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ORIGINAL ARTICLE

Long-term mortality in heart failure with mid-range ejection fraction: systematic review and meta-analysis

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Abstract

Aims Heart failure patients with mid-range ejection fraction (HFmrEF) have overlapping clinical features, compared with patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). We aim to perform a meta-analysis of studies reporting long-term outcomes in HFmrEF compared with HFrEF and HFpEF.

Methods and results Data from 18 eligible large-scale studies including 126 239 patients were pooled. Patients with HFmrEF had a lower risk of all-cause death than those with HFrEF [risk ratio (RR) = 0.92; 95% CI = 0.85–0.98; $P < 0.001$]. This significant difference was seen in the follow-up at 1, 2, and 3 years. Patients with HFmrEF had significantly lower risk of cardiovascular (CV) deaths than HFrEF (RR = 0.77; 95% CI = 0.65–0.92; $P < 0.001$). Subgroup analysis showed that studies recruiting >50% of males had higher risk of deaths with HFrEF (RR = 1.15; 95% CI = 1.04–1.26; $P = 0.006$). When compared with HFpEF, patients with HFmrEF had comparable risk of all-cause death (RR = 1.02; 95% CI = 0.96–1.09; $P = 0.53$). Similarly, there were no differences in the 1, 2, and 3 year deaths; CV and non-CV deaths were insignificant between HFmrEF and HFpEF.

Conclusions The results of the study support that HFmrEF has better prognosis than HFrEF but similar prognosis when compared with HFpEF. Gender disparity between studies seems to influence the results between HFmrEF and HFrEF. Transition in left ventricular ejection fraction (LVEF), which could not be addressed in the study, may play a decisive role in determining outcomes. PROSPERO review registration number CRD42021277107.

Keywords Systematic review; Meta-analysis; Heart failure; Mid-range ejection fraction; Mortality; Gender differences

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Introduction

Mortality in patients with symptomatic chronic heart failure varies from 25% to 80% at 5 years, depending on the stage of heart failure.[1] Left ventricular ejection fraction (LVEF) is an important prognostic indicator for the risk of all-cause mortality as well as sudden cardiac death in chronic heart failure patients.[2] Since the introduction of categories of chronic heart failure based on LVEF, heart failure with mid-range (borderline) ejection fraction (HFmrEF) is recognized as an entity with overlapping clinical, treatment, and outcome characteristics compared with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[3]

Large-scale registries, multi-centre, and single-centre studies have reported their observations on prognosis in each of these categories of heart failure.[4–21] However, only a few meta-analyses have been carried out comparing the prognosis of HFmrEF with HFrEF and HFpEF.[22–24] Moreover, these meta-analyses did not then have studies adequately powered to examine the annual mortality risk in the follow-up between these groups. Additionally, none of the meta-analyses have

explored the difference in outcomes according to certain important subgroups, which could be important moderators influencing the results. To explore these gaps in knowledge, we proposed a systematic review and meta-analysis to determine the long-term cumulative and annual mortality risk, cardiovascular and non-cardiovascular deaths in patients with HFmrEF compared with those with HFrEF and HFpEF.

Methods

Objectives

The primary objective was to determine the effect size of long-term cumulative mortality risk and all-cause mortality risk at 1, 2, 3, 4, 5, and 10 years; in persons with HFmrEF compared with HFrEF and HFpEF. Our secondary objectives were to (1) explore the long-term cause-specific mortality risk for deaths from cardiovascular, non-cardiovascular, heart failure, and sudden cardiac deaths in persons with HFmrEF compared with HFrEF and HFpEF and (2) identify clinical variables influencing the long-term mortality risk estimates.

Search strategy and eligibility criteria

We followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines in conducting this systematic review and the meta-analysis.[25] We searched MEDLINE, PubMed, EMBASE, Web of Science, and Cochrane Library from inception to 30 September 2021, for studies reporting mortality outcomes between persons with heart failure with mid-range/borderline ejection fraction (40%–49%, HFmrEF) compared with reduced (<40%, HFrEF) or preserved ejection fraction (≥50%, HFpEF). The key search terms used were 'ejection-fraction', 'heart-failure', 'death*', 'mortality*', and 'hazard-ratio*'. The detailed search strategy is in Supporting Information, *Table S1*. To identify additional studies, we manually searched the reference lists of the included studies. This study is registered at the PROSPERO review database (CRD42021277107).

The inclusion criteria were full-text peer reviewed papers in English, randomized controlled trials, cohort studies, observational studies with consecutive recruitment of patients with heart failure; standard case definition of heart failure, studies defining HFmrEF or borderline heart failure ejection fraction as 40%–49%, HFrEF as <40%, and HFpEF as ≥50% in adults aged 18 years and above; reporting cumulative all-cause deaths in HFmrEF and HFrEF/HFpEF/both along with annual all-cause, cardiovascular, non-cardiovascular, heart failure deaths or sudden cardiac deaths; follow-up ≥1 year; the sample size ≥100 with HFmrEF and the total sample size of heart failure patients ≥1000 when the power of the study was not listed. When there were ≥2 articles on the same group of patients, we selected the newest study best representing the cohort and the inclusion criteria.

The exclusion criteria were study protocols, brief reports, case studies, abstracts, theses, reviews, duplicate studies, incomplete and unpublished studies, studies of pregnant women, participants with a specific disease or a health condition in addition to heart failure and duplicate studies reporting outcomes from the same study population.

