

Heart failure cohort in Singapore with defined criteria: clinical characteristics and prognosis in a multi-ethnic hospital-based cohort in Singapore

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ABSTRACT

Introduction: There are limited data on heart failure (HF) cohorts with objective clinical definition of HF. Many observational HF studies were based on discharge diagnosis codes, making them subjective. Many did not have contemporaneous left ventricular function assessment. This study was done to evaluate the characteristics and one-year prognosis of a single centre multi-ethnic Asian inpatient HF cohort, with these limitations addressed, with the aim of yielding a more accurate picture of true HF.

Methods: This was an observational prospective study. Patients who fulfilled the modified Framingham criteria for clinical HF and study inclusion criteria of serum creatinine level less than 267 micromol/L, serum albumin level greater than 28 g/L, and a contemporaneous trans-thoracic echocardiography (TTE) study were enrolled. TTE studies ordered were attempted within 72 hours.

Results: 173 patients were enrolled into the study. TTE was done within 72 hours of admission for 86.1 percent (n = 149) of the participants. Diastolic HF constituted 22.0 percent of the cohort. The mean age of the participants was 68.7 (standard deviation, 12.0) years. The prevalence of elderly patients, diabetes mellitus, hypertension and ischaemic cardiomyopathy were high. The one-year mortality rate was 20.8 percent (n = 36). The one-year death or readmission for any cause rate was 69.4 percent (n = 120). The mean time in hospital for any cause within the one year was 11.8 +/- 17.9

days. Ethnicity had prognostic implications. Being elderly, having elevated random blood glucose or serum creatinine levels were associated with a worse prognosis.

Conclusion: With strict methodology, HF is truly a disease of the elderly, with significant one-year mortality and morbidity consequences. Prognostic characteristics are reviewed.

Keywords: Framingham criteria for heart failure, heart failure, hypertension, ischaemic cardiomyopathy, trans-thoracic echocardiography

Singapore Med J 2007; 48(5):408-414

INTRODUCTION

Heart failure (HF) is a major health problem with a significant disease burden on society and suffering for the individual.⁽¹⁾ In Singapore, between 1991 and 1998, it accounted for 4.5% of all hospital admissions and 2.5% of overall mortality in the geriatric age group.⁽²⁾ There is limited data in Southeast Asia on the HF cohort with a strict objective clinical definition for HF. The purpose of this study was to evaluate the clinical characteristics, and one-year prognosis and disease burden of a single centre multi-ethnic Asian in-patient HF cohort. We used validated objective clinical criteria for HF, rather than basing it on subjective discharge diagnosis code.

METHODS

This was an observational prospective study. Waiver of consent was obtained from the hospital's institutional review board. Strict patient anonymity and confidentiality were maintained. Singapore is an urban island city-state with a population of 4.24 million people.⁽³⁾ It has a total land area of 660 km² and is situated at the southern tip of the Malayan peninsular.⁽⁴⁾ Changi General Hospital is an

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800-bed general hospital serving a population of 800,000 people in the eastern part of Singapore. The population is multi-ethnic, but is predominantly Chinese, Malay, Indian and Eurasian. The study team reviewed clinical records of patients admitted to the Department of Medicine, including its divisions of Cardiology and Geriatric Medicine, diagnosed with HF or suspected HF between November 10, 2003 and April 10, 2004. The case records were reviewed at 24 hours, 72 hours and before discharge. Five medical doctors constituted the study review team. Patients who fulfilled the modified Framingham criteria for clinical HF⁽⁵⁾ and the study inclusion criteria were enrolled.

