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Special prognostic phenomenon for patients with mid-range ejection fraction heart failure: a systematic review and meta-analysis

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Abstract

Background: Clinical features and outcomes of heart failure (HF) with mid-range ejection fraction (HFmrEF) remain controversial. Thus, we systematically reviewed literatures of clinical research to assess and analyze characteristics and prognosis of patients with HFmrEF.

Methods: PubMed, Embase, and Web of Science were searched for cohort studies up to April 23, 2019. Clinical features and multivariate adjusted hazard ratios (HRs) of endpoints of short-term all-cause mortality (SAM), long-term all-cause mortality (LAM), long-term cardiovascular death (LCD) and long-term HF rehospitalization (LHR) among patients with HFmrEF and HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF) were well addressed. The primary outcome was LAM.

Results: Totally 19 studies were included in this study with 164,678 patients enrolled. The follow-up time of LAM was 3.6 ± 2.5 years. HRs of LAM, SAM, LCD, LHR indicated that the risks of patients with HFmrEF were higher than HFpEF patients but lower than HFrEF patients, as for LAM, HFmrEF:HFpEF (reference) HR: 1.07, 95% confidence interval (CI): 1.00–1.15 ($I^2 = 63\%$, $P = 0.0005$); HFmrEF:HFrEF (reference) HR: 0.80, 95% CI: 0.73–0.88 ($I^2 = 70\%$, $P < 0.0001$). However, HFmrEF patients had the lowest rate in LAM (30.94%), SAM (2.73%), LCD (17.45%), LHR (26.36%) compared with the other two groups.

Conclusions: This systematic review and meta-analysis compared features and prognosis between patients with HFmrEF and HFpEF, HFrEF by HRs. There appeared a special "separation phenomenon" showing rates of endpoints were inconsistent with their hazards in patients with HFmrEF compared with HFpEF patients.

Keywords: Heart failure; Ejection fraction; Mid-range; Prognosis; Meta-analysis

Introduction

As a common consequential condition of a wide variety of cardiac diseases, heart failure (HF) is a frequent burden of global medical resources. Left ventricular ejection fraction (LVEF) draws additional attention as an essential reference for the detailed diagnosis and treatment strategy of HF since it characterized the state of systolic and diastolic function to a heart[1]; however, relationship between LVEF and prognosis of HF remains conflicting. On the basis of LVEF, previous studies have historically established two distinct entities including HF with reduced ejection fraction (HFrEF, LVEF <40%) and HF with preserved ejection fraction (HFpEF, LVEF ≥50%). While in 2013 the American College of Cardiology Foundation/American Heart Association HF guidelines introduced HF with borderline preserved ejection fraction (HFbEF, LVEF 41%–49%) as a new sub-group.[2] Then in 2016 the conception of HF with mid-range ejection fraction (HFmrEF, LVEF 41%–49%) was proposed into a three-category classification of HF by the European Society of Cardiology HF guidelines along with HFrEF and HFpEF.[3] Data showed that HFmrEF accounted for a proportion of 11.9% to 24.0%[4-6] of HF and was characterized by mild systolic dysfunction and diastolic dysfunction.[3] As for biological markers of HFmrEF, Tromp's study[7] revealed that markers related to both inflammatory responses and cardiac stretch had been frequently involved. Clinical studies focusing on HFmrEF have not yet met in agreement prognostically and therapeutically.

Therefore, we investigated studies with HFpEF, HFmrEF, and HFrEF patients to quantitatively analyze and compare

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the baseline characteristics and prognosis among them by systematic review and meta-analysis.

Methods

Search strategy

This study was designed in adherence to preferred reporting items for systematic reviews and meta-analyses requirements[8] and registered in the PROSPERO international prospective register of systematic reviews (CRD42019133109). PubMed, Embase, and Web of Science databases were searched for studies concerning outcomes of HF patients from the inception up to 23 April 2019 without language restriction. The search terms used were as follows: Heart Failure [MeSH Terms] or Heart Diseases or Cardio-Renal Syndrome or Dyspnea, Paroxysmal or Edema, Cardiac or Heart Failure, Diastolic or Heart Failure, Systolic or HFmrEF or mid-range ejection or borderline ejection fraction or HFbEF or intermediate ejection fraction or heart failure rehospitalization or cardiovascular death or mortality. References of targeted studies and systematic reviews, meta-analyses were hand searched for relevant studies. Abstracts, meeting proceedings, and letters were excluded from this study. Initial search and assessments of titles and abstracts for considered citations were conducted by two independent reviewers. Full texts of potentially eligible studies were reviewed and discrepancies were settled by further discussion with a third reviewer when needed. Authors were contacted to provide any clarification of missing information. If a same population cohort was repeatedly reported, we retained data of study with the largest sample.

Selection criteria

Inclusion criteria were as follows: (1) studies focusing on human; (2) observational studies (prospective or retrospective cohort studies); (3) studies reported at least one endpoint among all-cause mortality, HF rehospitalization and cardiovascular death; (4) hazard ratios (HRs) and confidence intervals (CIs) of the above endpoints were available or could be estimated.

Exclusion criteria were as follows: (1) duplicate publication data; (2) HRs have not been adjusted by multiple factors; (3) population sample size <100.