Data extraction

Retrieved studies were exported to Covidence[R]. I. S. (Indira Samarawickrema) and D. R. (Deep Raja) screened the titles and the abstracts independently in Covidence[R] for eligibility. R. P. (Rajeev Pathak) was the third independent reviewer. I. S. and D. R. independently extracted data from the eligible full-text studies into the custom designed data extraction tables in Covidence[R]. Corresponding authors of studies without data on mortality outcomes were contacted. We analysed for consensus to ensure reliability of the data. Inter-rater agreement in data extraction was calculated. We had meetings to come to a consensus to resolve any discrepancies.

The data collated comprised study design, dataset, study period, study population, definitions of mid-range or borderline, reduced and preserved ejection fraction in heart failure, mean follow-up and standard deviation, study power, sample size, mean age and standard deviation, proportion of males, number of patients at baseline, number of cumulative, cardiovascular, non-cardiovascular and sudden cardiac deaths and all-cause deaths at 1 year intervals up to 10 years.

Quality appraisal

I. S. and D. R. independently assessed the quality of eligible used Newcastle-Ottawa quality assessment scale (NOS) for cohort studies and Cochrane Risk of Bias tool for randomized clinical trials (RoB 2).[25] We calculated inter-rater agreement for quality assessment and consensus reached following discussions for the disagreements. The third independent reviewer was R. P. The objective of the quality appraisal was to exclude low quality studies, that is, NOS score <7 and RoB 2 score <2. This study did not have patient or public involvement.

Statistical analysis

Pooled data of mortality and survival data for HFmrEF were compared with HFrEF and HFpEF for cumulative, cardiovascular, non-cardiovascular, heart failure and sudden cardiac deaths; and cumulative deaths at 1, 2, 3, 4, 5, and 10 years; to determine the effect size [risk ratio (RR)] for the risk of death in the meta-analysis. To minimize potential of biases,

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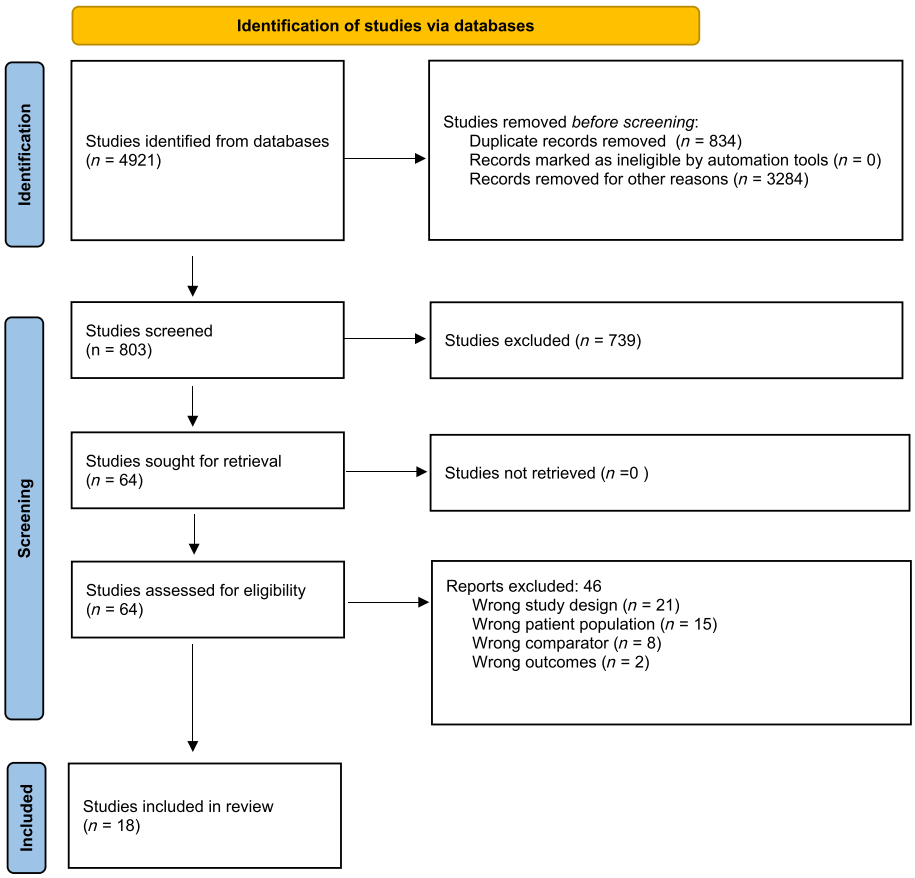
each meta-analysis required ≥2 studies. Heterogeneity was calculated as I^2, and the cut-off for low heterogeneity was $I^2 < 30\%$. We used random effects maximum likelihood model for $I^2 \geq 30\%$ and fixed effect model with inverse-variance for $I^2 < 30\%$. We reported exponentiated effect sizes from the log risk ratios. The effect size for death was determined as a risk ratio with 95% confidence intervals in the meta-analysis.

We explored heterogeneity between studies due to publication bias with visual inspection of funnel plots and Egger's linear regression test for the influence from small studies. Sensitivity analysis excluding one study at a time was also performed to examine the influence of individual study on the effect size. We examined potential factors for between-study heterogeneity with clinically and epidemiologically relevant covariates (moderators) in the subgroup analysis and in the random-effects meta-regression. The covariates included were the proportion of men below or above 50%, mean age of the participants below or above 50 years, studies recruiting outpatients versus hospitalized patients, studies recruiting de novo versus chronic heart failure patients, single versus multi-centre studies, and follow-up period ≤2 versus > 2 years. We conducted statistical analyses with Stata 17.0 (STATA Corporation, Texas, USA).

