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The COmprehensive Registry and rEsearch on Heart Failure (CORE-HF): 2 Years Report from Single-Centre Indonesian Heart Failure Clinic Registry

Irnizarifka*, Habibie Arifianto

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sebelas Maret; Heart Failure Clinic of Universitas Sebelas Maret Hospital, Indonesia

ARTICLE INFO

*Corresponding author
Email:
dr.irnizarifka@staff.uns.ac.id

Address:
Sukoharjo, Jawa Tengah, Indonesia

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ABSTRACT

Introduction: Heart failure (HF) remains a rising global epidemic with a lack of population-based data, especially in Indonesia. The COmprehensive Registry and rEsearch on Heart Failure (CORE-HF) is a single-centre registry of Sebelas Maret HF Clinic as part of the ongoing national HF registry under InaHF. This paper was designed to give an overview of HF epidemiological data, thus improving HF service quality, especially in the Surakarta region.

Methods: The CORE-HF is a cohort, prospective, single-center registry, which enrolls all patients consecutively with chronic HF at the outpatient clinic of Sebelas Maret HF Clinic. Both enrollment and follow-up have been performed since January 2018 until December 2020. Variables recorded consist of baseline characteristics, risk factors, subjective indicators, objective diagnostic assessments, pharmacological therapy, and outcomes.

Results: HFpEF outnumbered other HF subgroups. HFrEF has a significant association with a higher number of rehospitalization and all-cause mortality at any time ($p<0.001$) compared to the group of HFmrEF and HFpEF. While 12 and 24-months cardiac-related rehospitalization ensued significantly more in the HFrEF group compared to other groups ($p<0.001$), rehospitalization in HFpEF was dominated by non-cardiac causes ($p=0.381$). Cumulative all-cause mortality is significantly highest in HFrEF group for any period ($p<0.001$).

Conclusion: CORE-HF showed epidemiological data of HF in the Surakarta region. From this registry, we appreciate cumulative 12- and 24-months all-cause mortality of HFrEF was clinically and statistically higher. As secondary outcomes, HFrEF subgroup also had significantly higher 12- and 24-months cardiac rehospitalizations compared to other subgroups of HF. Through HF Clinic system, we assure not only the optimal GDMT for all indicative patients, but also patient's compliance.

INTISARI

Latar Belakang: Gagal jantung (HF) masih menjadi epidemi global yang terus meningkat dimana terdapat kekurangan data berbasis populasi, terutama di Indonesia. *The COmprehensive Registry and rEsearch on Heart Failure* (CORE-HF) adalah registri pusat tunggal klinik gagal jantung Sebelas Maret sebagai bagian dari registri gagal jantung nasional yang sedang berlangsung di bawah InaHF. Jurnal ini dirancang untuk memberikan gambaran tentang data epidemiologi gagal jantung, sehingga dapat meningkatkan kualitas pelayanan gagal jantung khususnya di wilayah Surakarta.

Metode: Metode penelitian CORE-HF menggunakan analisis kohort, prospektif, registri tunggal dan terpusat yang memasukkan semua pasien dengan gagal jantung kronis. Subyek direkrut secara berurutan dari poliklinik rawat jalan klinik gagal jantung RS Akademik UNS. Pendaftaran dan tindak lanjut dilakukan sejak Januari 2018 hingga saat ini. Variabel yang dicatat terdiri dari karakteristik dasar, faktor risiko, indikator subjektif, penilaian diagnostik objektif, terapi farmakologis, dan indikator hasil.

Hasil: Jumlah HFpEF melebihi subgrup HF lainnya. HFrEF memiliki hubungan yang signifikan terhadap angka rehospitalisasi dan mortalitas yang lebih tinggi (p<0,001). Rawat inap ulang terkait jantung 12 dan 24 bulan lebih banyak terjadi pada kelompok HFrEF dibandingkan kelompok lain (p<0,001), sedangkan rehospitalisasi pada HFpEF didominasi oleh penyebab non-jantung (p=0,381). Kumulatif semua penyebab kematian secara signifikan tertinggi terdapat pada kelompok HFrEF untuk setiap periode waktu (p<0,001).