Data extraction

Data extraction was carried out by two independent investigators according to a pre-designed form. Terms of publication information (including first author, country of the author's affiliate, publication year, study design, sample size), demographic characteristics, clinical items (including type of HF, follow-up period, interventions, complications, endpoints, and adjusted HRs with 95% CIs) were extracted and then pooled together into the three-category groups.

Outcomes

Endpoints targeted for synthesis include long-term all-cause mortality (LAM), short-term all-cause mortality (SAM), long-term cardiovascular death (LCD) and long-term HF rehospitalization (LHR). Long-term endpoints were followed-up at least one year while short-term endpoint less than one year. The primary outcome was LAM. Secondary outcomes were SAM, LCD, and LHR.

Quality assessment

Quality assessments of literature were conducted independently by two reviewers with discrepancies properly resolved. Evaluation of risk of bias for included studies was performed using Newcastle-Ottawa scale (NOS) with results displayed in Supplementary Table 1, http://links.lww.com/CM9/A166. In our research, studies that achieved five or more stars on the modified NOS were considered high quality.

Statistical analysis

Baseline data were pooled and expressed as either mean ± standard deviation (SD) for continuous variables or simple summation and proportion for categorical variables. The weighted mean difference method was applied to obtain means and their SDs. Baseline data were tested by Student's test or Chi-squared test. HRs and their 95% CIs were used to evaluate risks of different endpoints between HF sub-groups. Transformation of HR was achieved by Hamling conversion formula[9] (http://www.pnlee.co.uk/software.htm) when the reference group of HR was different among studies. Random-effects model was applied for all meta-analyses. Heterogeneity across studies was examined by the Cochran Q test and I^2 statistic value. Sources of heterogeneity were explored by subgroup analysis and sensitivity analysis When $I^2 > 50\%$ with over eight studies. Sub-group analyses were established and interaction for each subgroup was evaluated by random-effects analysis.[10] In sensitivity analysis, the influence of every single study on overall estimates was assessed. Publication bias and selective reporting were investigated firstly by funnel plot and then Egger's and Begg's tests to detect statistical significance.

Statistical analyses were performed with either Stata (version 15.0, StataCorp, College Station, TX, USA), Reviewer Manager (RevMan, Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark), and Excel (version 2016). A two-tailed P value <0.05 was considered statistically significant.

Results

Literature search strategy

The initial search identified 1085 records, of which 193 duplicates and 831 irrelevant papers based on titles and abstracts were excluded. Detailed retrieving of the remained 61 full-text articles eventually yielded 19 studies eligible for this study [Figure 1].[4,6,11-27] Information of the selected studies was listed in Table 1. All included studies were of high quality, as indicated by individual NOS scores ranging from 5 to 8.

Baseline information

A total of 164,678 patients were enrolled in this study, including 63,998 HFpEF patients, 26,614 HFmrEF