Results

The search process is outlined in *Figure 1*, and the search strategy is listed in Supporting Information, *Table S1*. Eighteen eligible studies were included in the meta-analysis of the mortality outcomes between HFmrEF and HFrEF, and 17 eligible studies were included in meta-analysis of the mortality outcomes between HFmrEF and HFpEF. All studies were follow-up of patient cohorts from observational studies and there were no eligible randomized controlled trials. Inter-rater reliability in data extraction was 0.91, and Cohen's kappa was 0.39. The quality of evidence of each selected study is listed in Supporting Information, *Table S2*. Inter-rater reliability in quality appraisal was 0.84, and Cohen's kappa was 0.67.

Figure 1 Flow chart of search process and results.



Study and patient characteristics

There were 14 prospective and 4 retrospective cohort studies; 13 including hospitalized patients; 3 including outpatients; 14 multi-centre and 4 single-centre studies; 13 studies with enrolments before 2010; and 5 studies with enrolments during or after 2010 (*Table 1*). The participant follow-up ranged from 1 to 10 years. The noteworthy large-scale studies were the 1 and 5 year data from the Get With The Guidelines–Heart failure (GWTG-HF) registry, 3 year data from the Swedish Heart Failure Registry, and 1 year data from the ESC Heart Failure long-term registry.[5,8,15,19] Choi *et al*. reported outcomes for both de novo heart failure and acute decompensated chronic heart failure patients and was hence considered as two separate studies.[9]

The included studies had 126 239 heart failure patients inclusive of; 64 779 patients with HFrEF (51.3%); 20 301 patients with HFmrEF (16.1%); and 41 159 patients with HFpEF (32.6%). The average age of the patients was 71.9 years. The proportion of men in the overall cohort was 60.6% with 60.5% in HFrEF, 69% in HFmrEF and 40.4% in HFpEF. The HFmrEF group had significantly reduced proportion of patients with hypertension, diabetes mellitus, kidney disease, atrial fibrillation, and coronary artery disease (9.7%, 5.2%, 3.2%, 7%, 8.1% respectively) than both HFrEF (29%, 17%, 11%, 19%, 27% respectively) and HFpEF groups (23%, 11%, 8.5%, 14.6%, 12.2% respectively) (Supporting Information, *Table S3*).

Risk of all-cause mortality

Patients with HFmrEF had a significantly lower risk of all-cause death than those with HFrEF (Risk Ratio (RR) = 0.92; 95% CI = 0.85–0.98; $P < 0.001$), using the random-effects model (*Figure 2*). Subgroup analysis (*Figure 3*) revealed that studies recruiting >50% of men had a lower risk ratio for HFmrEF versus HFrEF (RR = 0.87; 95% CI = 0.79–0.96; $P = 0.006$). This translated into a higher risk of deaths with HFrEF in studies recruiting >50% of males (RR = 1.15; 95% CI = 1.04–1.26; $P = 0.006$). However, studies ≤50% of men had insignificant differences in the risks of deaths (HFmrEF vs. HFrEF: RR = 1.00; 95% CI = 0.99–1.03; $P = 0.63$). Subgroup analysis also revealed that studies including only outpatients had lesser risk of death with HFmrEF (RR = 0.78; 95% CI = 0.65–0.93; $P = 0.006$) than studies including only hospitalized patients (RR = 0.97; 95% CI = 0.94–1.01; $P = 0.13$).

Patients with HFmrEF had comparable risk of all-cause death with HFpEF (pooled RR = 1.02; 95% CI = 0.96–1.09; $P = 0.53$) using the random-effects model (*Figure 2*). Subgroup analysis (*Figure 3*) revealed higher risk of deaths in HFmrEF, than HFpEF, in single-centre studies (RR = 1.13; 95% CI = 1.03–1.24; $P = 0.008$) compared with multi-centre studies (RR = 1.00; 95% CI = 0.92–1.07; $P = 0.91$).

There was high level of heterogeneity between the included studies for HFmrEF versus HFrEF (I^2 = 87%) as well as for HFmrEF versus HFpEF (I^2 = 80.2%). To assess publication bias, a sensitivity analysis was conducted by exclusion of individual studies and the smaller studies, and this was found to not affect the results. Meta-regression analysis for between-study variance in overall mortality risk ratio between HFmrEF and HFrEF identified that studies on hospitalized patients and multi-centre studies contributed to 98.6% variance ($P = 0.0001$). Meta-regression analysis for between-study variance in overall mortality risk ratio between HFmrEF and HFpEF identified that multi-centre studies attribute to 53.7% of variance ($P = 0.005$).

Annual all-cause mortality in the follow-up

Analysis of studies with annual all-cause deaths showed that patients with HFmrEF had a significantly lower risk of all-cause death than those with HFrEF at 1 year (7 studies; pooled RR = 0.84; 95% CI = 0.74–0.95; $P = 0.03$; I^2 = 54%), 2 years (4 studies; pooled RR = 0.86; 95% CI = 0.75–0.98; I^2 = 34%), and 3 years (2 studies; pooled RR = 0.38; 95% CI = 0.32–0.44; I^2 = 88%) (*Figure 3*). The differences were insignificant at 5 years (4 studies) and 10 years (2 studies). In contrast, patients with HFmrEF had comparable risk of all-cause death with HFpEF at all the specified years (*Figure 4*).

