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ORIGINAL PAPER

Age-dependent differences in clinical phenotype and prognosis in heart failure with mid-range ejection compared with heart failure with reduced or preserved ejection fraction

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Abstract

Background HFmrEF has been recently proposed as a distinct HF phenotype. How HFmrEF differs from HFrEF and HFpEF according to age remains poorly defined. We aimed to investigate age-dependent differences in heart failure with mid-range (HFmrEF) vs. preserved (HFpEF) and reduced (HFrEF) ejection fraction.

Methods and results 42,987 patients, 23% with HFpEF, 22% with HFmrEF and 55% with HFrEF, enrolled in the Swedish heart failure registry were studied. HFpEF prevalence strongly increased, whereas that of HFrEF strongly decreased with higher age. All cardiac comorbidities and most non-cardiac comorbidities increased with aging, regardless of the HF phenotype. Notably, HFmrEF resembled HFrEF for ischemic heart disease prevalence in all age groups, whereas regarding hypertension it was more similar to HFpEF in age ≥ 80 years, to HFrEF in age < 65 years and intermediate in age 65–80 years. All-cause mortality risk was higher in HFrEF vs. HFmrEF for all age categories, whereas HFmrEF vs. HFpEF reported similar risk in ≥ 80 years old patients and lower risk in < 65 and 65–80 years old patients. Predictors of mortality were more likely cardiac comorbidities in HFrEF but more likely non-cardiac comorbidities in HFpEF and HFmrEF with < 65 years. Differences among HF phenotypes for comorbidities were less pronounced in the other age categories.

Conclusion HFmrEF appeared as an intermediate phenotype between HFpEF and HFrEF, but for some characteristics such as ischemic heart disease more similar to HFrEF. With aging, HFmrEF resembled more HFpEF. Prognosis was similar in HFmrEF vs. HFpEF and better than in HFrEF.

Keywords HFmrEF · HFrEF · HFpEF · Age · Prognosis

Introduction

The 2016 European Society of Cardiology (ESC) heart failure (HF) guidelines propose ejection fraction (EF) 40–49%, namely HF with mid-range EF (HFmrEF), as a distinct phenotype from HF with preserved (HFpEF) and reduced (HFrEF) EF and call for studies to define the different pathophysiology, clinical characteristics, treatments and prognosis across these three HF subtypes [1].

Xiaojing Chen, Gianluigi Savarese equally contributed as first author. Lars H. Lund, Michael Fu equally contributed as last author.

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Aging is associated with changes in cardiac structure and function and increased incidence and prevalence of HF [2, 3]. An aging population worldwide is contributing to a "HF pandemic". However, in a previous analysis reporting trends in HF prevalence in 1990–2007 in Sweden, fears of an impending HF 'epidemic' because of aging could not be confirmed since an overall slight decrease in age-adjusted prevalence was observed, but, at the same time a substantial increase in HF prevalence was reported in the very old [4]. Moreover, as we and others have previously shown, older HF patients differ from their younger counterparts regardless of EF [5–7], with HFrEF characteristics different from those in HFpEF across all the age ranges [8, 9].

There is currently not much data comparing HFmrEF, HFrEF, and HFpEF specifically across different age groups. The aim of the current analysis was to investigate the age-dependent differences in demographical and clinical characteristics and outcomes among HFmrEF, HFrEF, and HFpEF.

Methods

Study protocol and setting

The Swedish Heart Failure Registry (SwedeHF; www.SwedeHF.se) has been previously described [10]. Briefly, it was created in 2000 and spread throughout Sweden in 2003. Approximately 80 variables are recorded at discharge from hospital or after out-patient clinic visit on a web-based case report form and entered into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden (www.ucr.uu.se). The protocol, case report form and annual reports are available at www.SwedeHF.se.

The Swedish Tax Agency (www.skattverket.se) administers the population registry which provided the data of death. The Swedish Board of Health and Welfare (www.socialstyrelsen.se) administers the Patient Registry which provided additional baseline comorbidities and the HF hospitalization outcome, defined according to ICD-10 codes in the first position. Statistics Sweden (www.scb.se) maintains socioeconomic data on all Swedish citizens and provides additional baseline data. All Swedish citizens have unique personal identification numbers that enable linking of disease-specific health registries and governmental health and statistical registries.

Establishment of the Swede HF registry and its linking with other registries (disease-specific health registries and governmental health and statistical registries) were approved by a multisite ethics committee. Individual patient consent is not required, but patients in Sweden are informed of entry into national registries and allowed to opt out.

EF is categorized as < 30%, 30–39%, 40–49%, and ≥ 50%. In the current study, HFpEF was defined as EF ≥ 50%, HFmrEF as EF = 40–49% and HFrEF as EF < 40%. Patients with no missing data for EF were included. There were no missing data for age, which was categorized as < 65, 65–80 and ≥ 80 years. When a patient reported more than one registration, the first one reporting EF was considered. Outcomes of the current analysis were all-cause death and all-cause, cardiovascular (CV) and HF hospitalization. The index date was defined as the date of hospital discharge or the date of outpatient visit occurring between 2000 and December 30, 2012. The outcomes were defined as between the index date and end of follow-up, December 31, 2012.

Statistical analysis

Baseline characteristics

Baseline characteristics were compared by analysis of variance (ANOVA) or Kruskal–Wallis test and by Chi-squared test to test continuous and categorical variables, respectively, in HFpEF vs. HFmrEF vs. HFrEF for each age category. Missing data were handled by multiple imputation ($n = 10$) in multivariable models.