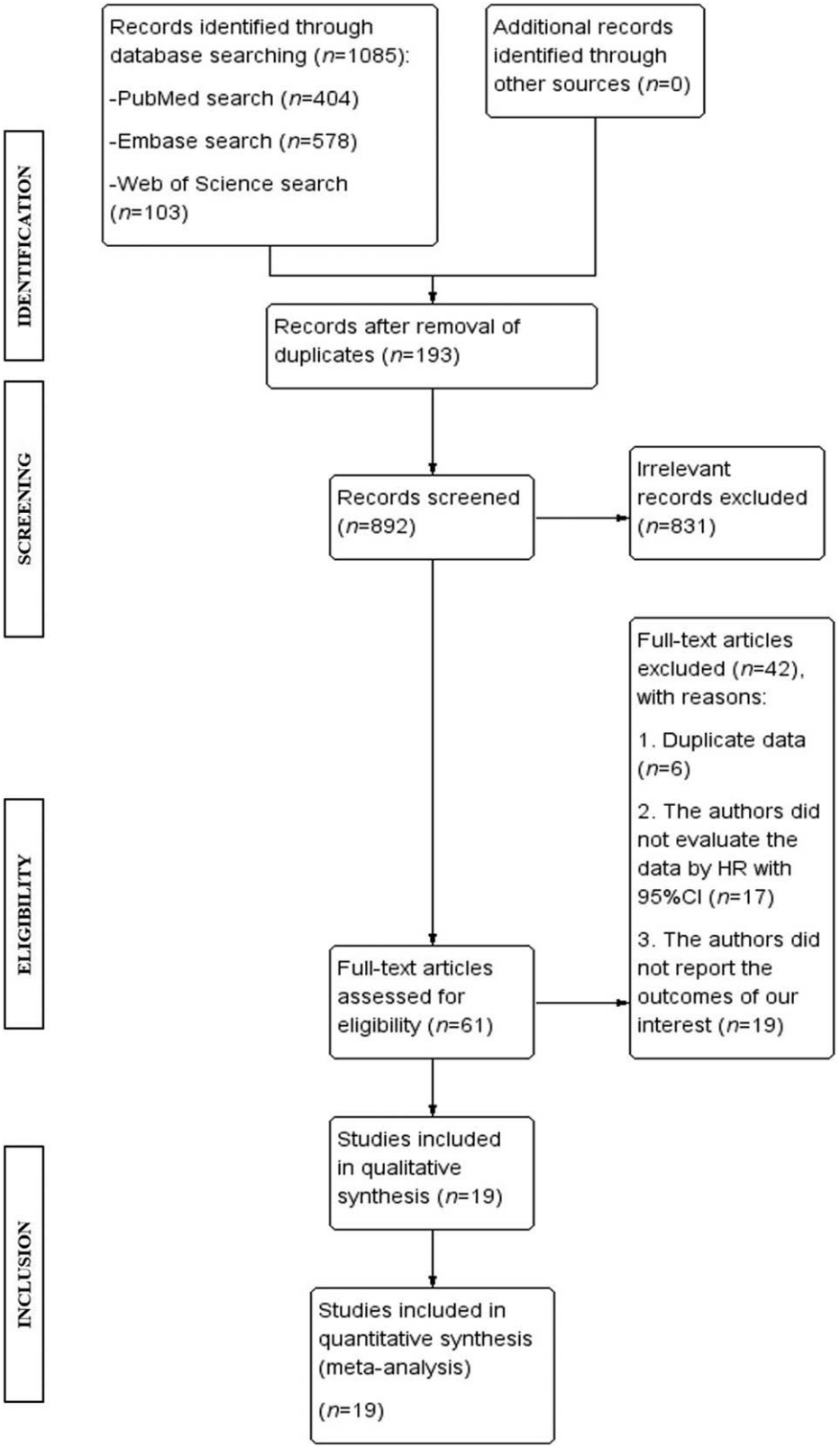

Figure 1: Meta-analysis flow chart showing search and selection of studies with HFpEF, HFmrEF, and HFrEF patients. HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

patients, and 74,066 HFrEF patients. Baseline information including demographic and clinical features and endpoints is shown in Table 2. Follow-up time was 3.6 ± 2.5 years for long-term endpoints while 30 days for short-term endpoints. Rates of the four endpoints named LAM, SAM, LCD, and LHR in HFpEF patients were higher than HFmrEF group but lower than HFrEF by the end of follow-up [Figure 2].

Table 1: Characteristics of included studies with HFpEF, HFmrEF, and HFrEF patients.

Author	Year	Scale	Short/long term follow-up	Follow-up time	Fund	Number of patients				Outcomes	Quality score	Quality of evidence
						All	HFpEF	HFmrEF	HFrEF			
Toma M[6]	2014	Multi-center	Short	30 days	YES	5687	539	674	4474	SAM	5	High
Margolis G[12]	2017	Single-center	Short	30 days	NO	2086	1013	858	215	SAM	5	High
Pascual-Figal DA[14]	2017	Multi-center	Long	41 (20–48) months	YES	3446	635	460	2351	LAM/LCD	7	High
Shah KS [16]	2017	Multi-center	Long	5 years	YES	39,982	18,299	3285	18,398	LAM/LHR	8	High
Farré N[18]	2017	Multi-center	Long	3.66 (1.69–6.04) years	NO	3580	844	504	2232	LAM/LHR/LCD	7	High
Farmakis D[20]	2017	Multi-center	Short	30 days	NO	3257	748	811	1698	SAM	6	High
Koh AS[21]	2017	Multi-center	Short/long	30 days, 3 years	YES	42,061	9640	9019	23,402	SAM/LAM	8	High
Wang K[26]	2017	Single-center	Long	2.30 ± 0.93 years	YES	1647	1202	238	207	LAM	6	High
Delepaul B[27]	2017	Single-center	Long	32.2 ± 14.3 months	NO	482	109	115	258	LAM	6	High
Choi KH[13]	2018	Multi-center	Long	26 (16–37) months	YES	2547	613	383	1551	LAM	7	High
Lam CSP[4]	2018	Multi-center	Long	2 years	NO	2039	574	256	1209	LAM	8	High
Guisado-Espartero ME[15]	2018	Multi-center	Short/long	30 days, 1 year	YES	2753	1664	281	808	SAM/LAM	7	High
Lund LH[23]	2018	Multi-center	Long	2.9 ± 0.9 years	YES	7598	1953	1322	4323	LAM/LHR/LCD	8	High
Avula HR[24]	2018	Multi-center	Long	3.5 (1.4–6.3) years	YES	28,914	14,883	4657	9374	LAM/LHR	8	High
Miro O[25]	2018	Multi-center	Long	1 years	YES	3958	2449	580	929	LAM	6	High
Borovac JA[11]	2019	Single-center	Long	1 years	NO	342	86	133	123	LAM/LHR	6	High
Miró Ò [17]	2019	Multi-center	Short	30 days	YES	6856	4393	982	1481	SAM	7	High
Shiga T[19]	2019	Multi-center	Long	19 (3–26) months	YES	1245	538	263	444	LAM	5	High
Siontis GC[22]	2019	Multi-center	Short/long	30 days, 5 years	YES	6198	3816	1793	589	SAM/LAM/LCD	8	High

All values are expressed as the mean ± standard deviation, median (1st Quartile–3rd Quartile) or median (range interquartile), or number as appropriate according to the primary studies. HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFrEF: Heart failure with reduced ejection fraction; SAM: Short-term all-cause mortality; LAM: Long-term all-cause mortality; LCD: Long-term cardiovascular death; LHR: Long-term HF rehospitalization.