Kesimpulan: CORE-HF menunjukkan data epidemiologi HF di wilayah Surakarta. Dari data ini, HFrEF memiliki kematian kumulatif 12 dan 24 bulan dari semua penyebab yang secara klinis dan statistik lebih tinggi. Sebagai hasil sekunder, subkelompok HFrEF juga memiliki rawat inap ulang jantung 12 dan 24 bulan lebih tinggi secara signifikan dibandingkan dengan subkelompok gagal jantung lainnya. Melalui sistim Klinik HF, kami tidak hanya menggunakan GDMT yang optimal untuk semua pasien yang terindikasi, namun juga memastikan kepatuhan pasien.

Introduction

Heart failure (HF) remains a rising global epidemic with an estimated prevalence of >37.7 million individuals globally.[1] Many developing nations are in the midst of an epidemiological transition as the disease burden rapidly shifts from infections to chronic degenerative diseases observed in the older population. Although a diagnosis of HF portends increased mortality and loss of quality-adjusted life years, advances in evidence-based HF therapies and the quality of care in the modern era have substantially improved outcomes for patients.[1, 2]

The magnitude of the problem of HF cannot be assessed with precision since reliable, population-based estimates of its prevalence, incidence, and prognosis are lacking.[3] Epidemiological data that could help to improve management approaches to address this burden in Asia-Pacific regions are limited, but suggest patients with HF in the Asia-Pacific are younger and have more severe signs and symptoms of HF than those of Western countries. HF is associated with a significant socioeconomic burden in this region, representing an important cause of hospital admissions and readmissions, loss of work and productivity, and death.[4, 5] The data from a multi-center study across Asia clearly shows that HF is a significant healthcare problem across the region. An accurate account of HF in this region is critical and has the potential to influence clinical management, which may improve patient outcomes over the short and long term.[4, 6, 7]

The Asian-HF study reported >5% prevalence of HF in Indonesia. Four countries in this study spent more than 20% of their healthcare budgets on pharmaceuticals, and it includes Indonesia, with an average cost of HF hospitalization reaching 813 US$ (2.8% of GDP). Moreover, despite HF guidelines available in this country, beta-blockers use still became the lowest among Asia (32%). Therefore, it was no surprise that mortality rates at 30 days are highest in Indonesia (17%). Unfortunately, for around 256 million people in Indonesia, this data is only represented by one single hospital centre, which may not be generalized to the whole country.[6] Indeed, more data is still demanded.

COmprehensive Registry and rEsearch on Heart Failure (CORE-HF) is a registry of chronic HF which was first initiated in 2018 as a part of the ongoing national HF registry publication under the Indonesian Heart Failure Working Group (InaHF), but with a longer duration of outcome evaluation. This registry took place in Sebelas Maret HF Clinic (Surakarta, Indonesia), covering the Surakarta region with the surrounding hinterland, covering a 5.677 km^2 area, more than 6 million population, and becomes the only HF Clinic in Central Java Province. This paper was designed to give an overview of HF epidemiological data and its 2-years clinical outcomes.

Methods

Subjects

The CORE-HF is a cohort, prospective, single-center registry which enrolls all patients with chronic HF. Subjects were recruited consecutively from the outpatient clinic of Sebelas Maret HF Clinic at UNS Hospital. Both enrollment and follow-up have been performed since January 2018 until December 2020.

The HF diagnosis and decision to include a subject were made by cardiologists of HF Clinic by using the current 2016 European Society of Cardiology (ESC) HF Guideline[8] and also the 2015 InaHF HF National Guideline[9] at that time, in which terminology of HFrEF, HFmrEF, and HFpEF are exist. According to those guidelines, those sub-groups

were defined consecutively as HF with EF < 40%, EF 40-49%, and EF > 50%.

Subjects enrolled have to meet the following inclusion criteria:

- Age 18 years or older
- Fundamentally have minimal two major criteria or one major with two minor criteria of Framingham Criteria on HF[10], and proved by existing diastolic and/or systolic dysfunction by echocardiography according to 2016 ESC HF Guideline.[8]

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

Variables

Until now, CORE-HF only contains patients with chronic HF. Variables recorded consist of baseline characteristics, risk factors, subjective indicators, objective diagnostic assessments, therapies, and outcomes (readmission and mortality) (Table 1). In 2019, approximately one-half of this data was sent to be merged as Indonesian HF registry.

