over time due to developing myocardial infarction or inadequately treated cardiovascular co-morbidities may consequently decline to a lower LVEF category.\textsuperscript{21} As a result, it is most likely that HFmrEF is a heterogeneous category comprising patients of different origins with different clinical profiles constituting a mixture of subcategories, who can be classified as HFIEF, HF with stable EF, and HF with worsened EF. However, more pathophysiological research, prospective studies, and retrospective data analyses are needed to consolidate these concepts.

Although LVEF is still considered as an important prognostic surrogate and classification tool of patients with CHF, other well-investigated and relevant parameters have also demonstrated great potential roles characterizing the syndrome of CHF. Circulating biomarkers such as brain natriuretic peptides, echocardiographically measured left atrial size, and myocardial global longitudinal strain and size of myocardial scar tissue measured by magnetic resonance imaging are similarly important prognostic predictors that may guide management of CHF beyond LVEF. Accordingly, new concepts based not solely on LVEF may aid prognosticating and classification of patients with CHF. In future studies, possibly, some of these measures may help to understand the non-linear relation between LVEF and outcome in CHF.

Finally, the important clinical issue beside characterization of HFmrEF patients may be the identification of predictors of deterioration and backward transition to the HFrEF category, in order to prevent further worsening and to improve prognosis. A number of the included studies in the current meta-analysis examined the possible predictors of mortality and effect of the medications used at baseline in patients with HFmrEF.\textsuperscript{6,7,10,13,18} There was no consistency in their findings concerning age, gender, atrial fibrillation, or hypertension. Interestingly, subanalyses of the prognostic impact of medications used at baseline showed consistent mortality reduction by beta-blockers in patients with HFmrEF,\textsuperscript{7,13,18}, however, in the study by Koh et al.,\textsuperscript{18} this effect was limited to patients with IHD. Because of the presence of IHD and cardiovascular co-morbidities, clinicians do treat HFmrEF patients as HFrEF to some extent, but in the absence of randomized

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controlled trials, the evidence is still too weak to treat HFrEF patients as HFrEF guidelines recommend. It is not unlikely that aldosterone antagonists, beta-blockers, and even prophylactic ICD in subgroups of patients with HFrEF may improve their survival \(^2,24,25\) but large-scale randomized controlled trials are required to confirm the beneficial effect of these therapies. Currently, circulating blood biomarkers and various advanced cardiac imaging modalities can certainly also contribute valuable knowledge in this field and may guide treatment.

**Limitations**

The included studies were of an observational nature, and the investigated populations were heterogeneous concerning the baseline characteristics and the size of prevalence of comorbidities. Another source of heterogeneity was due to variation in sizes of the included studies, where few larger studies imposed higher impact on the results. Thus, running the mortality and hospitalization analyses in the fixed-effects model was more realistic. The overrepresentation of the HFrEF population, which constituted almost half of the whole analysed population, and the small number of the HFrEF population may not represent the community-based prevalence of the disease and may be attributed to imbalanced recruitment and registration. Thus, compared with well-treated populations in randomized controlled trials, the mortality estimates may be higher and a time effect is possible. Moreover, some studies did not provide sufficient data for analyses of all baseline characteristics and co-morbidities. This study accounted for the available key baseline characteristics and did not include body mass index, anaemia, stroke, serum brain natriuretic peptide, or HF-related echocardiographic parameters other than LVEF in the analyses. The analysis on HF hospitalization and cardiovascular death as important endpoints may have lacked power because only five studies provided such data. Accordingly, the results of this study should be interpreted cautiously.

**Conclusions and perspectives**

The results of this study support the notion of HFrEF as a distinct category that is characterized by a mid-position between HFrEF and HFpEF categories with respect to risk factor profile but is associated with the lowest all-cause and cardiovascular mortality. Despite the superior prognosis, a substantial portion of HFrEF patients still died of all and cardiovascular causes after approximately 3 years of follow-up, and the all-cause mortality was only slightly lower than that in patients with HFrEF. These findings should encourage more research on patient characterization, mortality predictors, and effect of HF therapies to improve outcomes of patients with HFrEF.

**Conflict of interest**

None declared.

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