Table 2: Baselines information of included studies with HFpEF, HFmrEF, and HFrEF patients.

Items	Studies (*n*)	HFpEF (63,998 patients)	HFmrEF (26,614 patients)	HFrEF (74,066 patients)	HFmrEF *vs.* HFpEF		HFmrEF *vs.* HFrEF	
					x^2/t^*	*P* values	x^2/t^*	*P* values
Demographic characteristics								
Age (years)	18	76.56 ± 11.84	72.43 ± 13.27	72.05 ± 12.71	–46.12*	<0.001	165.39*	<0.001
Male	19	27,957 (43.68)	16,470 (67.46)	50,367 (68.00)	2491.63	<0.001	328.42	<0.001
Complications								
IHD	12	15,046 (42.26)	9127 (53.54)	32,866 (54.72)	591.45	<0.001	7.45	0.006
Hypertension	17	46,465 (77.59)	17,777 (69.03)	45,731 (63.23)	704.31	<0.001	280.14	<0.001
AF	15	19,281 (48.61)	10,206 (46.77)	21,054 (38.52)	19.07	<0.001	438.91	<0.001
Diabetes	19	23,701 (37.03)	9295 (34.93)	25,581 (34.54)	36.10	<0.001	1.30	0.255
COPD	10	14,134 (31.76)	3351 (28.56)	9636 (26.16)	44.46	<0.001	26.06	<0.001
CKD	11	7175 (20.91)	2150 (23.02)	5795 (23.04)	19.53	<0.001	<0.01	0.969
Clinical indicators								
NYHA III–IV	11	8673 (36.70)	5254 (35.68)	18942 (48.25)	4.08	0.043	684.35	<0.001
LVEF%	12	59.74 ± 7.51	45.42 ± 6.97	28.43 ± 11.19	–266.92*	<0.001	104.96*	<0.001
eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)	7	60.32 ± 24.64	62.00 ± 24.61	62.97 ± 24.08	9.35*	<0.001	–5.60*	<0.001
Medical treatments								
ACEI/ARB	18	38,568 (61.23)	18,306 (71.07)	56,386 (76.35)	769.25	<0.001	283.44	<0.001
Beta-blockers	18	42,078 (66.81)	19,378 (75.24)	57,122 (77.35)	610.17	<0.001	47.75	<0.001
Diuretics	14	37,497 (66.04)	16,259 (70.13)	50,658 (71.71)	125.27	<0.001	21.24	<0.001
AAS	15	7926 (13.69)	4749 (20.13)	21,658 (29.70)	528.49	<0.001	820.88	<0.001
Digoxin	10	7912 (21.08)	3575 (19.07)	11,276 (22.63)	30.86	<0.001	101.69	<0.001
Non-medicine treatments								
ICD	11	290 (0.59)	424 (1.98)	3450 (5.06)	284.72	<0.001	372.01	<0.001
CRT	9	208 (0.45)	180 (0.91)	1680 (2.65)	50.31	<0.001	208.80	<0.001
PCI	6	3037 (13.22)	1476 (17.31)	2273 (14.08)	84.41	<0.001	45.13	<0.001
CABG	7	1801 (7.51)	1111 (11.34)	2729 (13.38)	129.43	<0.001	24.91	<0.001
Endpoints								
LAM	15	23,114 (39.82)	7357 (30.94)	27,092 (39.94)	569.40	<0.001	608.55	<0.001
SAM	5	715 (4.15)	322 (2.73)	1046 (3.44)	41.07	<0.001	928.60	<0.001
LCD	3	605 (17.63)	399 (17.45)	2458 (27.60)	0.03	0.865	98.49	<0.001
LHR	5	10,353 (28.71)	2610 (26.36)	12,466 (36.19)	21.11	<0.001	330.85	<0.001

All values were expressed as the mean ± standard deviation or number (%) as appropriate according to the primary studies. * *t* values. The count data were directly summed up of each study as well as the measurement data were summed up by weighted combination of mean and standard deviation. HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFrEF: Heart failure with reduced ejection fraction; IHD: Ischaemic heart disease; AF: Atrial fibrillation or flutter; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; NYHA: New York Heart Association class; LVEF: Left ventricular ejection fraction; AAs: Aldosterone antagonists; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronization therapy; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; LAM: Long-term all-cause mortality; SAM: Short-term all-cause mortality; LCD: Long-term cardiovascular death; LHR: Long-term HF rehospitalization.

