Heart Failure in Different Asian Populations

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13.1 Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity all over the world. The transition from communicable to non-communicable diseases as the main contributor to overall mortality occurred in the developing countries in the mid-1990s. Heart failure (HF) is emerging as one of the main contributors to CVD burden in both the developed and the developing world [1, 2].

HF is a clinical syndrome where symptoms and signs are due to structural and/or functional cardiac abnormalities that result in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise [1]. The overall prevalence of HF is 1–2%, but prevalence increases sharply with advancing age [2]. HF is categorised based on the left ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (HFrEF; LVEF <40%), HF with mildly reduced ejection fraction (HFmrEF; LVEF 40–49%) and HF with preserved ejection fraction (HFpEF; LVEF >50%) [3].

HF is a disease with high morbidity and mortality. Management of HF is resource intensive and the vast majority of patients with HF require lifelong therapy. HF is also an important contributor to disability-adjusted life years (DALYs) [4]. Outcomes for patients with HF are often poor, with 1- and 5-year mortality rates of 30% and 50–60% respectively, which is worse than some common malignancies such as breast and colon cancer [5].

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Although there is a substantial body of data on HF in Western populations, there is comparatively less data from the developing world, especially Asian countries. Given that the Asian region is home to 60% of the world's population, it is likely to have a huge burden of HF. In addition, the Asian region is unique because of differences in ethnicity and the size and distribution of the population.

13.2 Hypertensive Heart Failure

Patients with persistent and uncontrolled hypertension initially develop left ventricular (LV) hypertrophy which progresses to HF. Significant LV hypertrophy results in diastolic dysfunction and patients initially develop HFpEF. Later, the LV starts dilating and systolic dysfunction is predominant. Degrees of heart involvement in patients with hypertension are defined in Fig. 13.1, while the different forms of cardiac involvement and progression from hypertension to HF and death are summarised in Fig. 13.2.

13.3 HF Registries from Asia

Even though there is less data on the incidence and prevalence of HF from the Asian region, data from various registries in the region is starting to emerge. This provides the scientific community with reasonably good data about HF-related morbidity and mortality, and HF management practices in the region (Table 13.1).

The Trivandrum Heart Failure Registry (THFR) was setup in 2013 and enrolled 1205 patients [8]. The most common forms of heart disease were coronary artery disease and rheumatic heart disease. Major comorbidities included hypertension (58%), diabetes mellitus (55%), chronic kidney disease (CKD; 18%) and chronic obstructive pulmonary disease (COPD; 15.4%). HFpEF was found in 19.6% of patients, HFmrEF in 18% and HFrEF in 62.4%. Patients with HFpEF were more likely to be female, have a lower prevalence of CAD, tobacco use and diabetes, a higher prevalence of atrial tachyarrhythmia, and were less likely to be receiving treatment with beta-blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors.

Only 25% of patients with LV systolic dysfunction were being treated with guideline-directed medical treatment (GDMT; a combination of beta-blockers and RAAS inhibitors). The rate of hospital readmissions at 1 year was 30%, with no gender bias. Major predictors of hospital readmission were GDMT and New York Heart Association (NYHA) class IV symptoms. The median duration of hospital stay was 6 days, and rates of in-hospital and 90-day mortality were 8.5% and 18%, respectively. Mortality rates at 1, 3 and 5 years were 30.8%, 44.8% and 58.8%, respectively. Important predictors of mortality were lack of GDMT, increasing age, increasing serum creatinine, and NYHA functional class IV HF at presentation [9].

The Medanta Heart Failure Registry (MHFR) is a single centre registry from Delhi. Over the period 2014–2017 it enrolled 5590 patients with HFrEF (mean age

Heart disease resulting from hypertension can be divided into four degrees of severity

- Degree I : Isolated LV diastolic dysfunction with no LVH
- Degree II : LV diastolic dysfunction with concentric LVH
- Degree III : Clinical heart failure (dyspnea and pulmonary edema with preserved ejection fraction)
- Degree IV : Dilated cardiomyopathy with heart failure and reduced ejection fraction

Fig. 13.1 Stages of hypertensive heart disease. *LV* left ventricular, *LVH* left ventricular hypertrophy