Outcome analysis

The relationship between HF phenotype and time-to-outcomes was assessed specifically in each age category as well as the relationship between age category and time-to-outcomes in each EF group, and the raw number of events and the unadjusted event rates and hazard ratios (HR) with 95% confidence intervals (CI) were reported. Unadjusted survivor functions were estimated using Kaplan–Meier method. The size of the association between HF phenotype and event rates in each age category and the HRs with 95% CIs were estimated with unadjusted Cox proportional hazard models. Predictors of all-cause mortality were identified by multivariable Cox proportional hazard models performed separately in each age category and adjusted for all the variables labelled with asterisk in Table 1. Since the focus for all analyses was a comparison between HFpEF vs. HFmrEF vs. HFrEF in each age category, statistical interactions with EF were tested using a Wald-type test.

For all the analyses, a p value of < 0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed by Stata 14.2 (StataCorp LLC, College Station, Texas, USA) or IBM SPSS Statistics 24.0 (IBM Corp, Armonk, NY, USA).

Results

Between May 8, 2000 and December 30, 2012, 69,260 registrations were recorded from 42,987 unique patients, 23% with HFpEF, 22% with HFmrEF and 55% with HFrEF, and

Table 1 Patient baseline characteristics in three HF phenotypes (HFmrEF, HFpEF, and HFrEF) by age

	< 65 years (n=9033, 21%)				65-80 years (n=18,019, 42%)				≥80 years (n=15,935, 37%)			
	HFpEF (n=1170)	HFmrEF (n=1723)	HFrEF (n=6140)	p value	HFpEF (n=3755)	HFmrEF (n=3919)	HFrEF (n=10,345)	p value	HFpEF (n=5032)	HFmrEF (n=3583)	HFrEF (n=7320)	p value
Demographics												
Age, mean (SD), years	56 ± 8	55 ± 8	55 ± 8	< 0.001	73.6 ± 4.1	73.0 ± 4.2	72.5 ± 4.3	< 0.001	85.3 ± 3.8	84.9 ± 3.8	84.6 ± 3.6	< 0.001
Sex (%)*				< 0.001				< 0.001				< 0.001
Male	705 (60)	1255 (73)	4795 (78)		1914 (51)	2508 (64)	7571 (73)		1896 (38)	1833 (51)	4583 (63)	
Female	465 (40)	468 (27)	1345 (22)		1841 (49)	1411 (36)	2774 (27)		3136 (62)	1750 (49)	2737 (37)	
Location (%)*												
Inpatient	588 (50)	627 (36)	2769 (45)	< 0.001	2290 (61)	1931(49)	5216 (50)	< 0.001	3801 (76)	2437 (68)	5049 (69)	< 0.001
Outpatient	582 (50)	1096 (64)	3371 (55)		1465 (39)	1988 (51)	5129 (50)		1231 (24)	1146 (32)	2271 (31)	
Specialty (%)*												
Cardiology	660 (60)	964 (58)	3852 (64)	< 0.001	1711 (51)	1960(54)	5658 (56)	< 0.001	2076 (46)	1588 (48)	3531(50)	< 0.001
Internal medicine or geriatrics	441 (40)	686 (42)	2192 (36)		1634 (49)	1676 (46)	4364 (44)		2464 (54)	1724 (52)	3511 (50)	
Planned follow-up referral specialty (%)*												
Primary care or other care	270 (25)	258 (16)	648 (11)	< 0.001	1566 (44)	1243 (33)	2490 (25)	< 0.001	3196 (69)	2038 (61)	3733 (56)	< 0.001
Cardiology or internal medicine	821 (75)	1394 (84)	5195 (89)		1956 (56)	2490 (67)	7383 (75)		1406 (31)	1288 (39)	3016 (44)	
Follow-up referral to outpatient HF nurse-led clinic (%)*	390 (36)	796 (48)	3347 (57)	< 0.001	1069 (30)	1490 (40)	4866 (50)	< 0.001	882 (19)	874 (26)	2189 (32)	< 0.001
Smoking (%)*				0.001				< 0.001				< 0.001
Current	228 (23)	357 (24)	1452 (27)		333 (12)	400 (13)	1215 (14)		143 (4)	90 (4)	269 (5)	
Previous	391 (40)	648 (43)	2287 (42)		1317 (45)	1515 (47)	4138 (49)		1152 (35)	953 (38)	2091 (41)	
Never	365 (37)	487 (33)	1676 (31)		1263 (43)	1283 (40)	3148 (37)		2045 (61)	1449 (58)	2735 (54)	
Family type (%)*				0.854				< 0.001				< 0.001

Table 1 (continued)