Cardiovascular, non-cardiovascular deaths, heart failure, and sudden cardiac deaths

Patients with HFmrEF had significantly lower risk of cardiovascular deaths than HFrEF (pooled RR = 0.77; 95% CI = 0.65–0.92; $P < 0.001$; I^2 = 76%) (*Figure 4*, Supporting Information, *Figures S1–S3*). Patients with HFmrEF had significantly lower risk of SCD than in HFrEF (pooled RR = 0.59; 95% CI = 0.41–0.85; $P < 0.001$; $I^2 = 0$). Patients with HFmrEF had trends of lower risk of heart failure related deaths than in HFrEF (pooled RR = 0.72; 95% CI = 0.43–1.21; $P = 0.21$; I^2 = 86%). However, the risk of non-cardiovascular deaths was comparable (pooled RR = 1.20; 95% CI = 1.05–1.37; $P = 0.15$; I^2 = 12.7%) between HFmrEF and HFrEF groups.

In contrast, patients with HFmrEF and HFpEF had comparable risks of cardiovascular deaths (pooled RR = 1.10; 95% CI = 0.99–1.21; $P = 0.38$; I^2 = 6%), heart failure deaths (pooled RR = 0.93; 95% CI = 0.70–1.24; $P = 0.62$; I^2 = 44%), SCD (pooled RR = 1.33; 95% CI = 0.85–2.09; $P = 0.27$; I^2 = 23%), and non-cardiovascular deaths (pooled RR = 1.05; 95% CI = 0.77–1.44; $P = 0.76$; I^2 = 77%) (*Figure 5*).

Table 1 Characteristics of the included studies

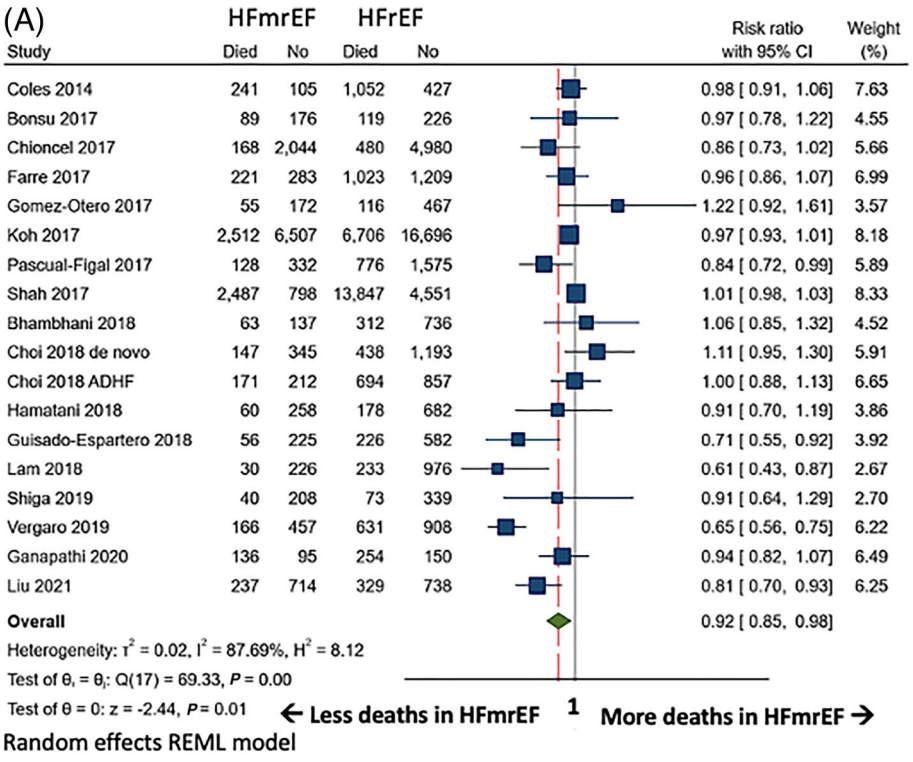
Source[a]	Study design	Country	Study period	Follow-up in years	Age[b] (years) (mean ± SD/ median ± IQR)	Total sample size	Number of patients					
							HFrEF (<40%)		HFmrEF (40%–49%)		HFpEF (≥50%)	
							No.	Male %	No.	Male %	No.	Male %
Bonsu *et al*., 2017	Retrospective single hospital registry	Ghana	January 2009 to December 2013	5	60.8 ± 14.6	1488	345	48.1	265	50.2	878	43.3
Cheng *et al*., 2014	Prospective multi-hospital registry	USA	January 2005 to December 2011	1	80 ± 74–86	40 239	15 716	60	5626	49.5	18 897	32.7
Chioncel *et al*., 2017	Prospective multi-hospital registry	Europe and Mediterranean countries	May 2011 to April 2013	1	68.6 ± 13.7	9134	5460	78.4	2212	68.5	1462	52.1
Choi *et al*., 2018 de novo	Prospective multi-hospital registry	South Korea	March 2011 to February 2014	4	71.7 ± 14.5	2867	1631	61.8	492	50	744	42.3
Choi *et al*., 2018 ADHF	Prospective multi-hospital registry	South Korea	March 2011 to February 2014	4	72.6 ± 12.0	2547	1551	60.7	383	43.9	613	33.8
Coles *et al*., 2014[+]	Prospective multi-hospital registry	USA	1995, 2000, 2002, 2004	4	76.5 ± 11.9	3604	1479	56.5	346	45.4	1779	33.4
Farre *et al*., 2017	Prospective multi-hospital registry	Spain	Aug 2001 to Jun 2015	10	73.5 ± 11.4	3580	2232	75.7	504	66.9	844	44
Ganapathi *et al*., 2020	Retrospective single hospital registry	India	January 2001 to December 2010	10	48.8 ± 14.7	1502	404	78.2	231	74.5	867	51.7
Gomez-Otero *et al*., 2017	Prospective multi-hospital registry	Spain	October 2013 to December 2014	1	72.5 ± 11.1	1420	583	76.7	227	67	610	46.7
Guisado-Espartero *et al*., 2018	Prospective multi-hospital registry	Spain	February 2008 to February 2009	1	81 ± 76–86	2753	808	62.5	281	58	1664	37.4
Hamatani *et al*., 2018	Prospective multi-hospital registry	Japan	June 2005 to April 2016	5	77 ± 11	1792	860	71.2	318	64.5	614	47.4
Koh *et al*., 2017	Retrospective multi-hospital registry	Sweden	January 2000 to December 2012	3	77 ± 11	42 061	23 402	71.2	9019	60.8	9640	45.4
Lam *et al*., 2018	Prospective multi-hospital registry	New Zealand, Singapore	March 2010 to August 2014	2	71.5 ± 11.8	2039	1209	83.5	256	69.9	574	52.3
Liu *et al*., 2021[+]	Retrospective single hospital registry	Germany	July 2009 to December 2017	8	69 ± 13	2018	1067	76.3	951	74.2	--	--
Pascual-Figal *et al*., 2017	Prospective multi-hospital registry	Spain	April 2003 to January 2011	4	72.1 ± 12.2	3446	2351	76.8	460	73	635	42.8
Shah *et al*., 2017	Prospective multi-hospital registry	USA	January 2005 to 30 December 2009	5	82 ± 75–87	39 982	18 398	59	3285	48.5	18 299	32.4
Shiga *et al*., 2019	Retrospective multi-hospital registry	Japan	April 2013 to March 2014	2	81 ± 72–87	1156	412	68.2	248	53.2	496	39.5
Vergaro *et al*., 2019[+]	Prospective single hospital registry	Italy	January 2000 to December 2016	5	71 ± 12	2791	1539	76.3	623	71.6	629	4.5