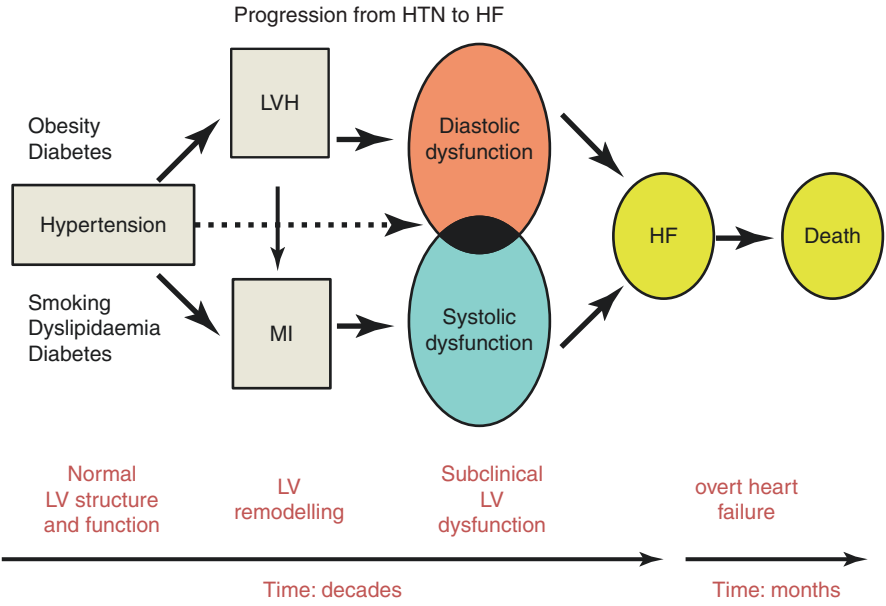

Fig. 13.2 Evolution of hypertensive heart disease in patients with hypertension and other risk factors. *HF* heart failure, *LV* left ventricular, *MI* myocardial infarction

59.1 ± 11.8 years, M:F ratio, 4.9:1). CAD was the most common aetiology for HF (in 78% of patients), while 7.8% of patients had underlying RHD. Diabetes and hypertension were present in 49% of patients. The mean estimated glomerular filtration rate (eGFR) was 76.1 ± 27.7 ml/min/m^2. Treatments included beta-blockers, RAAS inhibitors and diuretics in 81.8%, 65.8% and 79.4% of patients, respectively. Rates of implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) device implantation were 4.3% each. The 1-year mortality rate was 17.6%, and major predictors of mortality were age >50 years, higher NYHA class, LVEF <30%, renal dysfunction, anaemia and lack of GDMT [10].

Table 13.1 Baseline characteristics of patients enrolled in representative HF registries

Name [Ref]	Region/country	*N*	Enrolment, years	Mean age (SD), years	Female, %	Aetiology	Mortality
Heart failure registries from Asia							
Kerala HF Registry [6]	India	7512	2016–2018	64 (13)	36%	CAD: 65% HFrEF: 67.5% HFmrEF: 17.8%	In-hospital: 6.1% 90-day: 10.3%
India National HF Registry [7]	India	7500	2019–2020	60 (14)	31%	HFrEF: 61% HFpEF: 14.9% CAD: 65%	In-hospital: 6.1%
Trivandrum HF Registry [8, 9]	India	1205	2013	61 (14)	31%	CAD: 71% RHD: 8% HFrEF: 62%	1-year: 30.8 3-year: 40.8 5-year: 44.8
Medanta HF registry [10]	India	5590	2014–2017	59 (12)	17%	CAD: 78% RHD: 4.8%	1-year: 17.6%
ASIAN-HF [11]	North, South-East, and South Asia	6480	2012–2016	61 (13)	27%	CAD: 73% RHD: 6.3% HFpEF:13% HFrEF: 67%	1-year: 9.6%
CHART-1 [12]	Japan	1278	2001–2004	69 (13)	33%	HFrEF: 55% CAD: 25%	1-year: 7% 2-year: 16% 3-year: 22%
CHART-2 [13]	Japan	4375	2006–2010	69 (12)	32%	CAD: 53% HFrEF: 20%	
CHINA-HF [14]	China	13,687	2015	65 (15)	41%	CAD: 49.6% HFrEF: 39.6%	In-hospital: 4.1%
NCCQI-HF [15]	China	34,938	2020	67 (14)	39%		