	< 65 years (*n* = 9033, 21%)				65-80 years (*n* = 18,019, 42%)				≥ 80 years (*n* = 15,935, 37%)			
	HFpEF (*n* = 1170)	HFmrEF (*n* = 1723)	HFrEF (*n* = 6140)	*p* value	HFpEF (*n* = 3755)	HFmrEF (*n* = 3919)	HFrEF (*n* = 10,345)	*p* value	HFpEF (*n* = 5032)	HFmrEF (*n* = 3583)	HFrEF (*n* = 7320)	*p* value
Married/ cohabitating	579 (50)	864 (50)	3023 (49)		1931 (52)	2218 (57)	5827 (56)		1677 (33)	1442 (40)	3272 (45)	
Living alone	584 (50)	855 (50)	3023 (51)		1818 (48)	1699 (43)	4491 (44)		3355 (67)	2139 (60)	4041 (55)	
Education (%)*												
Compulsory school	384 (33)	509 (30)	1976 (33)	0.019	1849 (50)	1865 (48)	5024 (49)	0.311	3020 (61)	2062 (58)	4246 (59)	0.030
Secondary school	552 (48)	833 (49)	2998 (49)		1305 (35)	1454 (37)	3714 (36)		1408 (28)	1067 (30)	2208 (30)	
University	219 (19)	366 (21)	1102 (18)		564 (15)	565 (15)	1491 (15)		522 (11)	412 (12)	776 (11)	
Medical history cardiac												
Hypertension (%)*	576 (49)	666 (39)	2169 (35)	< 0.001	2308 (61)	2109 (54)	4708 (46)	< 0.001	2981 (59)	1935 (54)	3503 (48)	< 0.001
Ischemic heart disease (%)*	323 (29)	680 (41)	1965 (34)	< 0.001	1439 (39)	2019 (53)	5528 (56)	< 0.001	1995 (41)	1827 (53)	4292 (61)	< 0.001
Coronary revascularization (%)*	221(19)	545 (32)	1419 (23)	< 0.001	867 (24)	1295 (34)	3468 (34)	< 0.001	751 (15)	798 (23)	1829 (26)	< 0.001
Atrial fibrillation (%)*	460 (39)	638 (37)	2188 (36)	0.046	2353 (63)	2317 (59)	5575 (54)	< 0.001	3533 (70)	2420 (67)	4452(61)	< 0.001
Valvular disease (%)*	277 (24)	223 (13)	832 (14)	< 0.001	914 (25)	726 (19)	1958 (19)	< 0.001	1565(32)	974 (28)	1957 (28)	< 0.001
Non-cardiac												
Diabetes mellitus (%)*	313 (27)	395 (23)	1352 (22)	0.002	1181 (31)	1141 (29)	2869 (28)	< 0.001	1042 (21)	715 (20)	1563 (21)	0.232
Peripheral artery disease (%)*	81 (7)	94 (5)	334 (5)	0.123	415 (11)	459 (12)	1164 (11)	0.633	531 (11)	400 (11)	830 (11)	0.380
Stroke/TIA (%)*	120 (10)	124 (7)	496 (8)	0.011	668 (18)	688 (18)	1710 (17)	0.127	1180 (23)	739 (21)	1527 (21)	0.001
eGFR*				< 0.001				< 0.001				< 0.001
< 60 ml/min (%)	128 (12)	109 (7)	518 (9)		1466 (43)	1390 (38)	4305 (44)		3853 (84)	2791 (84)	5926 (86)	

Table 1 (continued)

	< 65 years (n=9033, 21%)				65-80 years (n=18,019, 42%)				≥80 years (n=15,935, 37%)			
	HFpEF (n=1170)	HFmrEF (n=1723)	HFrEF (n=6140)	p value	HFpEF (n=3755)	HFmrEF (n=3919)	HFrEF (n=10,345)	p value	HFpEF (n=5032)	HFmrEF (n=3583)	HFrEF (n=7320)	p value
≥ 60 ml/min (%)	920 (88)	1424 (93)	5179 (91)		1976 (57)	2227 (62)	5489 (56)		756 (16)	535 (16)	968 (14)	
Lung disease (%)*	340 (29)	323 (19)	1155 (19)	< 0.001	1251 (33)	1082 (28)	2619 (25)	< 0.001	1405 (28)	921 (26)	1788 (24)	< 0.001
Anemia (%)*	322 (28)	367 (21)	1178 (19)	< 0.001	1425 (38)	1272 (32)	3207 (31)	< 0.001	2331 (46)	1555 (43)	3121 (43)	< 0.001
Musculoskeletal disease (%)*	347 (30)	386 (22)	1216 (20)	< 0.001	1351 (36)	1190 (30)	2689 (26)	< 0.001	1783 (35)	1150(32)	2021(28)	< 0.001
Cancer (%)*	78 (7)	123 (7)	360 (6)	0.120	581 (15)	522 (13)	1365(13)	0.002	839 (17)	583 (16)	1230 (17)	0.780
Clinical characteristics												
Heart rate, mean (SD), beats/min*	73.4 ± 15.5	71.2 ± 14.9	75.2 ± 16.1	< 0.001	73.8 ± 15.9	72.5 ± 15.5	73.5 ± 15.7	0.001	74.2 ± 15.1	74.0 ± 15.2	74.7 ± 15.2	0.035
Blood pressure, mean (SD), mmHg												
Systolic	128.8 ± 22.0	125.9 ± 20.5	121.3 ± 20.5	< 0.001	133.3 ± 21.4	131.5 ± 20.7	124.9 ± 20.4	< 0.001	134.5 ± 22.1	131.9 ± 21.1	126.0 ± 20.4	< 0.001
Diastolic	76.0 ± 13.2	75.9 ± 12.5	76.1 ± 12.9	0.873	73.6 ± 12.3	74.2 ± 11.9	73.1 ± 11.9	< 0.001	72.0 ± 12.1	72.2 ± 11.9	71.3 ± 11.7	< 0.001
Pulse pressure, mean (SD), mmHg	52.9 ± .16.7	49.9 ± 15.1	45.3 ± 14.6	< 0.001	59.7 ± 18.6	57.3 ± 17.4	51.9 ± 16.2	< 0.001	62.5 ± 19.3	59.7 ± 18.2	54.7 ± 17.0	< 0.001
Body mass index, mean (SD), kg/m^2*	29.9 ± 7.3	29.0 ± 6.2	28.2 ± 6.0	< 0.001	28.8 ± 6.2	28.0 ± 5.4	26.6 ± 4.9	< 0.001	25.7 ± 5.0	25.2 ± 4.5	24.5 ± 4.1	< 0.001
NYHA class*												
I–II (%)	670 (75)	1162 (83)	3290 (65)	< 0.001	1549(41.3)	2032(52)	4408(43)	< 0.001	1617 (54)	1347(56)	2149 (42)	< 0.001
III–IV (%)	226 (25)	240 (17)	1749 (35)		840(22.4)	851(22)	3686(36)		1389 (46)	1043 (44)	2923 (58)	
Laboratory characteristics												
NT-pro-BNP, median (IQR), pg/ml*	936 (315–2052)	838 (338–2207)	1870 (760–4227)	< 0.001	1676 (737–3503)	1943 (930–4130)	3000 (1455–6547)	0.001	2800 (1367–5548)	3630 (1761–7320)	5480 (2580–11,652)	< 0.001
eGFR, mean (SD), ml/min	101.4 ± 37.2	104.4 ± 33.4	100.3 ± 33.4	< 0.001	68.5 ± 27.5	69.2 ± 26.3	66.0 ± 25.0	< 0.001	43.8 ± 17.5	43.8 ± 17.2	42.5 ± 16.6	0.001
Hemoglobin, mean (SD), g/L	134.8 ± 18.6	138.7 ± 17.3	140.9 ± 16.7	< 0.001	129.2 ± 17.1	132.8 ± 17.1	134.5 ± 16.9	< 0.001	124.9 ± 15.9	127.1 ± 16.1	129.0 ± 16.1	< 0.001