Registry Protocols

Data were registered for all patients with HF admitted to an outpatient clinic. The registration data process has been developed to ensure data accuracy and standardize patient procedures taken from all cardiologists. The Principal Investigator (PI) of CORE-HF is obliged to regularly ensure that the indicators reflect the quality of data and that the collection of data is simple and feasible in routine clinical settings. Systematic literature reviews were also performed regularly together with HF Clinic Board to ensure the updated GDMT, with the latest review, was conducted in mid-2018.

Data on baseline characteristics, risk factors, subjective indicators, and therapies were obtained using the hospital medical record system and history taking process. While ECG and laboratory examinations were done through general hospital services, cardiologists did echocardiography measurement trans-thoracically (TTE) using Philips Epiq7c (Philips N.V, The Netherland). The image acquisition and confirmation were based on the American Society of Echocardiography (ASE) guidelines[11, 12] that prevailed in our hospital practice. Moreover, any CT angiography done in our HF Clinic was using 64-sliced Philips Ingenuity CT MRC 880/ 989000086371 (Philips N.V, The Netherland).[12] Image validation and confirmation were done by a cardiovascular imaging consultant who was dedicated to this registry. Cardiovascular events incidence such as rehospitalizations, myocardial infarctions, coronary intervention procedures, and mortality during this registry period that happened outside our hospital were confirmed directly to the patient/patient's family through phone calls.

Data Collection

The CORE-HF is led by one PI and assisted by cardiologists and research assistants who are dedicated to the registry. 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 had approved those data collection process and registry protocol.

Primary and Secondary Outcomes

The primary outcome was all-cause mortality among sub-group of HF, which were evaluated periodically on 6, 12, and 24 months after enrollment. The secondary outcomes were rehospitalization within 12 and 24 months, non-cardiac cause rehospitalization, 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) or median and interquartile range (IQR) depending on normality data distribution after tested with the Shapiro Wilk or Kolmogorov Smirnov test, categorical data were presented in percentage. Association between groups was analyzed using the 3x2 Chi-square test.

Table 1. Depiction of Variables in CORE-HF

Main Group	Group of Variables	Operational Definition
Baseline characteristics	Gender	Male/female
	Age	Age at initial enrollment
	Date enrollment	Date at initial enrollment
Risk factors	History of HT; history of smoker	Yes/no; Yes, if had ever diagnosed HT; if had ever smoke
	History of pre-DM/DM	Graded from no history, until had ever diagnosed with impaired fasting glucose or impaired glucose tolerance or DM
	History of CAD	Yes/no; proven significant lesion by CT angiography or coronary angiography
	History of revascularization	Yes/No; Yes, if had ever been treated with PCI/CABG
Subjective indicators	NYHA functional class	Functional class at initial enrollment and at follow up time; graded from I-IV
	Compliance	Good/bad; Good, if never stop any of HF medications independently
Objective assessments	Basic hemodynamic	Blood pressure and heart rate measurement at initial enrollment and follow-up time
	ECG	Heart rhythm and presence of bundle branch block at initial enrollment
	Laboratory	All standard laboratory tests at initial enrollment and follow-up time
	Echocardiography Measurement	It consists of LVEDD, LVESD, EF, TAPSE, significant (moderate to severe) mitral or aortic valve problem (yes/no), diastolic function
Pharmacological Therapies	Diuretic, ACEi, ARB, ARNI, beta blocker, MRA, ivabradine, digoxin, CCB, nitrates	Usage (yes/no), type and dose of each therapy at initial enrollment and follow-up time
	ACEi intolerant	Yes/no and intolerant type
Outcomes	Readmission	Cardiac-related rehospitalization (yes/no) and count within several follow-up time
	Mortality	All-cause mortality within several follow-up time

HT = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; NYHA = New York heart association; HF = heart failure; ECG = electrocardiography; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; EF = ejection fraction; TAPSE = tricuspid annular plane systolic excursion; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; CCB = calcium channel blocker.