Abbreviations: ADHF, acute decompensated heart failure patients; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

[a]Studies have been mentioned in order of first author followed by year of publication; additionally, these studies had defined HFmrEF as 41%–49%, remainder of the studies defined HFmrEF as 40%–49%.

[b]Average age is presented as mean and 95% standard deviation or median with 25th and 75th interquartile ranges.

Figure 2 Forest plots demonstrating all-cause deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF. HFmrEF, heart failure with mid-range (borderline) ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.



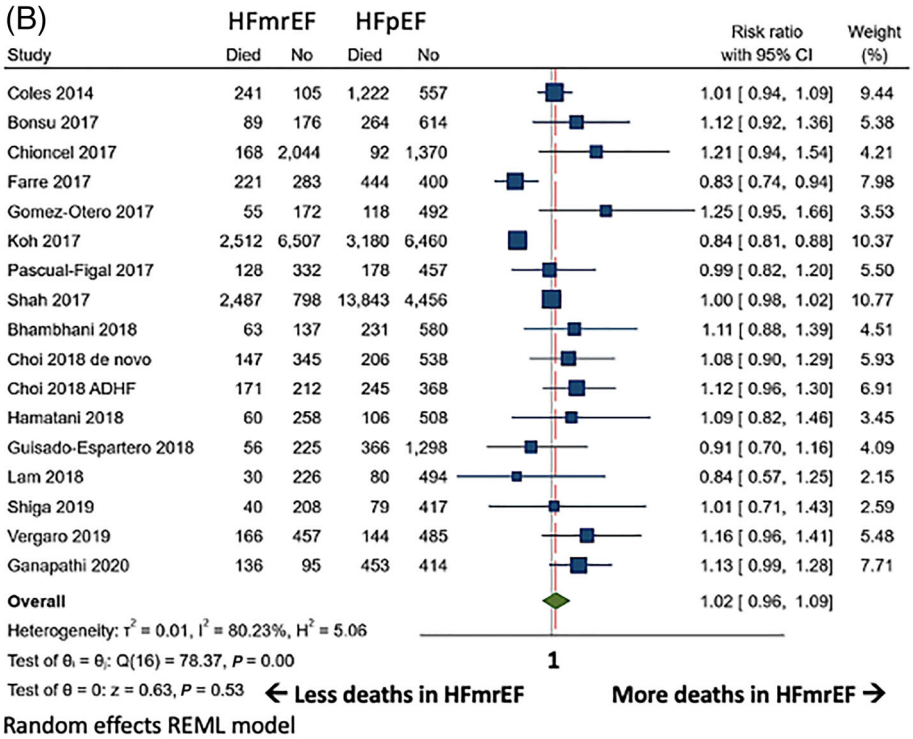
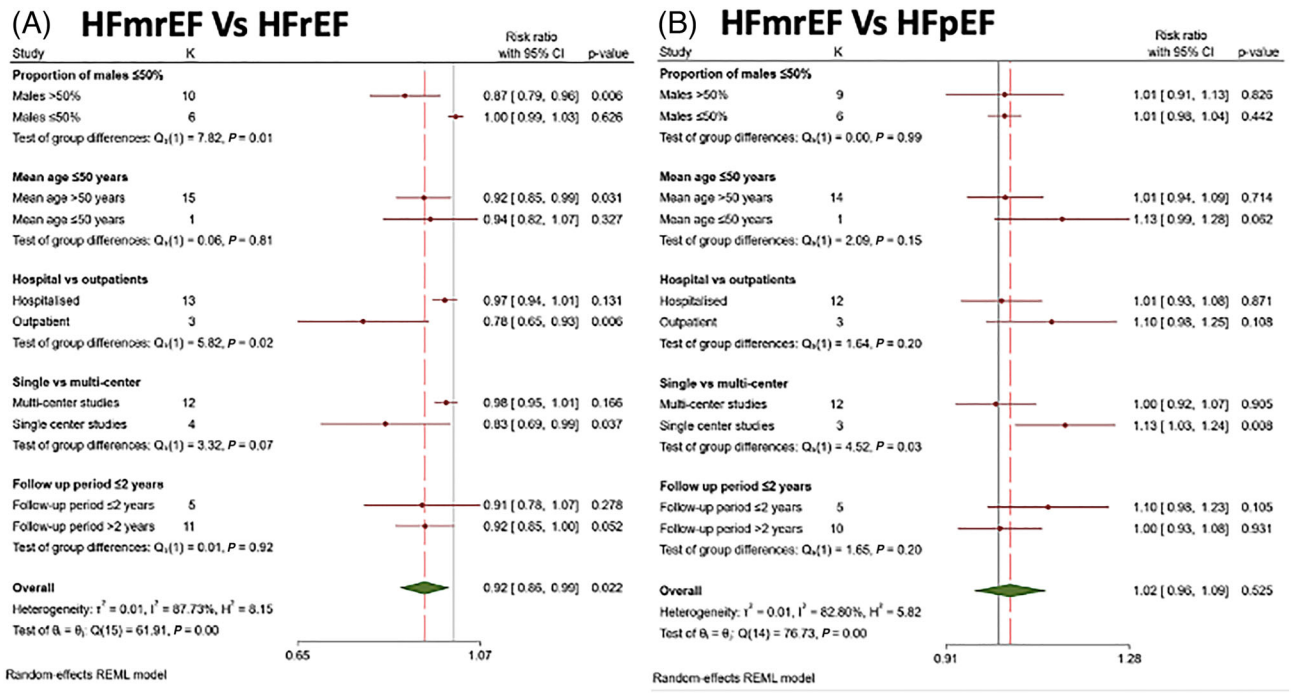