Table 1 (continued)

	< 65 years (*n* = 9033, 21%)				65-80 years (*n* = 18,019, 42%)				≥ 80 years (*n* = 15,935, 37%)			
	HFpEF (*n* = 1170)	HFmrEF (*n* = 1723)	HFrEF (*n* = 6140)	*p* value	HFpEF (*n* = 3755)	HFmrEF (*n* = 3919)	HFrEF (*n* = 10,345)	*p* value	HFpEF (*n* = 5032)	HFmrEF (*n* = 3583)	HFrEF (*n* = 7320)	*p* value
Medical therapy												
ACEI/ARB (%)*	912 (79)	1577 (92)	5906 (97)	< 0.001	2897 (78)	3432 (88)	9535 (93)	< 0.001	3251(65)	2639 (74)	5929 (82)	< 0.001
β-Blocker (%)*	935 (80)	1513 (88)	5730 (94)	< 0.001	3009 (81)	3416 (88)	9416 (91)	< 0.001	3809 (76)	2938 (83)	6249 (86)	< 0.001
Aldosterone antagonist (%)*	279 (24)	360(21)	2243 (37)	< 0.001	998 (27)	957 (25)	3490 (34)	< 0.001	1323 (27)	851 (24)	2020 (28)	< 0.001
Nitrate (%)*	99 (9)	108 (6)	351 (6)	0.002	568 (15)	576 (15)	1547 (15)	0.878	1139(23)	839 (24)	1849 (25)	0.004
Digoxin (%)*	154 (13)	193 (11)	1054 (17)	< 0.001	680 (18)	662 (17)	1892 (18)	0.149	961 (19)	630 (18)	1241 (17)	0.007
Statin (%)*	509 (44)	867 (50)	2753 (45)	< 0.001	1799 (48)	2232 (57)	5741 (56)	< 0.001	1505 (30)	1316 (37)	2807 (39)	< 0.001
Platelet inhibitor (%)*	459 (40)	848 (50)	2720 (45)	< 0.001	1595 (43)	1984 (51)	5300 (52)	< 0.001	2545 (51)	1992 (56)	4351 (60)	< 0.001
Oral Anti-coagulant (%)*	375 (32)	530 (31)	2369 (39)	< 0.001	1702 (46)	1712 (44)	4555 (44)	0.284	1731 (35)	1268 (36)	2347 (32)	0.001
Diuretic (%)*	794 (68)	859 (51)	4279 (66)	< 0.001	3107 (83)	2878 (74)	8198 (80)	< 0.001	4514 (90)	3105 (87)	6422 (88)	< 0.001
Device therapy (%)*				< 0.001				< 0.001				< 0.001
None	1063 (92)	1577 (92)	5450 (89)		3353 (90)	3434 (89)	8674 (85)		4338 (87)	3018 (85)	4072 (84)	
PM	58 (5)	67 (4)	192 (3)		321 (9)	350 (9)	788 (8)		606 (12)	489 (14)	938 (13)	
CRT-P	6 (0.5)	15 (1)	78 (1)		10 (0)	25 (1)	236 (2)		16 (1)	18 (1)	120 (2)	
CRT-D	6 (0.5)	12 (1)	158 (3)		8 (0)	9 (0)	221 (2)		1 (0)	7 (0)	35 (0)	
ICD	26 (2)	41 (2)	216 (4)		16 (1)	56 (1)	328 (3)		15 (0)	17 (0)	71 (1)	

Variables labelled with asterisk were included in the multivariable models. Blood pressure was included as mean blood pressure

HFpEF heart failure with preserved ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *SD* standard deviation, *TIA* transient ischemic attack, *eGFR* estimated glomerular filtration rate, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blocker, *PM* pacemaker, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter-defibrillator

according to different age group, 21% with age < 65 years, 42% with age 65–80 years and 37% with age ≥ 80 years.

Age-related differences according to HF phenotype and sex (Table 1)

In the overall population, mean age (± standard deviation) was 76 ± 12. HFrEF prevalence strongly decreased (68% in < 65 years old patients, 57% in 65–80 years old, 46% in ≥ 80 years old) whereas that of HFpEF strongly increased (13% in < 65 years old patients, 21% in 65–80 years old, 32% in ≥ 80 years old) with aging. HFmrEF prevalence only slightly increased with aging (19% in < 65 years old patients, 22% in 65–80 years old, 22% in ≥ 80 years old). The proportion of female patients increased with age, regardless of the HF phenotype; however, females became dominant in HFpEF but intermediate in HFmrEF.

Age-related differences in clinical characteristics and comorbidities (Table 1)

NYHA functional class, NT-pro-BNP and systolic blood pressure (BP) increased with age, but body mass index (BMI), estimated glomerular filtration rate (eGFR) and diastolic BP decreased, with HFmrEF and HFpEF more similar regarding these characteristics as compared with HFrEF.