Results

The database was registered from January 2018 until April 2020, yielded 857 patients. Of them all, 625 patients still have regular follow up at Sebelas Maret Heart Failure Clinic of UNS Academic Hospital, and 28 patients were excluded due to loss to follow up. The complete number of patient chart is shown in **Figure 1**. As can be shown in **Table 1**, the mean age of patients at first HF clinic admission was 59.8 years old. Men have outnumbered women in this database, with a proportion of 60.8% of all patients. From history-taking, 26.1% of patients already had diabetes mellitus (DM), 6.4% had pre-DM, 75.3% had any stages of hypertension (HT), and 46.2% had ever smoked. Almost half of the patients came to Sebelas Maret HF Clinic with NYHA functional class II. In line with other HF registries, the majority of initial diagnosis were proved to be HFpEF, comprising about 53.1%.

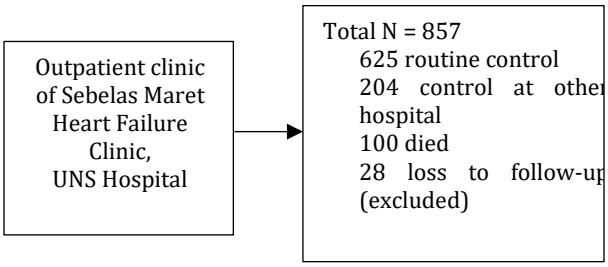

Figure 1. Flowchart of Patient Enrollment of CORE-HF

Table 2. Initial Demography and Clinical Data of CORE-HF Database

Characteristics (at first enrollment)	Total (N = 829) x
Age (year) [mean ± SD]	59.87 ± 11.65
Gender [n(%)]	
Male	504 (60.8)
History [n(%)]	
Diabetes	216 (26.1)
Pre-diabetes	53 (6.4)
Hypertension	624 (75.3)
Hyper/hypothyroid*	47(21.86)/22(10.23)
Smoker	383 (46.2)
Dialysis	16 (1.9)
Chemotherapy	3 (0.4)
Ischemic heart disease	442 (53.3)
Valve surgery	10 (1.2)
Revascularization (PCI or CABG)	67 (8.1)
Blood pressure (mmHg) [mean ± SD]	
Systolic	127.75 ± 20.47
Diastolic	79.25 ± 12.01
Heart rate (bpm) [mean ± SD]	75.83 ± 16.69
Atrial fibrillation [n(%)]	88 (10.6)
NYHA functional class [n(%)]	
I	304 (36.7)
II	413 (49.8)
III	82 (9.9)
IV	15 (1.8)
Heart failure classification [n(%)]+	
HFrEF	287 (34.6)
HFmrEF	86 (10.4)
HFpEF	440 (53.1)
Body Weight	63.41 ± 14.45

NYHA = New York heart association; HFrEF = heart failure wit reduced ejection fraction; HFmrEF = heart failure with mid-rang ejection fraction; HFpEF = heart failure with preserved ejectio fraction.
x) 28 of total 857 subjects were excluded due to loss to follow up
*) only assessed in 26% of total samples.
+)16 subjects had incomplete echocardiography result.

Generally, the HFrEF group had worsened objective echocardiography results, among others, when first diagnosed in this registry. Left ventricle (LV) geometry alteration was more evidenced in HFrEF group compared to other groups. In this group, dilated LV observed in 59.9% of all patients, while it only happened in 37.2% and 12% of HFmrEF and HFpEF consecutively. Their mean LVEDD value was 58.87 ± 8.59 mm (maximum value of 82 mm). In line with lower LVEF, the HFrEF group also had the lowest right ventricle (RV) function, among others (mean TAPSE 1.71 ± 0.52 cm). Moreover, moderate-severe mitral regurgitation (known as significant mitral regurgitation) occurred more in patients with HFrEF (54.7%), and this group of patients had the highest proportion of restrictive diastolic dysfunction. Complete initial echocardiography findings can be seen in **Table 2**.