KOR-AHF [16]	South Korea	5625	2011–2014	69 (15)	47%	CAD: 43% HFrEF: 60.5% Valvular: 14.3%	In-hospital: 7.6% 1-year 8.4%
Gulf CARE [17]	Middle East	5005	2012	59 (15)	37%	CAD: 53% HFrEF: 69%	In-hospital: 6.3% 1-year: 20.1%
Heart failure registries from the West							
ADHERE [18]	USA	105,388		72 (14)	43	HFrEF: 47% CAD: 57%	In-hospital: 4.3%
OPTIMIZE [19] HF	USA	41,267		73 (14)	38	HFrEF: 48.8% CAD: 22.9%	
EHFS II [20]	Europe	3580		70 (12)	43	HFrEF: 65.7% CAD: 53.6%	In-hospital: 6.7%

CAD coronary artery disease, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *RHD* rheumatic heart disease

The Kerala Acute Heart Failure Registry (KAHFR) enrolled 7512 patients with acute HF from 2016 to 2018. Mean age was 64.3 ± 12.9 years with a M:F ratio of 1.7:1. More than two-thirds of patients (67.5%) had HFrEF, while 17.8% had HFmrEF and 14.9% had HFmrEF and HFpEF. The aetiology of HF was CAD accounted in 65% of patients. Rates of GDMT were low, being 27.9% in patients with HFrEF and 20.2% in those with HFmrEF. In-hospital mortality was 6.1%, and 90-day mortality was 10.3%. Mortality rates per 100 person-days were 14.1, 10.7 and 10.9 in patients with HFrEF, HFmrEF or HFpEF, respectively. Key predictors of mortality were lack of GDMT, older age, CKD, stroke, CAD, atrial fibrillation (AF) and anaemia [6].

The National Heart Failure Registry was established in 2019 and has enrolled more than 10,500 patients from 51 centres all over India. Interim data from 7500 patients are available (Table 13.1). Mean age at enrolment was 60.3 ± 13.5 years, with a M:F ratio of 2.2:1. HFrEF was the most common type of HF (61% of patients), followed by HFmrEF (23%) and HFpEF (13%). The underlying HF aetiology was CAD in 73% and RHD in 6.3%. Major comorbidities included hypertension (49%), diabetes mellitus (43%), CKD (9%) and atrial arrhythmia (10%). Only 43% of patients were receiving GDMT. The in-hospital mortality rate was 6.1%. Patients with HFrEF had a higher prevalence of CAD and diabetes, with lower blood pressure and higher mortality. Patients with HFpEF had a higher prevalence of atrial arrhythmias and COPD. Use of GDMT was higher in patients with HFrEF [7].

The ASIAN HF registry recruited 6480 patients from three Asian regions from 2012 to 2015 [11]. South-East Asia included Thailand, Malaysia, Philippines, Indonesia and Singapore, North-East Asia included South Korea, Japan, Taiwan, Hong Kong and China, while South Asia included India. Mean age was 61.6 ± 13.3 years, and M:F ratio was 2.7:1. Ischaemic aetiology accounted for 43.8% of cases. HFrEF was common (81% of patients). Major comorbidities included hypertension (55%), diabetes mellitus (41%), CKD (35.6%) and atrial arrhythmias (12.8%). ICD use was seen in 4.3% of patients, and biventricular pacing in 1.4%. Drug therapy included diuretics in 76.5% of patients, beta-blockers in 72.2%, RAAS inhibitors in 70.4% and mineralocorticoid receptor antagonists (MRAs) in 49.7%. The 1-year mortality rate was 9.6% (10.6% in HFrEF and 5.4% in HFpEF), with major predictors being LV systolic dysfunction, advanced age, HF re-hospitalisation in the previous 6 months, obesity, NYHA class III/IV symptoms, lower systolic blood pressure (SBP) at admission, AF, and renal dysfunction. Patients from South-East Asia were younger, had a higher prevalence of comorbidities, and a higher 1-year mortality rate compared with patients from other Asian regions.

The CHART 1 registry from Japan included 1278 patients from 2000 to 2005 (mean age 68.3 ± 13.4 years, M:F ratio 2.1:1, 55% with HFrEF) [12]. One quarter had an ischaemic HF aetiology and 26.4% had valvular pathology. Prevalence rates of hypertension, diabetes mellitus and atrial arrhythmia were 47%, 19% and 41%,

respectively. Mortality at 1, 2 and 3 years was 7%, 16% and 22%, respectively. The main predictors of mortality were older age, diabetes mellitus, ventricular tachycardia, higher levels of B-type natriuretic peptide, LVEF <30% and higher NYHA functional class.