The prevalence of all cardiac comorbidities increased with age regardless of the EF category. Atrial fibrillation and valvular diseases were more common in HFpEF than in HFrEF, with HFmrEF more similar to HFpEF for atrial fibrillation but to HFrEF for valvular disease. Hypertension was more common in HFpEF vs. HFmrEF vs. HFrEF across all age categories, with HFmrEF more similar to HFrEF for hypertension in age < 65 years but to HFpEF in age ≥ 80 years. Ischemic heart disease prevalence increased with aging and was higher in HFmrEF vs. HFrEF vs. HFpEF in age < 65 years, in HFrEF and HFmrEF vs. HFpEF in age 65–80 years, in HFrEF vs. HFmrEF vs. HFpEF in age ≥ 80 years.

All non-cardiac comorbidities, except for diabetes mellitus, became more prevalent with age regardless of EF category and were more common in HFpEF (i.e., diabetes mellitus, pulmonary disease, anemia, and cancer) as compared with HFmrEF and HFrEF.

Age-related differences in HF treatment (Table 1)

Angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARBs) use decreased with aging, whereas beta-blocker use decreased only at and above the age of 80 years, with HFmrEF more similar to HFrEF regarding the use of these drugs. Mineralocorticoid receptor antagonist (MRA) use was higher in HFrEF vs. HFpEF and HFmrEF in age < 80 years but almost comparable in HFpEF and HFrEF in age ≥ 80 years. Their use increased with aging in HFpEF and HFmrEF but decreased in HFrEF. Diuretic use increased with aging and more patients with HFpEF and HFrEF received these drugs as compared with HFmrEF regardless of age.

Age-related differences in prognosis (Table 2)

Over a median follow-up of 2.2 [interquartile range (IQR) 0.9–4.1] years, all-cause death occurred in 16,866 (39%) patients, CV readmissions in 23,960 (56%) and HF readmissions in 15,111 (35%) (Table 2). Outcomes' incidence increased with aging, regardless of EF category.

Regardless of age, unadjusted mortality rates were highest in HFrEF, intermediate in HFmrEF and lowest in HFpEF. In the different age categories, unadjusted all-cause mortality rates were lower in HFmrEF vs. HFpEF and HFrEF in age 65–80 years, whereas it was comparable in HFmrEF vs. HFpEF but lower than in HFrEF in age < 65 and ≥ 80 years (Fig. 1).

All-cause readmission rates were similarly higher in HFpEF and HFrEF vs. HFmrEF in < 65 years old patients, but in age ≥ 65 years they were higher in HFpEF vs. HFmrEF and HFrEF. CV readmission rates were lower in HFmrEF vs. HFpEF and HFrEF in age < 80 years, but highest in HFrEF and comparable in HFmrEF vs. HFpEF in age ≥ 80 years. HF hospitalization rates were higher in HFpEF and HFrEF vs. HFmrEF in age < 65 years, but highest in HFrEF and comparable in HFmrEF vs. HFpEF in age ≥ 80 years.

Age-related differences in predictors of mortality (Fig. 2 and the Appendix table)

In age < 65 years, selected predictors of mortality that differed in HFpEF vs. HFmrEF vs. HFrEF were, e.g., ischemic heart disease (increased mortality in HFmrEF and HFrEF but neutral in HFpEF) and diabetes that was associated increased mortality in HFmrEF and HFrEF but not in HFpEF.

In age 65–80 years, hypertension was associated with reduced mortality in HFpEF and HFrEF, ischemic heart disease with increased mortality in HFmrEF and HFrEF, and lung disease with a significant increase in mortality in all the HF phenotypes.

In age ≥ 80 years, hypertension was associated with reduced risk of mortality in HFpEF and HFmrEF, ischemic heart disease with increased risk of mortality in all HF phenotypes, but diabetes, peripheral artery disease and stroke with increased mortality in HFmrEF and HFrEF.

Notably, lower eGFR (< 60 ml/min), higher HR (> 70 bpm), higher NYHA class (III–IV) and NT-proBNP levels above the median were associated with increased

Table 2 Outcomes in three HF phenotypes (HFmrEF, HFpEF, and HFrEF) by age

	All-cause mortality		All-cause readmission		Cardiovascular readmission		Heart failure readmission	
	No events (%) ER (*1000 py)	HR (95% CI) *p* value	No events (%) ER (*1000 py)	HR (95% CI) *p* value	No events (%) ER (*1000 py)	HR (95% CI)P value	No events (%) ER (*1000 py)	HR (95% CI) *p* value
< 65 years								
HFpEF	196 (16.8)	1.21 (0.99–1.45)	857 (73.3)	1.29 (1.19–1.42)	601 (51.4)	1.29 (1.16–1.44)	260 (22.2)	1.19 (1.01–1.40)
	46.6	0.055	518.7	< 0.001	241.4	< 0.001	72.3	0.038
HFmrEF	233 (13.5)	1.00 (ref)	1106 (64.2)	1.00 (ref)	727 (42.2)	1.00 (ref)	323 (18.8)	1.00 (ref)
	38.5		376.8		182.8		61.7	
HFrEF	1034 (16.8)	1.28 (1.11–1.47)	4087 (66.6)	1.15 (1.08–1.23)	3128 (50.9)	1.36 (1.26–1.48)	2103 (34.3)	2.11 (1.88–2.38)
	49.3	0.001	454.44	< 0.001	264.0	< 0.001	139.8	< 0.001
65–80 years								
HFpEF	1248 (33.2)	1.12 (1.04–1.22)	2915 (77.6)	1.16 (1.11–1.22)	2055 (54.7)	1.07 (1.01–1.14)	1133 (30.2)	1.08 (0.99–1.17)
	117.4	0.004	755.2	< 0.001	335.4	0.021	133.0	0.067
HFmrEF	1230 (31.4)	1.00 (ref)	2933 (74.8)	1.00 (ref)	2119 (54.1)	1.00 (ref)	1156 (29.5)	1.00 (ref)
	104.3		609.5		303.3		113.0	
HFrEF	3667 (35.5)	1.17 (1.10–1.24)	7678 (74.2)	1.04 (0.99–1.08)	5991 (57.9)	1.16 (1.11–1.22)	4036 (39.0)	1.48 (1.39–1.58)
	122.1	< 0.001	638.8	0.094	361.0	< 0.001	178.8	< 0.001
≥80 years								
HFpEF	2817 (56.0)	1.02 (0.96–1.08)	4054 (80.1)	1.08 (1.02–1.13)	2892 (57.5)	1.01 (0.95–1.07)	1804 (35.9)	0.99 (0.92–1.06)
	273.5	0.489	1035.7	0.003	476.8	0.753	225.2	0.685
HFmrEF	2008 (56.0)	1.00 (ref)	2796 (78.0)	1.00 (ref)	2079 (58.0)	1.00 (ref)	1310 (36.6)	1.00 (ref)
	267.2		948.4		464.8		226.1	
HFrEF	4433 (60.1)	1.12 (1.06–1.18)	5720 (78.1)	1.03 (0.99–1.08)	4368 (59.7)	1.09 (1.03–1.15)	2986 (40.8)	1.19 (1.11–1.27)
	301.1	< 0.001	968.0	0.197	509.4	0.001	272.7	< 0.001