Sebelas Maret HF Clinic follows current ESC/HFA and ACC/AHA/HFSA guidelines on the management of HF at that time.[8, 13] The initial medications given shown in **Table 3** above. Generally, all spectrums of HF had already given ACEi/ARB and beta-blockers in more than 90% of patients. Among ACEi users, intolerant accounted for 27.7%; 98.3% had dry cough while the rest experienced angioedema. While HFrEF prescribed more loop diuretic and MRA for symptom reliever, HFpEF used more CCB and nitrates to control the blood pressure. Moreover, CORE-HF database also showed extremely less prescription of digoxin in all groups.

Around one-half of patients were diagnosed with ischemic cardiomyopathy (ICM), which was established either by CT or invasive coronary angiography. For those patients, revascularization (CABG/PCI) done in those who still had symptoms of angina despite optimal medications. On other hand, half of patients had a history of non-compliance with medications at any time. This issue was related to various reasons, such as educational background, economic status, geographical difficulty, change-over of insurance policy, and others.

Furthermore, **Table 4** below showed that HFrEF has a significant association towards a higher number of rehospitalization and all-cause mortality at any time. Cumulative all-cause mortality is significantly higher in HFrEF group for any period of time, compared to other groups. Likewise, 12 and 24-months cardiac rehospitalization also ascended significantly in HFrEF group, whereas rehospitalization in HFpEF dominated by non-cardiac cause.

Table 3. Echocardiography Profile among Sub-groups of Heart Failure

Echocardiography Variables [n(%)]	HFrEF [287(35.3)]	HFmrEF [86(10.5)]	HFpEF [440(54.1)]
LVEDD (mm) [mean ± SD]	58.87 ± 8.59	51.50 ± 8.43	45.14 ± 7.13
LVEDD >52 mm [n(%)]	172 (59.9)	32 (37.2)	53 (12)
LVESD (mm) [mean ± SD]	50.85 ± 9.47	39.19 ± 7.36	28.44 ± 6.10
LVESD >36 mm [n(%)]	187 (65.2)	40 (46.5)	32 (7.3)
EF (%) [mean ± SD]	24.66 ± 8.35	44.23 ± 2.69	66.38 ± 8.37
TAPSE (cm) [mean ± SD]	1.71 ± 0.52	2.03 ± 0.43	2.24 ± 0.46
Significant mitral regurgitation [n(%)]	157 (54.7)	26 (30.2)	79 (18)
Significant mitral stenosis [n(%)]	8 (2.8)	4 (4.7)	11 (2.5)
Significant aortic regurgitation [n(%)]	25 (8.7)	8 (9.3)	28 (6.4)
Significant aortic stenosis [n(%)]	3 (1)	1 (1.2)	5 (1.1)
E/A > 2 [n(%)]	75 (26.1)	7 (8.1)	16 (3.6)
Pulmonary hypertension probable [n(%)]	109 (38)	25 (29.1)	137 (31.1)

HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserve ejection fraction; LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; EF = ejection fraction; TAPSE tricuspid annular plane systolic excursion.

Table 4. Initial Medications among Sub-groups of Heart Failure

Initial Medications	HFrEF	HFmrEF	HFpEF
Loop diuretic [n(%)]	198 (69)	35 (40.7)	93 (21.1)
ACE inhibitor [n(%)]	245 (85.4)	75 (87.2)	345 (78.4)
ARB [n(%)]	23 (8)	7 (8.1)	68 (15.5)
Sacubitril-Valsartan [n(%) of all ARB]	13 (4.5)	0	0
Beta Blocker [n(%)]	282 (98.3)	82 (95.3)	398 (90.5)
MRA (Spironolactone only) [n(%)]	106 (36.9)	13 (15.1)	39 (8.9)
Ivabradine [n(%)]	5 (1.7)	4 (4.7)	7 (1.6)
Digoxin [n(%)]	4 (1.4)	1 (1.2)	2 (.5)
All types of CCBs [n(%)]	30 (10.5)	14 (16.3)	119 (27)
All types of nitrates [n(%)]	19 (5.2)	6 (7)	36 (8.2)

HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoids-receptor antagonist; CCB = calcium channel blocker.