The Framingham HF criteria are classified as major or minor. The major criteria are paroxysmal nocturnal dyspnoea, orthopnoea, abnormal jugular venous distension, pulmonary rales, cardiomegaly or pulmonary oedema on chest radiographs, presence of third heart sound and central venous pressure > 16 cm H₂O. The minor criteria are oedema, night cough, dyspnoea on exertion, hepatomegaly, pleural effusion, tachycardia (> 120 beats/minute) and weight loss of ≥ 4.5 kg in five days (considered a major criterion if it occurred during therapeutic interventions for HF). To be accepted, a minor criterion could not be attributed to any other condition such as chronic obstructive lung disease, nephrotic syndrome, liver cirrhosis, ascites, significant pulmonary hypertension (> 50 mmHg on Doppler ultrasonography), hypoalbumin state or serum creatinine > 267 μmol/L. Diagnosis of definite clinical HF was made if two major, or one major and two minor, criteria were present concurrently. Further study inclusion criteria included serum creatinine < 267 μmol/L, serum albumin > 28 g/L, no decompensated HF episodes in the prior three months, no planned revascularisation within three months of index admission and a contemporaneous trans-thoracic echocardiography (TTE) study.

History and physical signs were as noted in the clinical records. Ethnicity was classified according to the National Registration Identification Card for citizens or permanent residents of Singapore. This is based on the major ethnic groups in Singapore, namely: Chinese, Malay, Indian (includes those from the Indian subcontinent), and Others (include Eurasians and other ethnic groups not in the above-mentioned categories). For non-residents, ethnicity was decided as above by the attending medical team. The presence or absence of comorbidities like diabetes mellitus (DM), hypertension, coronary artery disease (CAD), or acute myocardial infarction (AMI) during the index admission was as defined by the patient's attending medical team. This is from the conventional clinical process of history and physical examination, supplemented by investigations as and when necessary. The presence or absence of clinical

signs and symptoms of HF were as noted by the patient's attending medical team and recorded in the clinical records. There were no further clinical evaluations of the patient by the study review team.

The study review team used the New York Heart Association grading of dyspnoea, and the Killip and Kimball grading of the heart failure severity,⁽⁶⁾ after review of the clinical records if the patient's attending medical team had not already done it. The aetiology of the heart failure was broadly divided into ischaemic or non-ischaemic cardiomyopathies. Heart failure due predominantly to ischaemic heart disease was defined as ischaemic cardiomyopathy.⁽⁷⁾ Heart failure not predominantly due to ischaemic heart disease was defined as non-ischaemic cardiomyopathy. This would include hypertensive heart disease, valvular heart disease, tachyarrhythmia and idiopathic causes. The aetiology of the heart failure was determined by the attending medical team, based on conventional clinical grounds of history, physical examination and relevant investigations. The common investigations used to determine this were electrocardiography, TTE, functional stress tests like stress echocardiography or nuclear myocardial perfusion imaging and cardiac catheterisation. There was no intervention in the management of the enrolled patients. This was left to the patient's attending physician.

A TTE study, if ordered, was done within 72 hours for accurate assessment of the left ventricular ejection fraction (LVEF) at the time of heart failure.⁽⁸⁾ As per usual practice, a TTE was ordered for new heart failure patients, known heart failure patients that had not had a recent TTE, or if the attending physician deemed it to be clinically indicated. Each TTE study was done in the echocardiography laboratory with HP Sonos 2500 or GE Vingmed System 5 cardiac ultrasound machines by a ultrasonographer and reviewed by an echocardiography cardiologist. LVEF was assessed visually. The intra- and inter-individual variation in our echocardiography laboratory is 10%. In event of uncertainty over echocardiographical findings, the decision of the echocardiography cardiologist was final. Preserved systolic function was defined as LVEF ≥ 45%, and diastolic HF was presumed if there was heart failure with preserved systolic function and absence of concomitant lesions like moderate to severe valvular lesion, moderate to severe pulmonary hypertension, pericardial effusion, pericardial tamponade, or constrictive pericarditis to account for the HF.⁽⁹⁾ The echocardiographical characteristics analysed are listed in Table I. The patients' case records were reviewed for one-year follow-up information. If the patient had no contact with the hospital within one year, the study review team would telephone the patient or caregiver for an update of the patient's status. The one-year follow-up information included

Table I. Characteristics of heart failure patients.