Figure 3 Forest plots of sub-group analysis of long-term all-cause mortality in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF. HFmrEF, heart failure with mid-range (borderline) ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.



Discussion

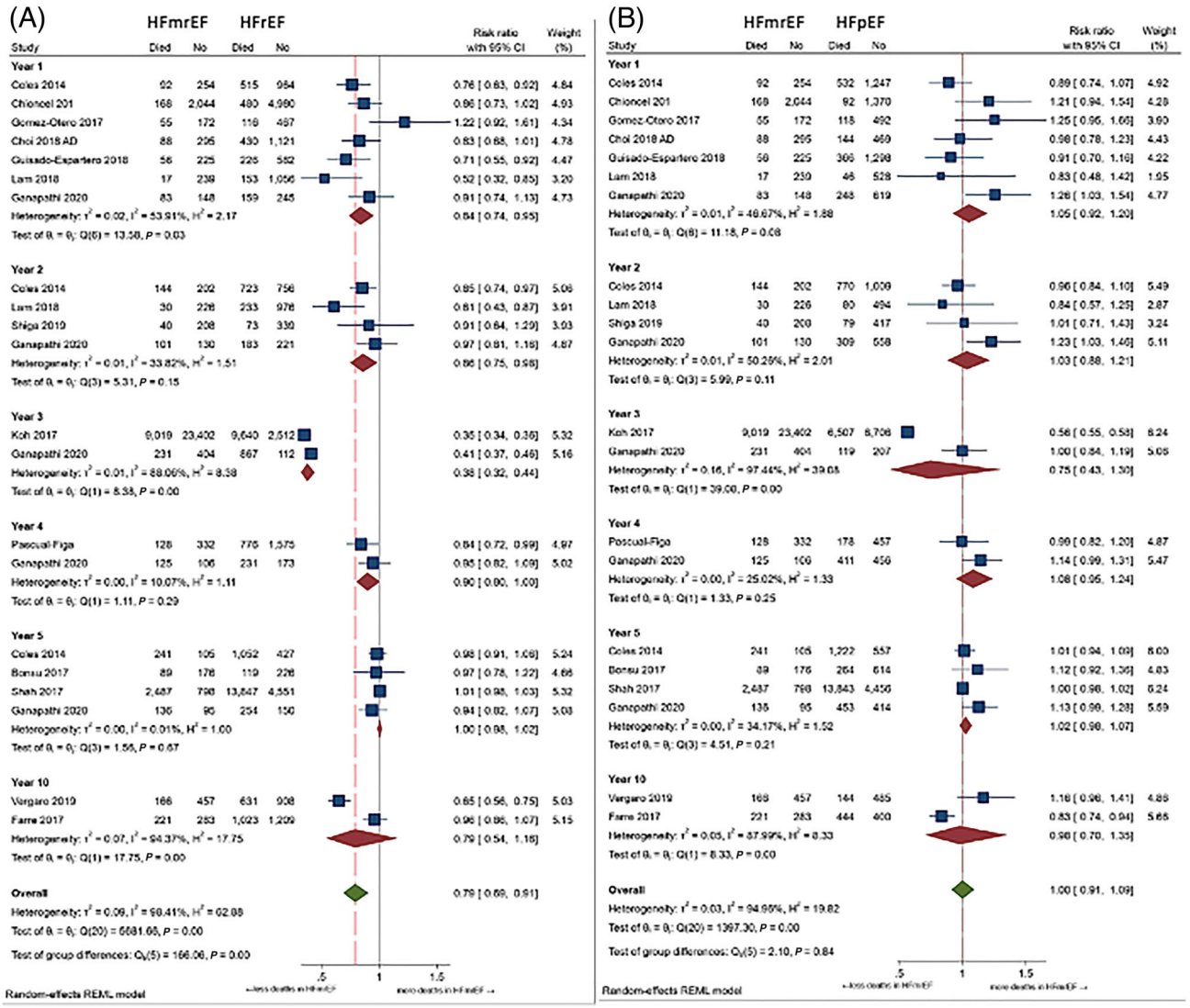
The salient features of our meta-analysis are (1) The risk of long-term all-cause mortality is reduced in patients with HFmrEF compared with HFrEF at 1, 2, and 3 years; beyond which the differences in mortality risk are insignificant; (2) the risk ratios for all-cause deaths between HFmrEF and HFrEF are different when accounting for gender disparity, while studies recruiting $>$ 50% men show a higher risk of deaths in the HFrEF category compared with HFmrEF, the risk ratios are indifferent in studies recruiting higher proportion of women; (3) the risk of long-term all-cause mortality, cardiovascular and non-cardiovascular deaths is similar between patients with HFmrEF and HFpEF.