Table 5. Diagnosis, Management, and Outcome Differences among groups of Heart Failure

	HFrEF[a]	**HFmREF**[b]	**HFpEF**[c]	**p-Value (Cramer's Vd)**
Etiology of ICM [n(%)]	207 (72.1)	65 (75.6)	162 (36.8)	<0.0001 (0.361)
Revascularization [n(%)]	25 (8.7)	13 (15.1)	24 (5.5)	0.06 (0.112)
Cardiac Rehospitalization within 12 months [n(%)]	95 (33.1)	21 (24.4)	86 (19.5)	<0.0001 (0.152)
Cardiac Rehospitalization within 24 months [n(%)]	29 (10.1)	5 (5.8)	15 (3.4)	< 0.0001 (0.261)
Non-Cardiac Cause Rehospitalization within 24 months [n(%)]	66 (23)	15 (17.4)	102 (23.2)	0.381 (0.048)
All-cause mortality within 6 months [n(%)]	18 (6.3)	5 (5.8)	9 (2)	0.011 (0.106)
All-cause mortality within 12 months [n(%)]	15 (5.2)	2 (2.32)	16 (3.63)	0.393 (0.048)
All-cause mortality within 24 months [n(%)]	20 (6.97)	2 (2.32)	12 (2.72)	<0.0001 (0.143)
Cumulative all-cause mortality within 12 months [n(%)]	33 (11.5)	7 (8.1)	25 (5.7)	0.018 (0.099)
Cumulative all-cause mortality within 24 months [n(%)]	53 (18.5)	9 (10.5)	37 (8.4)	<0.0001 (0.143)

[a] data from 285 subjects; [b] data from 86 subjects; [c] data from 440 subjects; [d] weak association if less than 0.3. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; ICM = ischemic cardiomyopathy.

Discussion

The CORE-HF is the first prospective registry of HF in Surakarta and Central Java, that aims to give an overview of HF burden. As primary outcome of this registry, 12 and 24 months cumulative all-cause mortality of HFrEF was clinically and statistically higher compared to other HF subgroups, even though international and national guidelines has been strictly used. Moreover, as secondary outcomes, HFrEF subgroup also had significantly higher 12 and 24 months cardiac rehospitalizations compared to other subgroups of HF. As we know from majority of epidemiological data, HFrEF has higher mortality compared than other subgroups of HF. Severe symptoms, lower systolic blood pressure, higher degree of neurohormones activation, larger LV, worse RV function, and greater diastolic disfunction were known to be the cause.[14]

General comparison between CORE-HF with other HF registries involving Indonesia showed in **Table 6**. Though mean age of firstly diagnosed HF in this registry (59.87 years-old) is equal with other Asia-based HF registries, it is younger than that in Western developed countries. Differences on socioeconomic status, education level, smoking habit and life-style are the main factor behind this.[10–12]

Table 6. Comparation of CORE-HF with other heart failure registries involving Indonesia

Registry	Participating Center	Total sample	Study focus	Study design	Study period	Mean age
CORE-HF	Universitas Sebelas Maret Academic Hospital	829	Chronic HF	Prospective	2018-2020	59.87
Yogyakarta Registry13	Dr. Sardjito General Hospital	853	Chronic HF	Prospective	2016-2018	59
ADHERE (Indonesia sub-study)14	5 different hospital in Indonesia	1687	Acute decompensated heart failure	Prospective	2006	60
ASIAN-HF15	44 hospital in 11 Asian countries	6480	Morbidity and mortality in HF	Prospective	2012-2016	61.6

Several epidemiological results are as follow. Since CORE-HF database was taken on the outpatient setting, plethora of patients have NYHA functional class I and II. Men still become predominant in HF; in most Asia countries, male predisposition varies from 45% to 75%.[6, 15] Our data show consistency with the rest of the world, which has significant proportion of male patients in the HF cohort registry. Atrial fibrillation incidence was 10.6%, which way smaller than those in Asia countries that range from 16-39% (HF across Asia).[6]