The CHART 2 registry included 10,219 patients from 2006 to 2010, with a mean age of 68.2 ± 12.3 years, M:F ratio of 2.3:1, 80% HFpEF [13]. HF has an ischaemic aetiology in 53% of patients and a valvular pathology in 19%. Major comorbidities included hypertension (76%), diabetes mellitus (23%), CKD (39%) and AF (23%). RAAS inhibitors were used by 63% of patients, beta-blockers by 40%, MRAs by 15%, and loop diuretics by 30%. At a median follow-up of 3.1 years, the mortality rate was about 50 per 1000 patient years.

The INTER CHF study enrolled 5813 patients worldwide from 2012 to 2014, of which 2661 (46%) were from Asia (M:F ratio 1.4:1) [21]. The Asian cohort had a mean age of 60.0 ± 0.3 years, older than the African population and younger than those from South America. HF aetiology was CAD in 48% of patients and RHD in 10%. Major comorbidities included hypertension (59%), diabetes mellitus (27.9%) and CKD (7.1%). HF therapy included diuretics in 62.1% of patients, RAAS inhibitors in 67.9%, beta-blockers in 60.8%, MRAs in 44% and digoxin in 27.6%. One-year mortality rates were highest in India (23%), followed by South-East Asia (15%), the Middle East (9%) and China (7%). Predictors of mortality included older age, lower body mass index, valvular heart disease, HF hospitalisation, lower SBP, LV dysfunction, COPD, illiteracy, and lack of treatment with beta-blockers and RAAS inhibitors [22].

The Gulf CARE Registry enrolled 5005 patients from 47 hospitals in seven Middle East countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen) between February and November 2012 [17]. Mean age of the population was 59 ± 15 years, with M:F ratio of 2.3:1. HFrEF was seen in 69%, and median LVEF was 35%. HF aetiology was CAD in 53% and valvular heart disease in 13%. Major comorbidities included hypertension (61%), diabetes mellitus (50%), atrial arrhythmia (14%) and CKD (15%). Diuretics were being used by 94% of patients, beta-blockers by 71%, RAAS inhibitors by 78% and MRAs by 43%; 2.1% had an implanted ICD and 1.1% had undergone CRT device implantation. In-hospital mortality was 6.3%, and re-hospitalisation rates at 3 and 12 months were 18% and 40%. Cumulative mortality rates at 3 and 12 months were 13% and 20.1%.

The HEARTS registry enrolled 1090 patients from Saudi Arabia from 2009 to 2011 (mean age 60.6 ± 15.3 years, M:F ratio 1.45:1) [23]. HFrEF was seen in 63.3% of patients, and 70.6% had severe LV dysfunction. Major comorbidities included hypertension (70.9%), diabetes mellitus (57.9%), CKD (29.8%) and atrial arrhythmias (15.7%). The most commonly used HF therapies were beta-blockers (95% of patients), diuretics (94%), RAAS inhibitors (86%) and MRAs (53%). ICD and CRD devices were implanted in 29.1% and 8.8% of patients, respectively. In-hospital, 30-day and 1-year mortality rates were 5.3%, 7.5% and 9%, respectively.

The Korean Acute Heart Failure registry (KorAHF) included 5625 patients from 2011 to 2014 (mean age 68.5 ± 14.5 years, M:F ratio 1.1:1) [16]. The most common form of HF was HFrEF (60.5% of patients). Aetiology was CAD in 42.9% of patients and valvular heart disease in 14.3%. RAAS inhibitors were used by 68.8% of patients, beta-blockers by 43% and MRAs by 37.1%. Comorbidities included hypertension (59.1%), diabetes mellitus (35.3%), CKD (14.3%) and AF (34.9%). In-hospital mortality was 7.6% and 1-year mortality was 8.4%. Predictors of mortality were older age, renal dysfunction, SBP <100 mmHg and lack of GDMT.

The China-HF registry enrolled 13,687 patients from 132 centres from 2012 to 2015 [14]. The mean age of the study population was 65 ± 15 years and the M:F ratio was 1.44. CAD was the underlying HF aetiology in 49.6% of cases, and 39.6% had HFrEF. Common comorbidities included hypertension (50.9%), CKD (46.7%), diabetes (21%) and AF (24.4%). The proportion of patients taking diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and beta-blockers was 30.1%, 27.0%, and 25.6%, respectively. The median length of hospital stay was 10 (range 7–15) days, and in-hospital mortality was 4.1 ± 0.3%. Predictors of mortality included low SBP, acute MI, infection, right bundle branch block, and elevated total bilirubin and blood urea nitrogen levels.