HFpEF heart failure with preserved ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *No* number; *HR* hazard ratio, *ER* event rate; *CI* confidence intervals

mortality in all the age categories regardless of HF phenotype. AF was associated with increased mortality in age < 65 and 65–80 years regardless of EF, but in age ≥ 80 years an increased mortality associated with AF was reported in HFmrEF and HFrEF but not in HFpEF.

Effect of increasing age on outcomes according to HF phenotypes in pre-specified subgroups (Fig. 3)

Figure 3 shows the association between a 1-year increase in age and all-cause mortality in the 3 EF categories separately, and for selected subgroups within each age category. There was some notable interaction between age and subgroups: in HFpEF, the impact of increasing age on mortality was slightly higher in the absence of diabetes; in HFmrEF, the impact of age was higher with lower BMI and NYHA class and in the absence of a diagnosis of hypertension; and in HFrEF, the impact of age was higher in the absence of diabetes and ischemic heart disease, presence of hypertension, and with lower NYHA class.

Discussion

There is an emerging literature on the new category HFmrEF and how it relates to HFrEF and HFpEF, but to our knowledge this is the first study to assess the role of these EF categories specifically according to age.

HFmrEF has been only recently proposed as phenotype distinct from HFpEF and HFrEF. Although at least 10–20% of HF patients have been estimated to have EF 40–50%, This HFmrEF population has been inadequately investigated; thus, the underlying pathophysiology, clinical characteristics and the course of HFmrEF still remain poorly defined [11–13]. Since HF is an age-related cardiovascular disease and aging is one of the most important contributors