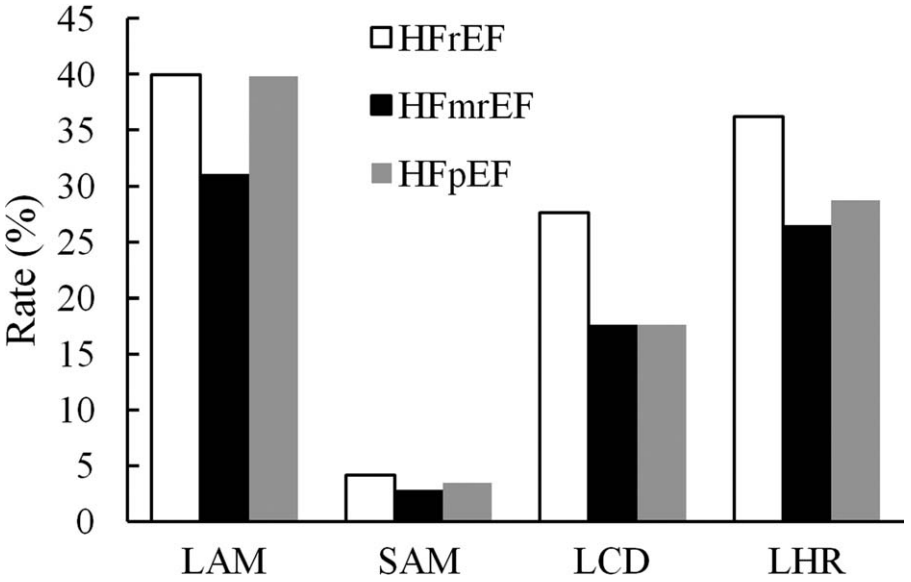

Figure 2: Rates of LAM, SAM, LCD, and LHR. LAM: Long-term all-cause mortality; LCD: Long-term cardiovascular death; LHR: Long-term heart failure rehospitalization; SAM: Short-term all-cause mortality.

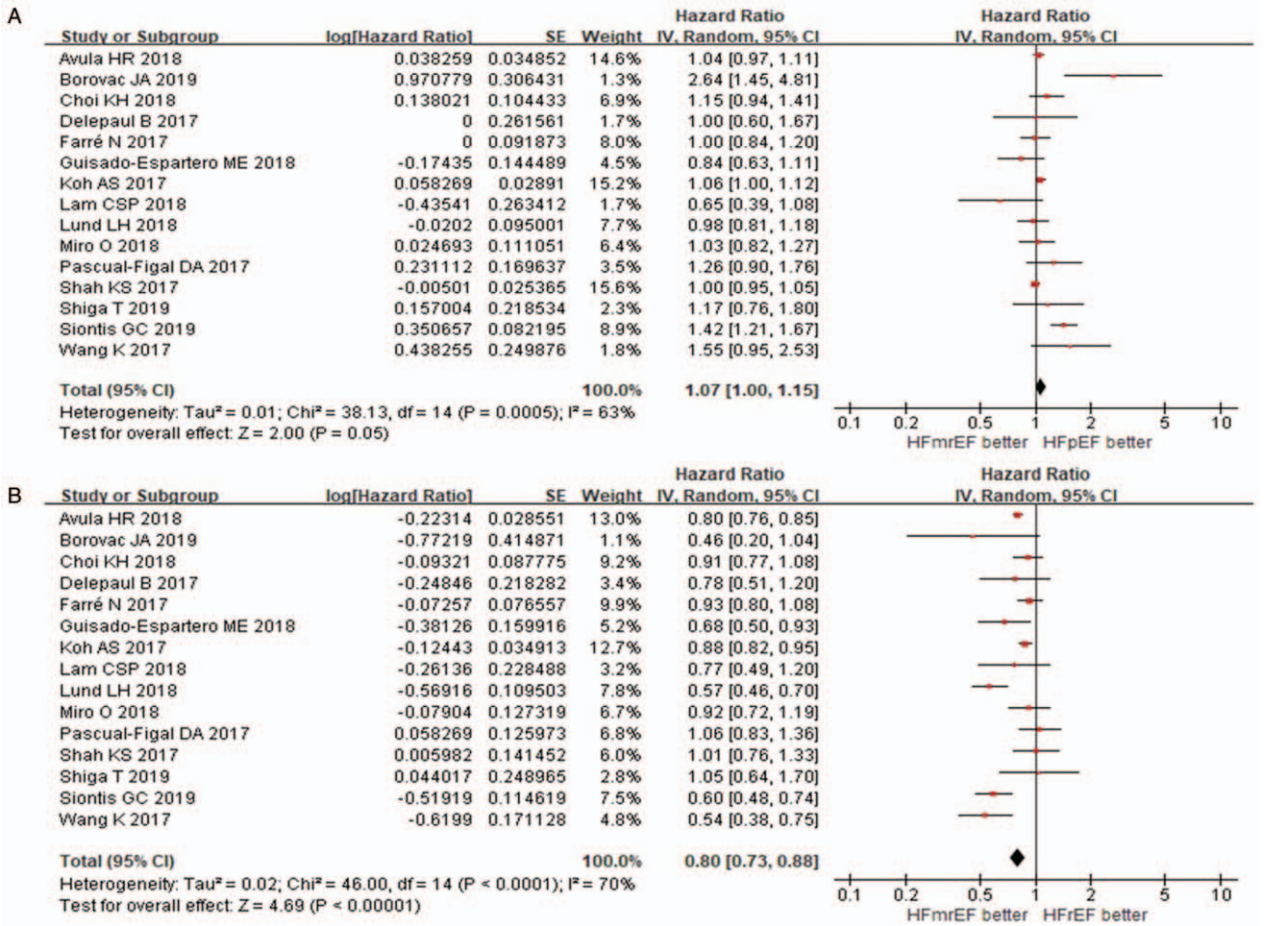

Figure 3: LAM of "HFmrEF *vs.* HFpEF" (A) and "HFmrEF *vs.* HFrEF" (B). Random effects hazard ratio (HR) and 95% confidence interval (CI) for LAM in 15 studies. HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; LAM: Long-term all-cause mortality.

