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Original Article

The Sub–Analysis of HFmrEF and HFrEF Group in CORE–HF Registry : When being Good is Not Enough

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Abstract

Background: As the prevalence of heart failure (HF) kept rising each year, the burden caused by it also escalated, especially in terms of economic burden. This is urging the physician to quickly tackle the problem. Although HFrEF medications were developing vastly, the outcome of HF in the real world still varies. This indicates another approach is still needed to manage HFrEF/ HFmrEF comprehensively. This paper is aimed to give an overview of HFrEF and HFmrEF epidemiological data, based on CORE-HF real-world data.

Methods: The CORE-HF is a single-center, prospective-cohort registry, which enrolls all patients with chronic HF, that were recruited consecutively from the outpatient Sebelas Maret HF Clinic. Both enrollment and follow-up have been performed since January 2018 until December 2022. Variables recorded consist of baseline characteristics, risk factors, subjective indicators, objective diagnostic assessments, therapies, and outcomes (readmission and mortality).

Results: The population of this registry was younger (58.7 ± 12.14) compared to other HF registries, with more multi-comorbidities. The number of HFrEF patients was higher than HFmrEF (77.7% vs. 22.3%), with a clinically higher mortality rate (7.2% in the 1st year and 18.2% in the next year). Although triple therapy initiation and up-titration were excellent in number, the mortality rate during the second year of follow-up was higher than in other registries. We found medication and lifestyle recommendation non-adherence to be responsible for those results.

Conclusion: Based on the CORE-HF sub-analysis of the HFrEF and HFmrEF groups, adherence to HF guidelines is the main but not the only key leading to lower mortality and rehospitalization. Our data provide satisfying low hard outcomes, but solving the non-adherence problem and optimizing the non-pharmacological approach should be done comprehensively by the HF team.

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Keywords: HFrEF, guideline adherence, big data.

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Introduction

Heart failure (HF) is a clinical syndrome due to structural and/or functional abnormality of the heart, leading to inadequate cardiac output and/or increased left ventricular filling pressure. It was classified into three categories, heart failure with preserved ejection fraction (HFpEF; LVEF ≥ 50%), mildly reduced ejection fraction (HFmrEF; 41-49%), and reduced ejection fraction (HFrEF; ≤ 40%).[1]

A study showed that between 1990 and 2017, the global number of HF cases had increased by 91.9%, while the prevalence of heart failure cases varies between 0.4% to 6%.[2,3] It is also well known that ejection fraction does influence cardiovascular outcomes, leading to more burden, including direct or direct cost.[4,5,6] Moreover, annual healthcare costs can be mounting up to €25,500 per year, with direct costs becoming the main driver.[7]

Improvement in the HFrEF pharmacological approach has recently been seen.[1,8] However, data on the optimal dose used is still unsatisfying. This sub-analysis of the CORE-HF registry will provide the epidemiological data of HFrEF and HFmrEF.

Methods

Subjects

The CORE-HF is a single-center, prospective-cohort registry, which enrolls all patients with chronic HF, that were recruited consecutively from the outpatient Sebelas Maret HF Clinic at Universitas Sebelas Maret (UNS) Hospital. Both enrollment and follow-up have been performed since January 2018. This sub-analysis will include all data up to December 2022.

The HF diagnosis and decision to include a subject were made by cardiologists of the HF clinic by using current guidelines when the subject was recruited[1,8,9,10,11] and the subjects had to meet the following inclusion criteria :

- Age 18 years or older
- Fundamentally have minimal two major criteria OR one major criterion with two minor criteria of Framingham Criteria of HF,[12] and proved by existing diastolic and/or systolic dysfunction by echocardiography to fulfill diagnostic criteria of current guidelines.

On the other hand, subjects without complete data on either vital signs, echocardiography, medications, and loss-to-follow-up were excluded.

Table 1. Initial Demography and Clinical Data of HFrEF and HFmrEF.