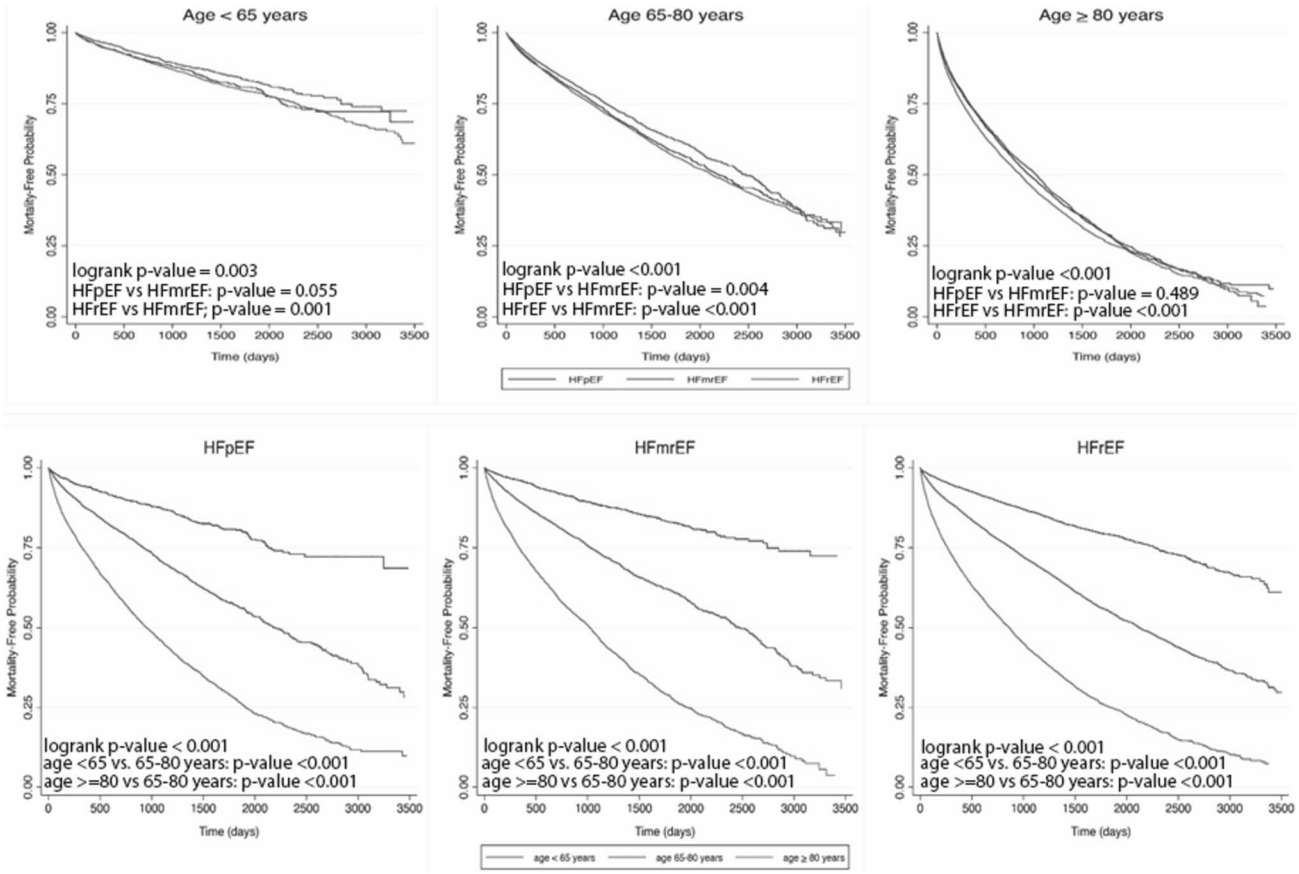

Fig. 1 Kaplan–Meier curves for all-cause mortality in HFpEF vs. HFmrEF vs. HFrEF by different age groups (upper) and in age < 65 vs. age 65–80 vs. age > 80 years by HF phenotype (lower). *p* values are illustrated in the figure

to HFpEF [14, 15], the potential impact of age on HFmrEF cannot be neglected. HFpEF is assumed to be a constellation of age, comorbidities, and frailty [16, 17]. Is this the case for HFmrEF as well? We and others have previously shown that older patients with HF, regardless of ejection fraction, differ from their younger counterparts [5–7]. Furthermore, HFrEF differs from HFpEF for clinical characteristics and outcomes, regardless of age. However, there are currently no studies evaluating whether there are age-related differences in HFmrEF vs. HFrEF and HFpEF.

In our analysis, we reported HFmrEF to represent the 22% of the SwedeHF population, which is coherent with or higher than earlier reports [11–13, 18, 19]. Previously it has been shown that patients with HFpEF were older, more likely to be women, to have hypertension, diabetes and atrial fibrillation and less likely to have history of ischemic heart disease compared with patients with HFrEF [13, 19–21]. Our study reaffirms and extends these data and provides new data about differences in HF characteristics across the ejection fraction spectrum, supporting the concept of HFmrEF as intermediate phenotype regarding clinical characteristics between HFpEF and HFrEF in different age categories for many characteristics, and more similar to HFrEF or HFpEF for some other characteristics Indeed, we reported that NYHA functional class, NT-proBNP and systolic blood pressure increased in parallel with age and that HFmrEF is more similar to HFrEF for ischemic heart disease prevalence regardless of age, whereas for hypertension it is more similar to HFpEF in age ≥ 80 years, to HFrEF in age < 65 years and intermediate in age 65–80 years. Yet, in terms of non-cardiac comorbidities HFmrEF is more similar to HFrEF than to HFpEF.

Prognostic studies comparing HFpEF vs. HFrEF have not been consistent, with some reporting better survival in patients with HFpEF, but others showing comparable survival rates [13, 20, 22–24]. Recently, we showed that patients with HFrEF had a worse prognosis compared to those with HFpEF in a single-center inpatient cohort [25]. Prognostic data on HFmrEF are limited. In a recent study enrolling patients ≥ 72 years old, all-cause mortality and HF-specific readmission rates were higher in HFrEF vs. HFmrEF vs. HFpEF [13]. In the current analysis, patients with HFrEF, compared to those with HFmrEF, had higher unadjusted all-cause mortality and