Our study is the largest meta-analysis of large-scale studies reporting long-term mortality outcomes in HFmrEF compared with HFrEF and HFpEF. The last meta-analysis on this topic included studies till end of April 2019 and had evaluated only the adjusted mortality ratios between these groups.[23] While two of the previous meta-analyses reported both short-term and long-term mortality ratios between the groups, only one meta-analysis reported the 1 year mortality ratios.[22,24] The results of our study on the cumulative all-cause mortality outcomes between HFmrEF and HFrEF as well as HFpEF groups are consistent with the earlier meta-analyses.[22,26] While HFmrEF bears a better long-term prognosis compared with HFrEF, the outcomes seem to be similar compared with HFpEF.

Our study, in addition, explores the annual mortality outcomes in the follow-up. Beyond 3 years, the risk differences seem to level out between HFmrEF and HFrEF. This observation could be due to either transition in LVEF from one group to the other in the follow-up, or inadequate power of the very long-term studies to detect differences in the deaths between the two groups. Transition of patients from one group to the other has not been reported uniformly in the registries. In a seminal study involving 4942 patients, amongst those patients with HFmrEF, 37% patients had worsened to HFrEF and 25% patients improved to HFpEF category. Also, 21% patients of HFpEF had progressive failing of LV function and shifted to HFmrEF category and 16% patients of HFrEF improved to the HFmrEF category.[27] This shows that HFmrEF is likely a heterogenous entity comprising patients with improved ejection fraction, stable left ventricular functions, and progressive LV dysfunction. Though LVEF helps to categorize these patients, the dynamic change in LVEF is an important consideration to keep in mind while interpreting the long-term outcomes.

Gender disparity between studies and its influence on the outcomes is revealed in our analysis. Studies with more proportions of women had comparable risk of deaths between HFmrEF and HFrEF, while those with more proportion of men had higher risk of deaths in HFrEF. Studies on gender dif-

Figure 4 Forest plots demonstrating annual all-cause deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF. HFmrEF, heart failure with mid-range (borderline) ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.



ferences in incidence and prognosis of heart failure show higher risk of HFrEF, incident heart failure and deaths in men compared with higher incidence of HFpEF amongst women.[28] Hospitalization is an important event in the natural history of HF that portends poor prognosis.[29] In our analysis, the studies including only outpatients had reported lesser all-cause mortality rates ranging from 7.6% to 28% in HFmrEF group compared with mortality rates ranging from 18% to 75% in the studies including only hospitalized patients. Predictably, our subgroup analysis showed a significantly reduced deaths in the HFmrEF compared with HFrEF only amongst the studies reporting outpatients.

An individual patient data meta-analysis showed no differences in the risks of all-cause mortality as well as cardiovascular deaths at LVEF ≥40%.[26] Our observation also shows no differences in absolute mortality, cardiovascular, non-cardiovascular and sudden cardiac deaths, between the HFmrEF and HFpEF groups. Thus, this group is a large cluster of heart failure patients, wherein LVEF fails to dictate prognosis. This underlines the need to look for additional non-cardiac and cardiac prognostic indicators like associated co-morbidities, cardiac MRI, and arrhythmia burden. Cardiac specific investigations need to be considered beyond the conventional echocardiogram in this subset. Recent large-scale studies have shown that cardiac MRI could identify subtle myocardial abnormalities in this subset that may portend a poor prognosis both in terms of worsening myocardial dysfunction and increase in risk of arrhythmias.[30]