LAM

Fifteen studies with 149,659 patients involving reported HRs of LAM among different HF groups. All studies but four,[14,16,22,25] applied transformation of HR. Pooled data significantly indicated that the types of HF were independently associated with LAM. The risk of HFmrEF patients was increased compared with HFpEF patients (reference) with HR: 1.07, 95% CI: 1.00 to 1.15, $I^2 = 63\%$, $P = 0.0005$ [Figure 3A],

Table 3: Sub-group analysis of long-term all-cause mortality of HFpEF, HFmrEF, and HFrEF patients.

Sub-group	HR (95% CI)	I^2 (%)	*P* values	*P* for interaction
Scale				
HFpEF *vs.* HFmrEF				
Multiple centers	1.05 (0.99–1.12)	58	0.0060	0.14
Single center	1.57 (0.93–2.65)	66	0.0500	
HFrEF *vs.* HFmrEF				
Multiple centers	0.83 (0.76–0.91)	71	<0.0001	0.03
Single center	0.60 (0.46–0.79)	11	0.3300	
Follow-up time (years)				
HFpEF *vs.* HFmrEF				
<2	1.08 (0.92–1.27)	53	0.0500	0.98
≥2	1.08 (0.99–1.17)	72	0.0007	
HFrEF *vs.* HFmrEF				
<2	0.80 (0.73–0.88)	70	<0.0001	0.56
≥2	0.77 (0.68–0.87)	81	<0.0001	
Fund				
HFpEF *vs.* HFmrEF				
Yes	1.07 (1.01–1.15)	61	0.0050	0.89
No	1.11 (0.71–1.72)	76	0.0050	
HFrEF *vs.* HFmrEF				
Yes	0.80 (0.72–0.89)	76	<0.0001	0.54
No	0.85 (0.71–1.02)	16	0.3100	
Number of patients				
HFpEF *vs.* HFmrEF				
<5000	1.09 (0.91–1.30)	58	0.0100	0.88
≥5000	1.07 (1.00–1.16)	74	0.0020	
HFrEF *vs.* HFmrEF				
<5000	0.82 (0.70–0.96)	53	0.0300	0.66
≥5000	0.78 (0.70–0.89)	82	<0.0001	
Publication year				
HFpEF *vs.* HFmrEF				
Before 2018	1.03 (0.98–1.10)	29	0.2200	0.48
After 2018	1.09 (0.95–1.25)	73	0.0003	
HFrEF *vs.* HFmrEF				
Before 2018	0.88 (0.77–1.00)	59	0.0300	0.09
After 2018	0.75 (0.66–0.86)	66	0.0030	

LAM: Long-term all-cause mortality; HR: Hazard ratio; HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFrEF: Heart failure with reduced ejection fraction.

while reduced compared with HFrEF patients (reference) with HR: 0.80, 95% CI: 0.73 to 0.88, $I^2 = 70\%$, $P < 0.0001$ [Figure 3B]. Subsequent analyses were conducted since notable heterogeneity appeared among different studies.

Heterogeneity analysis

Sub-group analysis

Sub-group analyses based on sample size, scale, follow-up time, publication year, and fund support were performed to explore impact on heterogeneity [results are shown in Table 3 and Supplementary Figures 1–6, http://links.lww.com/CM9/A166]. Scale was outlined to be a source of heterogeneity in comparison of HFrEF *vs.* HFmrEF (reference): in multi-center studies HR: 0.83, 95% CI: 0.76 to 0.91, $I^2 = 71\%$, $P < 0.0001$; in single-center studies HR: 0.60, 95% CI: 0.46 to 0.79, $I^2 = 11\%$, $P = 0.33$. It was statistically significant in interaction test ($P = 0.03$). Varied conditions among countries, ethnicities, environment, and medical conditions in multi-center studies may be a conspicuous source of heterogeneity. The remaining sub-groups were proofed innocent in heterogeneity.