In line with high prevalence of HT in Indonesia (23% of total population; predominantly 45 years old and above),[16] HT also prominent risk factor in this registry, comprises about 75.3% of total subjects. It explained the hazard ratio for HF development of hypertensive subjects in Framingham Heart Study was about 2-fold in men and 3-fold in women.[17] Smoking behavior also consistent as one of noticeable risk factor of cardiovascular disease; becoming second most frequent risk factor in CORE-HF. According to the ASEAN Tobacco Control Atlas 2013 and Indonesian Ministry of Health Tobacco Control Support Center, Indonesia has the second-largest population of smokers in the world, thus have a similar finding in our cohort.[18]

The key to manage HFrEF was the adequacy of the optimal combination dose of Renin Angiotensin Aldosterone System (RAAS) blockers, beta-blockers (BB), and MRA, parallel with volume status optimization. The utility of RAAS blockers (consist of ACE inhibitors, ARB, and the novel sacubitril-valsartan) in this registry is almost 100%. Roughly the same numbers, HFmrEF and HFpEF group have 95.3% and 93.9% use of RAAS blockers. Those results were in contrast to the usage of RAAS blockers in most Asia countries, which still below 90% (HF Across Asia).[6] Despite BB prescription in HF Across Asia range from 32%-87%,[6] BB use in HFrEF was also noticeable in this registry (98.3%). This number was also higher than that in northern Europe (82,8%), middle east (91,6%), eastern Europe (90,8%), southern Europe (84,8), and north African country (48,3%), and western Europe (92,2%).[19]

Above data has disparity with what written by American Heart Association (AHA) Guidelines initiative program, in term of RAAS blockers (ACE inhibitor) and BB usage as secondary prevention.[20] In that particular publication, ACE inhibitors were only used in 59.3% study population and BB used in 49.5%. The outcome was significantly different, in which the AHA Guidelines initiative had 40.5% overall annual death,[20] while 8.4-18.5% cumulative annual death occurred in our 2 years registry.

In our experience, adherence to HF guidelines is the key to create lower mortality and rehospitalization rate of HF, especially HFrEF. ACE inhibitors should be prioritized since they had broader pharmacokinetic coverage than ARB, with only less than one-third incidence of any forms of intolerance in this registry, mostly dry cough. Dry cough incidence due to ACE inhibitor intolerance previously noted only in one study, range from 5-20% of all patients.[21, 22]

Limitations

The CORE-HF database is a single hospital-based registry which enrolled subjects that was present at the outpatient HF clinic. Therefore, neither stage A nor B of HF subject number is sufficient. These findings are believed due to the habit that only people with symptoms came to the hospital. Though they cannot represent the entire HF population in Surakarta yet, but several primary care and hospitals started making referrals of patients with refractory HF to our HF Clinic. The national health insurance managed to change the referral system in 2019. Thus, a lot of our samples had no choice other than visiting other medical facilities to maintain their medications. This issue challenged us in terms of data completion. On the other hand, we had to manage the budget from the national health insurance in order to fulfill all procedures and medications needed. This is because currently, we did not receive any funding to ensure our objectivity of the database.

Conclusions

CORE-HF depicted epidemiological data of HF in Surakarta region. From this registry, despite we appreciate that HFpEF outnumbered other HF subgroups, but cumulative 12- and 24-months all-cause mortality of HFrEF was clinically and statistically higher. As secondary outcomes, HFrEF subgroup also had significantly higher 12- and 24-months cardiac rehospitalizations compared to other subgroups of HF. Through HF Clinic system, we assure not only the optimal GDMT for all indicative patients, but also patient's compliance.

Author Contributions

Irnizarifka MD FIHA FAPSC FAsCC, as Principal Investigator of CORE-HF year 2018-2022, also together with Habibie Arifianto MD MKes FIHA run the HF Clinic UNS Hospital with, under Siti Elkana Nauli MD FIHA FHFA as President of Indonesian working group on Heart Failure and Cardiometabolic (InaHF). Irnizarifka and Habibie Arifianto collected, compiled, and analyzed the CORE-HF database. All authors concepted and wrote the manuscript.

Author Contributions

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Conflict of Interest Statement

Authors declare no conflict of interest for this article, also have read and approved the final manuscript. This manuscript is already approved by InaHF before published.

Ethical Clearance and Approval

The Health Research Ethics Committee of the Faculty of Medicine Universitas Sebelas Maret approved this study.

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