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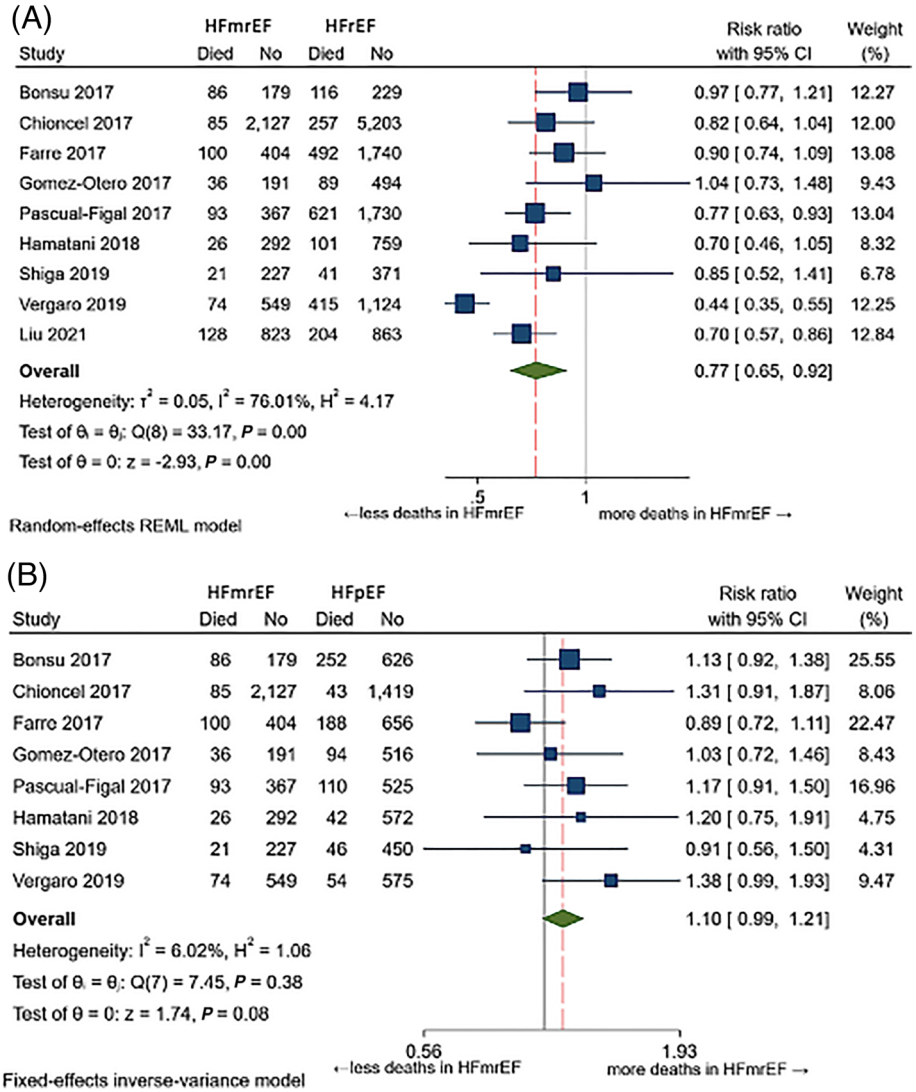
Figure 5 Forest plots demonstrating cardiovascular deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF. HFmrEF, heart failure with mid-range (borderline) ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.



Limitations

(1) In spite of application of strict eligibility criteria, our meta-analysis does bear a high level of heterogeneity between the included studies. This heterogeneity was adequately addressed statistically with appropriate sensitivity, subgroup and meta-regression analysis. The results seem to be unaffected by any of the included studies. (2) The lack of a standard reporting protocol of long-term outcomes in registries was evident during our systematic review, such as variable period of follow-up; gender disparity; variable age groups; variable outcomes in single and multi-centre studies; inclusion of both hospitalized and outpatients in a few studies; inclusion of both de novo and chronic heart failure patients in a few registers; and representation of more valvular heart diseases and myocardial infarction in a few registries. We have attempted to address this heterogeneity arising due to clinical variables in our subgroup analysis. (3) Medical therapy has improved enormously with regards to heart failure. However, due to considerable heterogeneity in the reporting of medical therapy in the included studies, we could not address this in the subgroup analysis. (4) It is possible that, the recruited studies did not have adequate power to detect significant differences in risk-ratios in heart failure deaths and very long-term (beyond 3 years) deaths between HFmrEF and HFrEF groups. Similarly, the single-centre studies may not have sufficient power to detect enough deaths in the HFpEF group.

Future directives

(1) Adoption of a standard reporting guideline on long-term outcomes with respect to the clinically relevant confounders could reduce the level of heterogeneity between studies; (2) transition in LVEF needs to be considered while analysing the outcomes in chronic heart failure; (3) additional risk-stratification tools should be aggressively sought to understand better the similarities and differences between HFmrEF and HFpEF.

Conclusions

Our meta-analysis concludes that risk of long-term all-cause mortality is less in patients with HFmrEF compared with HFrEF till 3 years; beyond which the differences in mortality risk were insignificant, for which transition in LVEF could play an important role. The insignificant differences in the risk-ratio between HFmrEF and HFrEF while considering studies representing greater proportion of women, suggests that gender disparity may play a divisive role in determining outcomes. The differences in risk of long-term all-cause mortality were comparable between patients with HFmrEF compared with HFpEF, thus suggesting the need to explore the mortality risks with tools other than LVEF.

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Conflicts of interest

Dr Sanders reports having served on the advisory board of Medtronic, Abbott Medical, Boston Scientific, CathRx and PaceMate. Dr Sanders reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Medtronic, Abbott Medical, and Boston Scientific. Dr Sanders reports that the University of Adelaide has received on his behalf research funding from Medtronic, Abbott Medical, Boston Scientific, BD, and Microport. All other authors have no disclosures. Dr Pathak reports having served on the advisory board of Medtronic, Abbott Medical, Boston Scientific. Dr Pathak reports that Canberra Heart Rhythm Foundation has received on his behalf lecture and/or consulting fees from Medtronic, Abbott Medical, Boston Scientific and Biotronik. Dr Pathak reports that Canberra Heart Rhythm Foundation has received on his behalf research funding from Medtronic, Abbott Medical, Boston Scientific, and Biotronik.

Supporting information

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

Figure S1: Forest plots demonstrating non-cardiovascular deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction.
Figure S2: Forest plots demonstrating heart failure deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction.
Figure S3: Forest plots demonstrating sudden cardiac deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction.
Table S1: Enumeration of the detailed search strategy.
Table S2: Newcastle-Ottawa quality assessment scale (NOS) for cohort studies.
Table S3: The distribution of patient characteristics between the three groups.

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