Characteristics	N = 610
Age (year [mean ± SD])	58.7 ± 12.14
Male (N [%])	420 (68.9)
Significant Coronary Arterial Disease (N [%])a	414 (67.9)
Impaired Glucose Tolerance/ Diabetes Mellitus (N [%])	177 (29.0)
Hypertension (N [%])	436 (71.5)
Smoking (N [%])	300 (49.2)
Dialysis (N [%])	12 (2.0)
Systolic Blood Pressure (mean ± SD)	125.8 ± 23.60
Diastolic Blood Pressure (mean ± SD)	77.1 ± 14.00
Heart Rate (mean ± SD)	78.0 ± 17.94
Atrial Fibrillation (N [%])	62 (10.2)
Bundle Branch Block (N [%])	43 (7.1)
NYHA Functional Class (N [%])	
I-II	481 (78.9)
III-IV	129 (12.1)
Heart Failure Classification (N [%])	
HFmrEF	136 (22.3)
HFrEF	474 (77.7)

[a] Confirmed using Coronary Multislice Computerized Tomography and/or Coronary Angiography

Overall, HFrEF patients had worse echocardiographic findings at the initial. As seen in Table 2, HFrEF patients clinically had larger mean LVEDD (58.1% vs. 50.0%) with more than three-quarter of them already categorized as dilated LVEDD. Moreover, mitral regurgitation occurred more in HFrEF (53.1% vs. 26.5%) and HFrEF also had a higher incidence of moderate-to-high pulmonary hypertension (PH) probability (32.2% vs. 18.6%).

Table 2. Echocardiography Profile among HFmrEF and HFrEF Group.

Echocardiography Variables	HFmrEF N 136 [22.3%]	HFrEF N 474 [77.7%]
Left Ventricular Ejection Fraction (%) [mean ± SD]	45.0 ± 2.54	25.4 ± 8.83
Dilated LVEDD (> 52 mm) (N [%])	50 (43.9)[a]	299 (76.7)[1]
LVEDD (mm) [mean ± SD]	50.0 ± 8.27[a]	58.1 ± 8.92[1]
Dilated LVESD (>36 mm) (N [%])	60 (57.1)[b]	336 (90.1)[2]
LVESD (mm) [mean ± SD]	38.0 ± 6.85[b]	50.5 ± 9.39[2]
TAPSE (mm) [mean ± SD]	28.9 ± 39.4[c]	27.1 ± 41.58[3]
Moderate-Severe Aortic Stenosis (N [%])	1 (0.8)[d]	3 (0.6)[4]
Moderate-Severe Aortic Regurgitation (N [%])	10 (7.6)[d]	47 (10.2)[4]
Moderate-Severe Mitral Stenosis (N [%])	5 (3.8)[d]	8 (1.7)[4]
Moderate-Severe Mitral Regurgitation (N [%])	35 (26.5)[d]	246 (53.1)[4]
Moderate-High Pulmonary Hypertension Probability (N [%])	24 (18.6)[e]	145 (32.2)[5]

HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction ; HFrEF = Heart Failure with Reduced Ejection Fraction ; LVEDD = Left Ventricular End-Diastolic Diameter ; LVESD = Left Ventricular End-Systolic Diameter ; TAPSE = Tricuspid Annular Plane Systolic Excursion
[a]114 Subjects ; [b]105 Subjects ; [c]127 Subjects ; [d]132 Subjects ; [e]129 Subjects
[1]390 Subjects ; [2]373 Subjects ; [3]455 Subjects ; [4]463 Subjects ; [5]451 Subjects

Variables

CORE-HF only enrolls patients with chronic HF. Variables recorded consist of baseline characteristics, risk factors, subjective indicators, objective diagnostic assessments, therapies, and hard outcomes (readmission and mortality).

Registry Protocols

The registry protocols used were as stated in the main CORE-HF publication.[13] The image acquisition and confirmation were based on the American Society of Echocardiography guidelines adopted by our HF clinic.[14,15] Cardiovascular events incidence such as rehospitalizations, myocardial infarctions, coronary intervention procedures, and mortality during this registry period, that happened outside the hospital, were confirmed directly to the patient/patient's family through phone calls.

Data Collections

The CORE-HF was led by one PI and assisted by dedicated research assistants. All data were collected, compiled, and subsequently inputted into the SPSS program of the CORE-HF central database by research assistants. Registry team meeting was done monthly to ensure and maintain the quality of the data. The Health Research Ethics Committee of the Faculty of Medicine – Universitas Sebelas Maret has approved the data collection process and registry protocol since 2018.