13.4 Special Features in Asian Population

The data above indicate that, compared with Western populations, the Asian population of HF patients is a decade younger in terms of mean age, with male predominance. The proportion of patients with HFrEF is significantly higher and the proportion with HFpEF much lower. RHD aetiology was only specifically mentioned in studies from India. The prevalence of CAD was highest in the Indian cohorts, but similar to Western data in other groups [18–20]. Asian cohorts also showed a high in-hospital mortality rate. Some registries reported long-term mortality. One of these was the THFR, which reported 1-year, 3-year and 5-year mortality rates of 30%, 45% and nearly 60%, respectively [24].

Rates of optimal GDMT usage and cardiac device implantation of devices were much lower in Asian cohorts compared with Western data. This could be due to issues relating to availability, accessibility and affordability. Late referral in patients with acute coronary syndromes and not getting evidence-based therapy (e.g., timely revascularisation) may be another reason underlying the high mortality rates.

As a comparison, the THESEUS registry reported data from Africa (2007–2010; $n = 1006$; mean age 52.3 ± 18.3 years; M:F ratio 0.97:1) [25]. The cause of HF was most commonly hypertension (45.4% of patients), followed by RHD (14.3%) and CAD (7.7%). Renal dysfunction, diabetes mellitus and AF were present in 7.7%, 11.4% and 18.3% of patients, respectively. The prevalence of HIV was quite high (13%), while the median duration of hospitalisation was 7 days. In-hospital and

6-months mortality rates were 4.2% and 17.8%, respectively. The patients in this cohort were a decade younger than the Asian patients, with a similar proportion of males and females. Surprisingly, the prevalence of CAD was significantly lower, with similar in-hospital mortality but higher 6-month mortality.

13.5 Intra-continental Variation

Comparing data between Asian regions, age distribution was similar but the proportion of male patients was slightly higher in India and Gulf nations compared with South-East Asia. The prevalence of CAD was highest in patients from India, while CKD was most prevalent in those from China, despite this group having the lowest prevalence of diabetes mellitus. Rates of GDMT prescription were lowest in patients with HF from China, while this country also had the lowest in-hospital mortality rate. Data on the contribution of RHD to HF is lacking from China and the Middle East, while this aetiology was present in one-fifth of patients from India, Korea and Saudi Arabia. Despite the high prevalence of HFrEF in these countries, the use of MRAs was low. Implantation of devices (CRT and ICD) was very low in all Asian countries, but higher in patients from Saudi Arabia. HF patients from Japan tended to be older, with a higher prevalence of HFpEF, renal dysfunction and hypertension, although medication usage was similar to that in the rest of the Asian cohort.

13.6 What Lies in the Future?

These HF registries are useful to describe the real-world clinical situation in different countries and regions. With an increasing proportion of elderly in many populations, lack of physical activity, low intake of fruits and vegetables, rising prevalence of diabetes mellitus, hypertension and CAD, the prevalence of HF in Asia is likely to rise over coming decades [26].

Treatment of HF is resource intensive and is not affordable for the majority of patients in Asia. Therefore, there needs to be a focus on the prevention of HF. These preventive measures can be primordial (e.g., cultivating healthy habits in the population at a young age), or primary (early identification and control of risk factors such as diabetes and hypertension). Secondary prevention is also important in HF by providing continued follow-up, risk factor control and evidence-based care. For HFrEF, this includes treatment with low-cost agents such as beta-blockers and RAAS inhibitors. With the advent of newer drug classes such as the angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransport 2 inhibitors, there is even more scope for improving the quality of life and outcomes in patients with HF.

Lack of adequate manpower and overcrowded public health facilities are other important issues in Asian countries. HF nurse-based follow-up is a very well accepted practice in the West, which can be adopted as a cost-effective solution.

In conclusion, the prevalence of HF in most Asian countries is high, and will likely increase due to factors such as greater longevity, a sedentary lifestyle and increasing prevalence of CAD. It is important to recognise differences in HF risk factors and outcomes in Asian populations, and design preventive and therapeutic protocols accordingly. Hypertension is a major risk factor for HF in the Asian population, meaning that good control of blood pressure will help to reduce the prevalence of HF.

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