Sensitivity analysis

Further sensitivity analyses [Supplementary Tables 2–3, http://links.lww.com/CM9/A166 and Supplementary Figure 7, http://links.lww.com/CM9/A166] demonstrated that Siontis's study[22] had driven high heterogeneity in the comparison of HFpEF *vs.* HFmrEF. The heterogeneity was significantly reduced after removing this study ($I^2 = 44\%$, $P = 0.04$). In Siontis's article, the disparity of ages and proportions of diabetes between patients with HFmrEF and HFpEF was significantly narrowed compared with that in our meta-analysis, thus the risk of LAM in HFmrEF patients was relatively high, making it a possible source of heterogeneity. However, meta-analyses in HFmrEF *vs.* HFpEF group had not changed much before (HR: 1.07, 95% CI: 1.00–1.15) and after the rejection (HR: 1.04, 95% CI: 0.98–1.10), which man-

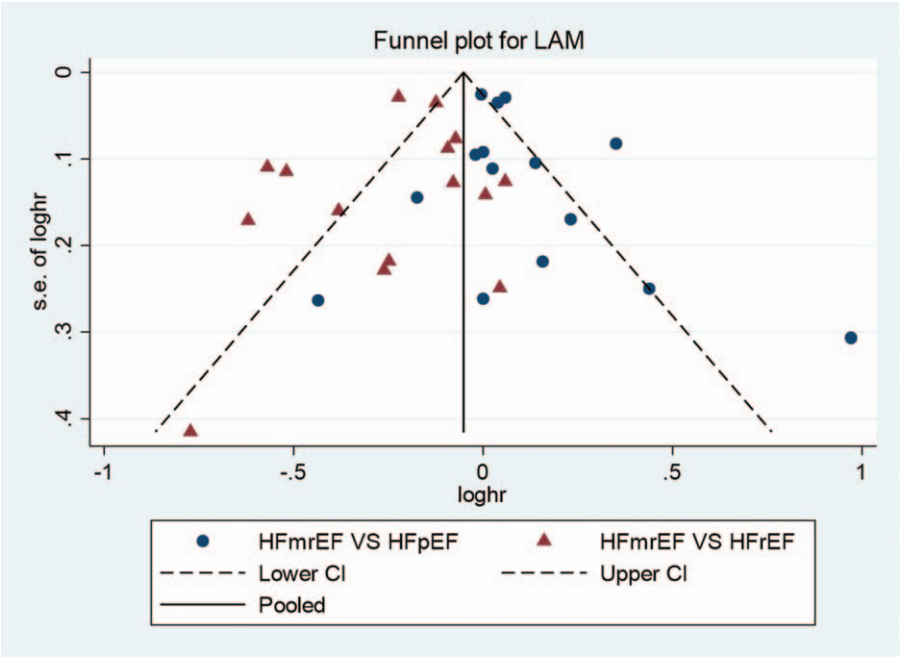

Figure 4: Funnel plot for LAM of "HFmrEF *vs.* HFpEF" (A) and "HFmrEF *vs.* HFrEF" (B). CI: Confidence interval; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; LAM: Long-term all-cause mortality.

ifested the stability of the original synthesis. No source of heterogeneity was confirmed in HFrEF *vs.* HFmrEF group. Considering that HR transformation may cause minor errors, we applied sensitivity analysis by excluding studies using this method [Supplementary Figure 8, http://links.lww.com/CM9/A166]. Results showed only a little difference of the HRs and I^2 after removing the studies using HR transformation but still in accordance with our primary outcome.

Publication bias

Egger's test and Begg's test [Supplementary Table 4, http://links.lww.com/CM9/A166] confirmed no statistically significant publication bias existed in the analyses performed although Funnel plot asymmetry were detected visually [Figure 4].

Secondary outcomes

Data of LHR from five studies (one[16] did not apply HR transformation) were pooled together [Supplementary Figure 9, http://links.lww.com/CM9/A166]. HFmrEF patients had a 7% higher rate of LHR (HR: 1.07, 95% CI: 0.95–1.21) compared with HFpEF patients, but a 19% rate lower than HFrEF patients (HR: 0.81, 95% CI: 0.73–0.91). Four studies of which two[14,22] did not use HR transformation reported the risk of LCD with results of meta-analyses showed (HR: 1.39, 95% CI: 1.08–1.79) for HFmrEF *vs.* HFpEF while (HR: 0.71, 95% CI: 0.54–0.94) for HFmrEF *vs.* HFrEF [Supplementary Figure 10, http://links.lww.com/CM9/A166]. Test of heterogeneity and publication bias were not performed because of limitations of study numbers, although considerable heterogeneity had presented in the mentioned meta-analyses above.

Pooling analyses were implemented for SAM using available information from seven studies (HR transformation were not applied in three studies[17,20,22]) one of which only provided data of HFmrEF *vs.* HFpEF group [Supplementary Figure 11, http://links.lww.com/CM9/A166]. HFmrEF patients still run a higher risk of SAM than HFpEF patients (HR: 1.13, 95% CI: 0.92–1.38) but a lower rate than HFrEF patients (HR: 0.74, 95% CI: 0.62–0.88). Satisfying syntheses were achieved owing to a low heterogeneity (I^2). The number of involving studies was too small to detect publication bias.

Discussion

This systematic review and meta-analysis investigated risks of endpoints including mortality and re-admission among patients with HFmrEF, HFmrEF, and HFmrEF using adjusted HRs as indicators. Baseline information of this study showed that HFmrEF was a unique subtype distinct from HFpEF and HFrEF since meta-analysis confirmed its distinctive characteristics including the lowest rate of New York Heart Association class (NYHA) III–IV, the lest use of digoxin, and the highest application of percutaneous coronary intervention (PCI). The rates of endpoint events were lowest in HFmrEF patients, followed by HFpEF patients, and highest in HFrEF patients, however, HRs of poor prognosis after multivariable analysis increased successively by HFpEF, HFmrEF, and then HFrEF.