Primary and Secondary Outcomes

The primary outcome was all-cause mortality among sub-groups of HFrEF and HFmrEF, which were evaluated periodically on 6, 12, and 24 months after enrollment. The secondary outcomes were cardiac-related hospitalization within 12 and 24 months, non-cardiac-related hospitalization, and all epidemiological data, including demography data, risk factors, and echocardiography profile.

Statistical Analysis

Descriptive analysis was performed using the SPSS version 26 program. While continuous data were presented in mean and standard deviation (SD), categorical data were presented in percentage.

Table 3. Initial and Optimal Medications Dose Proportion among HFmrEF and HFrEF Group.

Regiment	HFmrEF		HFrEF	
	Initial[1]	12 Month (Optimal)[2]	Initial1	12 Month [%] (Optimal [%])[4]
Furosemide (N [%])	46 (33.8)	16.7% (-)	313 (66.0)	46.0% (-)
ACEi (N [%])	116 (85.3)	74.4% (93.1%)	411 (86.7)	76.0% (98.4%)
ARB (N [%])	15 (11.0)	32.8% (94.7%)	42 (8.9)	17.6% (95.5%)
ARNI (N [%])	1 (0.7)	1.3% (100%)	21 (4.4)	6.0% (93.3%)
BB [(N [%])	132 (97.1)	98.7% (92.2%)	467 (98.5)	99.6% (92.8%)
MRA (N [%])	32 (23.5)	39.7% (41.9%)	231 (48.7)	70.4% (59.7%)
Ivabradine (N [%])	6 (4.4)	7.7% (-)	22 (4.6)	1.6% (-)
Digoxin (N [%])	1 (0.7)	0.0% (-)	4 (0.8)	0.4% (-)

[1]data from 136 Subjects ; [2]data from 78 Subjects ; [3]data from 474 Subjects ; [4]data from 250 Subjects
ACEi = Angiotensin-Converting Enzyme Inhibitor ; ARB = Angiotensin Receptor Blocker ; ARNI = Angiotensin Receptor/ Neprilysin Inhibitor ; BB = Beta-Receptor Blocker ; HCT = Hydrochlorothiazide ; HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction ; HFrEF = Heart Failure with Reduced Ejection Fraction ; MRA = Mineralocorticoid Receptor Antagonist.

Results

The database was registered from January 2018 until December 2022. Among 1295 chronic HF patients, 610 of them had LVEF below 50% at initial enrollment. As shown by **Table 1**, the mean age of the patients in this sub-analysis was 58.7 years old, with most of them being men (68.9%). From history-taking, 67.9% of patients had coronary arterial disease (CAD), 29.0% had impaired glucose metabolism, 71.5% had a history of hypertension, 49.2% was former or current smoker, and 2.0% was having routine dialysis.

Sebelas Maret HF Clinic was following current ESC/HFA and ACC/AHA/HFSA guidelines on the management on the management of HF at the time of patient enrollment.[1,8,9,10,11] In both the HFmrEF and HFrEF group, during the first visit, more than 95% of patients were already given either ACEi, ARB, or ARNI, and beta-receptor blocker. Initial use of MRA was low in the HFmrEF group but finally rose after 12 months of treatment. Just like any other registries, the overall use of MRA in HFrEF was not more than 60%. Interestingly, on the 12th month, ACEi/ARB/ARNI and BB doses were already optimal in more than 92% of patients in both groups. However, the MRA dose was optimal in only 41.9% and 59.7% of patients with HFmrEF and HFrEF groups, respectively.

Furthermore, we found that the HFrEF group had not only a higher rate of cardiac-related rehospitalization during the first 12 and 24 months, but also non-cardiac-related rehospitalization compared to the HFmrEF group. Cumulative all mortality also higher in HFrEF with a drastic upsurge in the second year. Remarkably, both groups shared the same high non-adherence history.

Discussion

Based on our CORE-HF sub-analysis, all-cause cumulative mortality was still higher in the HFrEF group, although the management was strictly based on national and international guidelines. Compared to the CORE-HF main publication,[13] cumulative mortality of the HFrEF group within 12 months was eventually lower (7.2% vs. 11.5%). HF nurses, who began to be very active in knowledge and skill enhancements, were believed behind this mortality reduction. Unfortunately, 24 months mortality was still in no change (18.2% vs. 18.5%).[13] A high proportion of non-adherence patients had an impact on this number. On the other hand, the cumulative mortality of the HFmrEF group was much lower in this publication, either within 12 months

Table 4. Follow-Up and Outcome Differences among HFmrEF and HFrEF Group.