Characteristic	Frequency
Mean age (SD) (years)	68.7 (12.0)
Age ≥ 55 years, n (%)	146 (84.4)
Age ≥ 65 years, n (%)	117 (67.6)
Age ≥ 75 years, n (%)	62 (35.8)
Gender, n (%)	
Male	89 (51.4)
Female	84 (48.6)
Ethnic group, n (%)	
Chinese	90 (52.0)
Malay	58 (33.5)
Indian	18 (10.4)
Others	7 (4.0)
Aetiology, n (%)	
Ischaemic	115 (66.5%)
Non-ischaemic	35 (20.2%)
Not determined	23 (13.3%)
NYHA class III or IV [#] , n (%)	148 (85.5)
AMI during index admission, n (%)	59 (34.1)
Killip and Kimball Class III or IV heart failure grade [#] , n (%)	74 (42.8)
Mean length of stay (SD) (days)	5.92 (5.05)
Comorbidities, n (%)	
Diabetes mellitus	87 (50.3)
Hypertension	117 (67.6)
Coronary artery disease	81 (46.8)
Atrial fibrillation [*]	29 (16.5)
Echocardiographical features	
Timing of study, n (%)	
TTE within 72 hours	149 (86.1)
TTE beyond 72 hours but during index admission	12 (6.9)
TTE before admission	12 (6.9)
Mean LVEF (SD), n (%)	34.5 (18.6)
LVEF < 45%, n (%)	111 (64.2)
LVEF > 45%, n (%)	62 (35.8)
LVEF ≥ 45% + concomitant lesion, n (%)	24 (13.9)
Diastolic heart failure, n (%)	38 (22.0)
Significant valve disease ^{**} , n (%)	51 (29.5)

[#]New York Heart Association (NYHA) class was not ascertained in 15 (8.7%) participants.

^{*}Killip and Kimball class was not ascertained in one (0.6%) case.

^{*}Rhythm was not ascertained in one (0.6%) participant.

^{**}Significant valve disease was indeterminate in six (3.5%) participants.

mortality, death or readmission for cardiovascular (CV) cause and death or readmission for any cause, and in-patient disease burden surrogates of total time in hospital for any cause and total time in hospital due to CV cause.

Categorical variables were expressed as percentages and compared using chi-square test for analysis. Continuous variables were reported as mean and standard deviation, and compared using Student's two-sample t-test

for analysis. To assess for predictors of one-year outcomes, logistic regression analysis was used. Candidate covariates included those identified in uni-variable analysis with < 0.1, and those identified in previous studies to have impact on mortality and morbidity.⁽¹⁰⁾ Statistical significance was reached if $p < 0.05$. All analysis was performed with the Statistical Package for Social Sciences version 12.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Altogether, 185 patients had clinical HF according to the Framingham criteria for clinical HF. Of these 185 patients, 173 patients (93.5%) also satisfied the study inclusion criteria, and had a contemporaneous TTE study. They were enrolled into the study. Of these 173 participants, 86.1% (n = 149) had their TTE done within 72 hours of admission, 6.9% (n = 12) had it done within the index admission, but more than 72 hours from admission, and 6.9% (n = 12) had it done recently before admission. The mean LVEF was 34.5 (18.6)%. The preserved systolic function HF group constituted 35.8% (n = 62) of the cohort. Significant valvular heart disease was present in 29.5% of the cohort. The proportion with presumed diastolic HF was 22.0% (n = 38).

The epidemiological characteristics of the HF cohort are shown in Table I. The ethnic Chinese, Malay, and Indian constituted 52.0%, 33.5% and 10.4% of the HF cohort, respectively. Those classified as "Others" constituted 4% of the HF cohort. The mean age of the HF cohort was 68.7 (\pm 12.0) years. Patients aged \geq 55, 65 and 75 years constituted 84.4% (n = 146), 67.6% (n = 117) and 35.8% (n = 62) of the HF cohort, respectively. The HF was of moderate to severe grade in 42.8% (n = 74) of the cohort. The HF was deemed to be of ischaemic aetiology in 66.5% (n = 115) of the cases. An AMI was present in 34.1% (n = 59) of the cases. The prevalence of DM, hypertension and history of CAD were 50.3% (n = 87), 67.6% (n = 117), and 46.8% (n = 81), respectively. Atrial fibrillation was present in 16.5% of the cohort (n = 29). The mean length of stay was 5.92 (5.05) days.

Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy and beta-blocker therapy on discharge were present in 75.1% and 41.6% of the heart failure cohort, respectively. Anti-platelet and warfarin prescription rates were 72.3% and 9.8%, respectively. (Table II). The one-year mortality rate was 20.8% (n = 36). The one-year death or readmission for CV cause was 54.3% (n = 94). The one-year death or readmission for any cause rate was 69.4% (n = 120). The mean time in hospital for CV cause within one year was 11.8 (\pm 17.9) days. The mean time in hospital for any cause within one year was 6.3 (\pm 13.7) days (Table III).

The predictors of one-year events are listed in Table IV. Chinese ethnicity (compared to non-Chinese ethnicity) and Malay ethnicity (compared to non-Malay ethnicity) were both associated with significantly lower probability of one-year mortality (odds-ratio [OR] 0.229, 95% confidence interval [CI] 0.058–0.907, p = 0.036; and OR 0.194, 95% CI 0.044–0.854, p = 0.030; respectively). There were strong trends toward increased probability for mortality within one year in patients with atrial fibrillation and in patients with elevated serum creatinine levels (OR 3.802, 95% CI 0.985–14.673, p = 0.053; and OR 1.012,

Table II. Medications on discharge.

Medication, n (%)	Frequency
ACEI or ARB	130 (75.1)
ACEI	118 (68.2)
ARB	13 (7.5)
Beta-blockers	72 (41.6)
Spironolactone	63 (36.4)
Diuretics	155 (89.6)
Digoxin	33 (19.1)
Nitrate	91 (52.6)
Anti-platelets	125 (72.3)
Warfarin	17 (9.8)

Table III. One-year outcomes.

Outcome	Frequency
Death*, n (%)	36 (20.8)
Death or readmission for cardiovascular cause**, n (%)	94 (54.3)
Death or readmission for any cause ∞ , n (%)	120 (69.4)
Mean time in hospital for any cause (SD) (days)	11.8 (17.9)
Mean time in hospital for cardiovascular cause (SD) (days)	6.3 (13.7)

*We were unable to ascertain the outcome status in 13 (7.5%) participants.

**We were unable to ascertain the outcome status in 9 (5.2%) participants.

∞ We were unable to ascertain the outcome status in 8 (4.6%) participants.

95% CI 1.000–1.025, p = 0.055), respectively. There were trends toward increased probability for mortality within one year in female patients (OR 3.336, 95% CI 0.913–12.184, p = 0.068), patients with an index AMI (OR 2.694, 95% CI 0.882–8.231, p = 0.082) and patients with elevated random blood glucose levels (OR 1.106, 95% CI 0.983–1.244, p = 0.095). Geriatric age (aged \geq 65 years), elevated random blood glucose levels, and elevated serum creatinine levels were associated with increased probability of one-year mortality or readmission for any cause. Malay ethnicity was associated with lower probability of one-year mortality or readmission for any cause (OR 0.095, 95% CI 0.013–0.685, p = 0.020).

DISCUSSION

This study is unique compared to previous HF studies with regard to methodology, as it was done with the common limitations of previous HF studies addressed. The previous studies had several limitations. Firstly, many HF studies were based on discharge diagnosis codes. With

Table IV. Clinical predictors of one-year outcomes. *

One-year outcomes	Covariate	OR (95% CI)	p-value
Mortality	Chinese ethnicity	0.229 (0.058–0.907)	0.036
	Malay ethnicity	0.194 (0.044–0.854)	0.030
	Index AMI	2.694 (0.882–8.231)	0.082
	Female gender	3.336 (0.913–12.184)	0.068
	Atrial fibrillation	3.802 (0.985–14.673)	0.053
	Random blood glucose	1.106 (0.983–1.244)	0.095
	Serum creatinine	1.012 (1.000–1.025)	0.055
Mortality or CV readmission	Random blood glucose	1.157 (1.028–1.301)	0.015
	Serum creatinine	1.013 (1.003–1.024)	0.014
Mortality or any readmission	Aged \geq 65 years	9.788 (1.534–62.470)	0.016
	Malay ethnicity	0.095 (0.013–0.685)	0.020
	Random blood glucose	1.188 (1.031–1.370)	0.018
	Serum creatinine	1.024 (1.006–1.043)	0.008