Evidences varied in prognosis of HFmrEF patients. Two meta-analyses, which were quite different from our findings,[28,29] summarized that HFmrEF patients had the lowest relative risk (RR) of all-cause mortality and cardiac deaths. Besides, the indicator RR could not assess

and prove the impact of time and other confounding factors on the results. Therefore, we applied multivariable adjusted HR as indicator in this study and obtained results that the risks of LAM, SAM, LCD, and LHR in HFmrEF patients were higher than that of HFpEF but lower than HFrEF, while rates of the mentioned endpoints in HFmrEF patients were the lowest. We named the inconsistency between the risks and rates of the endpoints as "separation phenomenon," which may partly because of the complexity of patient population and the diversity of complication in HFpEF group. Confounding factors that increase risks of endpoints including advanced age, renal insufficiency, and female sex, were all calibrated by the COX regression model, then the risk of HFmrEF highlighted. We also detected detailed source of heterogeneity of LAM. Results showed that study scale might be a potential source since multi-center studies involve more different countries, ethnicities, environment, and medical conditions than the singles; then Siontis study should be mentioned as well, because the disparity of ages and proportions of diabetes between patients with HFmrEF and HFpEF was significantly narrowed compared with that in our meta-analysis. The "separation phenomenon" unveiled the significance of HFmrEF and promoted the individual management for different types of HF in clinical work. For patients with HFmrEF, more aggressive cardiovascular-related treatments should be taken to improve their prognosis. While for HFpEF patients, treatment of complications and other chronic diseases should never be ignored, patients may benefit more from comprehensive treatment.

LVEF is a dynamic indicator intensively associated with cardiac function and risks of adverse outcomes. HFmrEF is an independent but unstable subtype with a changeful LVEF,[30] it resembles to the other two types in some features and could easily convert to them. HFmrEF in female patients or in those without ischemic heart disease (IHD) were more likely to convert to HFpEF,[31] while to HFrEF[5] in patients with IHD. Some studies even stated that HFmrEF was the early stage of HFrEF patients in those with IHD.[32] We also found proportion of IHD in patients with HFmrEF was similar to that of HFrEF but significantly higher than HFpEF patients. Conversion of HFmrEF to HFpEF was reported more common than to HFrEF; however, the latter would gradually increase with the growing of IHD as data from studies of Yamamoto *et al*,[33] Gwag *et al*,[34] Tsuji *et al*,[35] and Vedin *et al*[5] exemplified. This interrelated incremental relationship was more thoroughly revealed by Vedin and colleagues' study[5] in which the proportion of IHD in the HFmrEF cohort was as high as 60.7%, therefore, the conversion to HFrEF was higher than to HFpEF (36.5% *vs.* 23.6%) in his study. Accordingly, we consider that IHD plays a vital role in the conversion of HFmrEF, and will eventually affect prognosis of HF patients. As bewritten by Savarese *et al*,[30] that conversion from HFmrEF to HFpEF might reflect recovery after myocardial infarction, while downward conversion to HFrEF might indicate progressive HF or a new ischemic event. Therefore, additional attention should be paid to the history and recurrence of IHD in HFmrEF patients, and relatively aggressive treatments were recommended to prevent conversion to HFrEF if IHD was involved. Further studies are urgently required since the improvement, maintenance and deterioration of LVEF in HFmrEF patients remain inconclusive.

Patients with NYHA III–IV in HFmrEF group were lower than that in HFpEF group as depicted in this study (35.68% *vs.* 36.70%, $P = 0.043$), suggesting heavier symptoms of HFpEF patients in spite of preserved ejection fractions. Yet heavier symptoms may also due to an older population, various comorbidities especially the highest proportion of COPD, of which clinical manifestations may interfere with the judgment of NYHA. Given the inconsistency between LVEF, symptoms and other HF assessment scales, the value of LVEF on evaluating cardiac function should be taken with caution.[36] We also found that HFmrEF group used less digoxin than HFpEF group, although the latter had higher LVEF. The high proportion of atrial fibrillation or flutter in HFpEF group may explain this phenomenon because digoxin is also a kind of arrhythmia drugs controlling ventricular rate in patients with atrial fibrillation or flutter. Besides, the implementation of PCI was significantly more in HFmrEF group than in HFrEF group, although the latter companied with a higher IHD proportion. This may because of the favorable applying of CABG therapy or conservative treatment in HFrEF patients as many of them were too ill to accept PCI whereas most HFmrEF patients with IHD could withstand it.

Limitations should not be neglected alongside the results presented in this review. First, all studies included were of an observational nature which was highly subject to selection bias. Second, follow-up spans varied from 1 year to 5 years across studies reporting LAM, which may generate inconsistency of results. Furthermore, heterogeneity of LCD and LHR were high yet hard to discern due to the relatively small number of studies. And some HRs in this study were obtained by conversion which may cause minor errors.

In conclusion, distinctive characteristics especially "separation phenomenon" highlighted the remarkable significance of the new classification of HFmrEF. Further exploration is eagerly expected both in clinical management and prognosis of HFmrEF.

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Conflicts of interest

None.

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