Follow-Up	HFmrEF (136)	HFrEF (474)
Non-Adherence History [N (%)]	45 (33.1)	167 (35.2)
Rehospitalization History (at least once)		
- 0-12 Month ; Cardiac-Related [N (%)]	14 (10.3)	78 (16.5)
- 13-24 Month ; Cardiac Related [N (%)]	14 (10.3)	56 (11.8)
- Non-Cardiac Related [N (%)]	18 (13.2)	76 (16.0)
All-Cause Cumulative Mortality		
- Within 6 Months [N (%)]	2 (1.5)a	16 (3.4)1
- Within 12 Months [N (%)]	4 (2.9)b	30 (7.2)2
- Within 24 Months [N (%)]	5 (3.7)c	48 (18.2)3

[a]data from 136 Subjects ; [b]data from 124 Subjects ; [c]data from 77 Subjects ; [1]data from 474 Subjects ; [2]data from 418 Subjects ; [3]data from 264 Subjects.

(1.5% vs. 8.1%) or within 24 months (2.9 vs. 10.5%) than previous publication.[13]

As for cardiac-related rehospitalization, it was higher in the HFrEF group than the HFmrEF one, although the disparity was not that prominent. A study found that one of the main reasons for these higher rates was the NT-proBNP level in HFrEF is directly related to the transmural pressure gradient and chamber diameter and inversely to the wall thickness.[6] Another study showed that higher NT-proBNP levels were associated with a higher risk of all-cause death, independent of sex, LVEF, and many other covariates.[16] The NT-proBNP level can reveal subclinical congestion and predict recurrent decompensation within 60 days, while in the TRANSITION study, NT-proBNP can predict the patient response to therapy, thus also the prognosis. [17,18]

The CORE-HF population was relatively younger than the overall Southeast Asia population that was enrolled in the ASIAN-HF Registry (58.7 years vs. 60.6 years) and the population of the ESC-HF-LT Registry (58.7 years vs. 64.89 years).[19,20] This finding could be caused by the rapid "westernization" of diets in the population that had low health literacy, leading to multimorbidity (as shown in this study, almost 70% of patients had coronary arterial disease (CAD), more than 70% had hypertension, and almost 50% had a history of smoking) in younger population, leading to "premature" HF.[21] Our registry shares the same gender predisposition with that in 9 Asian countries, Europe, and the USA, ranging from 45% up to 75%.[3] Moreover, our registry had a slightly lower AFib proportion than the ASIAN-HF registry (10.2% vs. 13.2%).[19]

The management of HFrEF, according to the latest guidelines[1,8] was the four pillars consisting of RAAS blocker, beta-receptor blocker, MRA, and sodium-glucose co-transporter-2 inhibitor (SGLT2i). A very low prescription of SGLT2i was evinced in our registry since it is not yet covered by national insurance. However, RAAS (100.0% vs. 77.3%) and BB (98.5% vs. 81.8%) initiation of the HFrEF group of the CORE-HF population was far more than in the ASIAN-HF registry. Among them, more than 92% of patients are already in optimal doses at 12 months of enrollment, as the full intervention of RAAS should still be the main treatment goal.[22] Our MRA initiation was slightly lower than those in the ASIAN-HF registry[19] (48.7% vs. 55.1%). Better initiation and up-titration of the regimen could be the reason for lower all-cause mortality in the first year of the HFrEF group compared to the ASIAN-HF registry and ESC-HF-LT (7.2% vs. 10.6% vs. 8.3%).[19,20] Unfortunately, during the second year, cumulative all-cause mortality was surging nearly 3-fold. Non-adherence was believed to be the main problem.

Conclusion

Based on the CORE-HF sub-analysis of the HFrEF and HFmrEF groups, adherence to HF guidelines is the main but not the only key leading to lower mortality and rehospitalization. Our data provide satisfying low

hard outcomes, but solving the non-adherence problem and optimizing the non-pharmacological approach should be done comprehensively by the HF team.

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