*This was done using multivariate logistic regression analysis. Covariates analysed were age, age \geq 65 years, female gender, ethnicity (Chinese versus non-Chinese and Malay versus non-Malay), moderate to severe heart failure (Killip 3 or 4), diabetes mellitus, hypertension, index AMI, atrial fibrillation, hyponatraemia (serum Na $<$ 130 mmol/L), random blood glucose level, serum creatinine, serum haemoglobin, serum Hb $<$ 12 g/dL, LVEF, LVEF \geq 45%, and LV dilatation.

no consensus on the clinical definition of HF, this made the diagnosis subjective. Secondly, the symptoms and signs of HF are not specific. They can be due to causes other than the heart, including obesity or lung disease,⁽¹¹⁾ and the fluid-overloaded state secondary to renal failure or a low serum albumin state. Thirdly, many studies on HF had incomplete information on the assessment of left ventricular function.⁽¹²⁾ The TTE may not have been done, or if done, it was some time from the index admission for HF. A timely TTE study is important for an accurate assessment of left ventricular function.

We used the Framingham criteria for HF as the objective clinical criterion, as it has a high sensitivity and specificity for the detection of definite HF,⁽¹³⁾ and it is considered the best validated of the various standard criteria developed. To increase the specificity of the diagnosis of HF, further restrictions of serum creatinine $<$ 267 μ mol/L, and serum albumin $>$ 28 g/L were included. With these added criteria, the specificity of the HF diagnosis is increased. However, this is probably at the expense of sensitivity. This was done so that the symptoms and signs of these patients are more likely attributable to the heart, rather than to other organs.

All the enrolled participants had a TTE study. We attempted to do the TTE study within 72 hours. This was achieved in 86.1% of the cases. This is to increase the accuracy of the assessment of the left ventricular systolic function. This 72-hour deadline is based on studies by Gandhi et al.⁽⁸⁾ He showed that there was no significant difference in left ventricular systolic function measured on echocardiography at the time of presentation of decompensated HF by the patients and 72 hours after

the event, when the patients were treated and no longer in symptomatic HF. With the common limitations of HF studies addressed as outlined above, we propose that the results of this study are more accurate and reflective of the characteristics of true HF and its impact on the individual and healthcare system.

Like studies done in the developed nations, this study showed that HF is predominantly a disease of the elderly.⁽¹⁴⁾ However, the mean age of our cohort at 68.7 (\pm 12.0) years old was lower than the mean age in other studies.^(15,16) There was a high prevalence of hypertension, DM and CAD. This is not dissimilar to other studies.^(1,17) However, the prevalence of DM is higher in our cohort.^(18,19) It should be noted that an AMI was present in 34.1% (n = 59) of the cases. This highlights the importance of excluding acute coronary syndrome as a precipitant or cause in patients with decompensated HF. There were higher proportions of ethnic Malays and Indians in our HF cohort at 33.5% and 10.4%, respectively, compared to the general population at 13.8% and 8.4%, respectively.⁽²⁰⁾ The prevalence of preserved systolic function and presumed diastolic HF in our inpatient cohort at 35.8% and 22.0%, respectively, are similar to previous studies on inpatient HF cohorts.^(21,22) There was high prescription rate for ACEI or ARB. Beta-blocker and anticoagulation prescription rates were low because of significant proportion of patients with contraindications to these medications.

With regard to prognosis, the one-year mortality rate at 20.8% was lower than those of previous observational studies, which varied from 24% to 43%.^(23,24) This may have been due to the younger profile of our cohort, the

exclusion of patients without contemporaneous TTE or patients with significant renal impairment from our cohort, and the high use of evidence-based medications. Alternatively, it may be that our Asian population responds better to the present armoury of proven medications. More studies are needed to study this aspect. Our study shows that the disease burden of HF was no different from that of the developed nations. Rate of death or readmission for any cause within one year at 69.4% was similar to previous observational studies.^(18,19) Time in hospital within one year for CV cause or any cause was significant at 6.3 (\pm 13.7) and 11.8 (\pm 17.9) days, respectively. We cannot compare this with previous studies, as there are no previous studies that have used this as an indicator of disease burden.