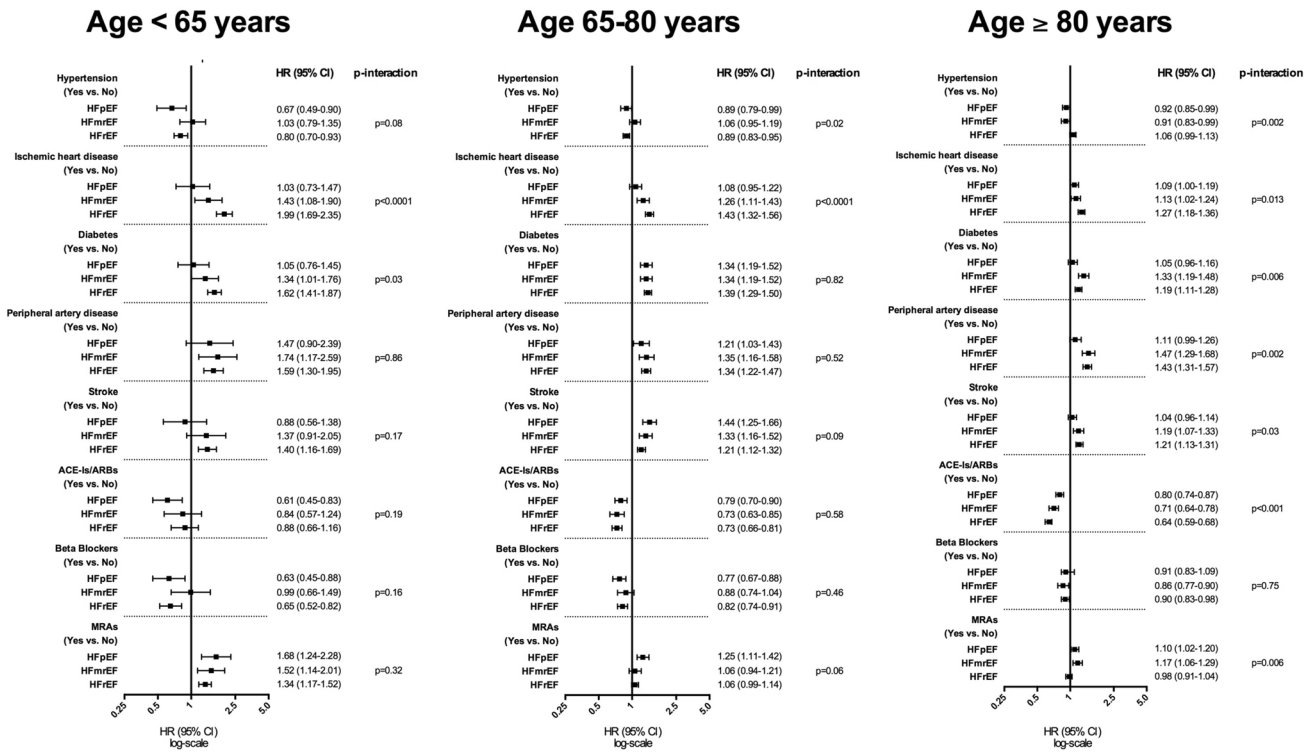

Fig. 2 Predictors of all-cause mortality in three HF phenotypes by age

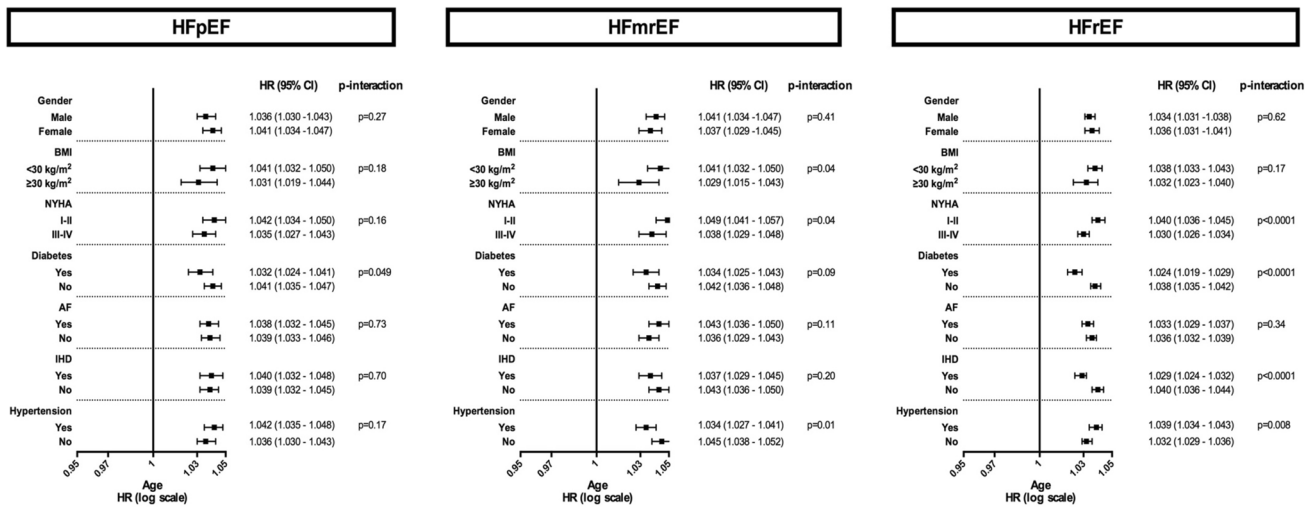

Fig. 3 Effects of 1-year increase in age on outcome in different subgroups: HFpEF, HFmrEF, HFrEF

cardiovascular and HF readmission rates across all age categories. On the other hand, HFmrEF resembled HFpEF for mortality, cardiovascular and HF hospitalization rates in ≥ 80 years patients, for mortality those with ≤ 65 years and for HF hospitalization in those with 65–80 years. Furthermore, our study extended previous finding about age as an independent risk factor for HF by showing that age is also independent risk factor for HFmrEF, like HFrEF and HFpEF. In this regard, HFmrEF and HFpEF are more alike than HFrEF not only in etiology but also in outcome especially for the higher age group.

Conclusions

In studies in the context of age, the relationships between HFpEF, HFmrEF, and HFrEF were multifactorial and complex. In general, HFmrEF appeared intermediate but with regard to certain characteristics such as ischemic heart disease more similar to HFrEF. However, HFmrEF became increasingly more similar to HFpEF with higher age, as for hypertension, atrial fibrillation, diabetes and kidney disease, and adjusted outcomes in HFmrEF were overall more similar to HFpEF and better than in HFrEF.

Limitations

This study has several limitations. First, given the observational nature of the study, unknown confounders could have influenced the results. Although Cox regression analyses were adjusted for multiple baseline differences, residual (measured and unmeasured) confounding may have influenced our findings. Second, because of the large number of patients in this study, small differences might result statistically significant but clinically irrelevant. Lastly, as a pitfall of our registry, we did not have serial EF data in our study and, thus, we cannot determine whether there were patients with HFmrEF who were previously diagnosed with HFrEF.

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Compliance with ethical standards

Conflict of interest Xiaojing Chen: none. Gianluigi Savarese: none relevant for the present work. Unrelated to the present work: Research funding from the Italian Society of Cardiology on behalf of MSD Italia-Merck Sharp & Dohme Corporation; travel grants from Heart and Lung Foundation. Ulf Dahlström: none. Lars H. Lund: research grants to author's institution: AstraZeneca, Novartis, Boston Scientiifc; speaker's honoraria: AstraZeneca, Novartis, StJude, Merck; consulting honoraria: AstraZeneca, Novartis, Sanofi, Bayer, Vifor Pharma, Relypsa, Merck, HeartWare. Micheal Fu: none relevant for the present work. Unrelated to the present work: research funding and/or honoraria from AstraZeneca, Novartis, TRIOMED, and SERVIER.

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