The finding of ethnicity and prognostic implications is not new in studies in American populations.^(25,26) However, this is novel in an Asian population. Chinese ethnicity (compared to non-Chinese ethnicity) and Malay ethnicity (compared to non-Malay ethnicity) were both associated with significantly lower probability of one-year mortality. Malay ethnicity was also associated with lower probability of one-year mortality or readmission for any cause. More studies are needed to look into this novel finding. Increasing age, atrial fibrillation and impaired renal function are well-documented predictors of worse prognosis.⁽²⁷⁾ Glycaemic control and its association with prognosis in HF are equivocal. Some studies show a worse prognosis with poorer control,⁽²⁸⁾ while others show an inverse relation between glycaemic control and prognosis.⁽²⁹⁾ Our study showed that elevated random blood glucose levels were associated with worse one-year outcomes.

There are limitations in this study. The sample size of the study was small, thus limiting the statistical power of the study, and increasing exposure to random confounding influences. The diagnosis of HF was a clinical one, based on the Framingham criteria. The sensitivity and specificity could have further been increased if serum B-Natriuretic Peptide tests were used.⁽³⁰⁾ Patients were enrolled only if they had a contemporaneous TTE study. This occurred in 93.5% (n = 173) of the 185 patients with clinical HF as defined by Framingham criteria. There was a possibility of selection bias as 12 patients (6.5%) with clinical HF did not have the contemporaneous TTE study and thus were not included in this study. If these 12 patients without a TTE study were included, our prognosis results could have been worse as shown in a study by Senni et al,⁽³¹⁾ that the underuse of echocardiography was associated with poorer survival and underuse of angiotensin-converting enzyme inhibitor therapy.

The diagnosis of the aetiology of the HF, the presence or absence of concomitant AMI and comorbid conditions, e.g. DM and hypertension, were determined by the

patient's attending team, and not based on a standardised criteria determined by the study. This may lead to some subjective variation, as different attending teams managed the patients. However, this is reflective of the true situation in the wards. The TTE studies were done by several ultrasonographers with two different machines, and the LVEF was assessed visually, thus there was a possibility of intra- and inter-individual variation in assessing the LVEF. The intra- and inter-individual variation in our echocardiography laboratory is 10%. At present, visual assessment of LVEF is an acceptable common practice, and has been established to be accurate and reproducible in several reports.^(32,33) The serum creatinine cut-off level of 267 μ mol/L and serum albumin cut of level of 28 g/L are arbitrary levels. However, based on pathophysiology⁽³⁴⁾ and clinical experience, patients with serum creatinine > 267 μ mol/L and/or serum albumin levels < 28 g/L are more likely to retain fluid, and thus confound the clinical picture of HF. Serum albumin of < 28 g/L was chosen as this is the value corresponding to Grade C in the Child's Pugh score of severity for liver dysfunction.

In conclusion, in our study of a single centre multi-ethnic Asian inpatient HF cohort in Singapore with objective criteria for HF, and contemporaneous TTE study, the accurate profile of our cohort is not dissimilar to that in the developed nations. HF is a disease of the elderly with high prevalence of hypertension, DM and CAD. It has significant one-year mortality of 20.8% and morbidity consequences with one-year rate of death or readmission for any cause of 69.4%, and mean time in hospital within one year for any cause at 11.8 (\pm 17.9) days. We found that ethnicity had prognostic implications. Elderly patients, patients with elevated random blood glucose or elevated serum creatinine levels were associated with a worse prognosis. More studies of similar methodology are needed to further look into the significant characteristics of the victims of true HF found in this study.

ACKNOWLEDGEMENTS

The authors would like to thank Drs Yew Seong Goh, Sea Hing Ong, Tsun Gun Ng, and Koh Brendan for their studious and meticulous data collection; Drs Lim Victor, Chong Hiok Tan, and Khim Leng Tong for their general guidance; and Ms Leng Leng Lee and her team of very helpful ultrasonographers at the echocardiography laboratory in the Clinical Measurement Unit. We are also very appreciative of Ms Soon Enn Sin for her secretarial support.

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