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ORIGINAL RESEARCH ARTICLE

Demographical and clinicopathological characteristics in heart failure and outcome predictors: a prospective, observational study

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Abstract

Aims The aims of the study were to study the demographical and clinicopathological characteristics of patients presenting with heart failure and evaluate the 1 year outcomes and to identify risk predictors if any.

Methods and results A prospective observational study was conducted in consecutive patients of systolic heart failure. The study was divided into two parts—an initial 6 month enrolment phase followed up for 1 year for major adverse cardiovascular events. All patients were treated according to the Institutional Heart Failure Protocol. Demographical and clinicopathophysiological characteristics were studied, and results were analysed. A total of 143 patients were enrolled. The mean age of subjects was 56.4 years with male subjects constituting almost two-thirds of the study population. The commonest aetiology of heart failure was ischemic with valvular heart disease being the commonest cause of non-ischemic heart failure. Bendopnea, a recently described symptom of heart failure, was found in a significant number of subjects. By univariate analysis, male sex ($P = 0.042$) and cardiomegaly ($P = 0.035$) were predictors of rehospitalization, whereas the univariate predictors of mortality were ischemic aetiology ($P = 0.000$), age $>$ 50 years ($P = 0.007$), hypertension ($P = 0.012$), worsening NYHA class ($P = 0.003$), diabetes mellitus ($P = 0.009$), and hypokalaemia ($P = 0.006$). Multivariate analysis performed showed age $>$ 50 years [$P = 0.007$; OR (CI) = 13.547 (2.034–90.238)], NYHA class [$P = 0.002$; OR (CI) = 32.300 (3.733–276.532)], and hypokalaemia [$P = 0.031$; OR (CI) = 7.524 (1.208–46.862)] as significant predictors of mortality during long-term follow-up.

Conclusions The study will definitely help us to throw more light in identifying risk predictors of heart failure and help in improving clinical outcomes.

Keywords Heart failure; Prognosis; Risk factors; Bendopnea; Hyponatraemia; Hypokalaemia

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Introduction

Heart failure (HF) is a major public health problem and has emerged as the leading cause of morbidity and mortality worldwide in the last decade. It is a complex pathophysiological disorder that is difficult to diagnose, often undertreated and associated with recurrent hospitalizations and poor outcomes. The clinical characteristics, treatment, and outcome of HF patients have been well described in the western population with registries and clinical trials contributing much to our present understanding of the disease. But, still differences exist between the western and the Indian population, and there are only limited data on HF from this part of the world.[1] Heart failure in the Indian population occurs at a comparatively younger age group with low level of education, poverty, and poor access to healthcare facilities associated with poor outcomes. Fuelled by diabetes and cardiovascular diseases in an ageing population, the incidence and prevalence of HF are slowly on the rise. But the exact incidence and prevalence of HF, aetiologies, and current trends in

patient care management are still lacking. Studies on HF will add to the long-term goal of prevention of complications or hospitalization, reducing mortality, improving quality of life, and lower the cost burden of HF treatment.

Methods

The objectives were to study the demographical and clinicopathological characteristics of patients presenting with HF, to evaluate the 1 year outcomes, and to identify risk predictors if any. The study was a prospective observational study conducted in consecutive patients of systolic HF attending the Department of Cardiology in a tertiary care centre from South India. The study was divided into two parts—the initial 6 months being the enrolment phase, after which the patients were followed up for a period of 1 year for major adverse cardiovascular events (MACE), which was defined as recurrent hospitalization and/or death. The inclusion criteria were patients of chronic systolic HF with ejection fraction (EF) of $<$50% and satisfying the Framingham's criteria and age of $>$18 years. The exclusion criteria were patients with acute coronary syndrome with HF, acute pulmonary thromboembolism, any acute onset HF, and unable to provide written informed consent. Chronic systolic HF was defined as systolic HF for at least 6 months with an EF of less than 50% and/or patients who are on standard HF medications, which include at least two groups of medications mentioned: ACEI/ARB, diuretics, or digoxin. The study conformed to the principles outlined in the *Declaration of Helsinki*, and the study commenced after approval from the Institutional Ethics Committee and obtaining written informed consent from the study subjects. A full demographical and clinical characterization of the patients was performed at study entry. Data recorded included age, height, weight, EF (measured by echocardiography in the preceding 1 month), smoking status (current smoker was defined as a person who has smoked $\geq$100 cigarettes in their lifetime and has smoked in the last 3 months and ex-smoker as a person who has smoked $\geq$100 cigarettes in their lifetime and last smoked over 3 months ago), previous myocardial infarction, history of hypertension (a systolic brachial blood pressure (BP) of $\geq$140 mm Hg and/or diastolic BP of $\geq$90 mm Hg for three consecutive readings at rest or prescription of a BP-lowering drug for high BP), diabetes mellitus [fasting blood glucose level of 7.0 mmol/L or more (126 mg/dL) or the use of an antidiabetic drug], peripheral vascular disease and hypercholesterolemia (total cholesterol levels of $>$ 5.2 mmol/L or $>$200 mg/dL or being prescribed a lipid lowering drug), clinical evidence of bendopnea defined as shortness of breath within 30 s of bending and laboratory evidence of electrolyte imbalances like hyponatraemia (serum sodium level $<$ 135 mmol/L or 135 mEq/L) and hypokalaemia (serum potassium level $<$ 3.5 mmol/L or 3.5 mEq/L), stroke, or revascularization procedures (coronary artery bypass surgery or percutaneous coronary intervention). The medications that the subjects were receiving at the time of admission was also recorded. All routine blood and urine examinations were performed at the time of enrolment into the study. The study subjects were managed as per Institutional Heart Failure protocol, and the subjects who were discharged were followed up for a period of 1 year. The follow-up was performed every 3 months via outpatient visits and/or telephone conversations. A questionnaire was drafted, and outcome was studied as either death and/or rehospitalization due to HF (MACE). The final follow-up at the end of 1 year was carried out as a mandatory outpatient visit except for severely debilitated patients who could not attend, in which case the follow-up was completed by telephone.

Statistical methods

Categorical variables were studied by using chi-square and analysis of variance test and continuous variables by using Student's *t*-test. Post hoc analysis of various groups analysed by analysis of variance test was also performed. Univariate analysis was first performed followed by multivariate analysis of the variables, which were found to be significant in univariate analysis. Multivariate logistic regression was performed by using Cox and Snell R square model. SPSS 16.0 software was used for analysis, and *P* value of $<$0.05 was taken as significant.

Results

The study was conducted in a tertiary care centre in Kerala state of India from April 2013 to September 2014 spanning a total duration of 18 months. A total of 205 consecutive patients of HF were screened from which 143 patients were enrolled finally after applying the study criteria. *Figure 1* shows the study disposition.

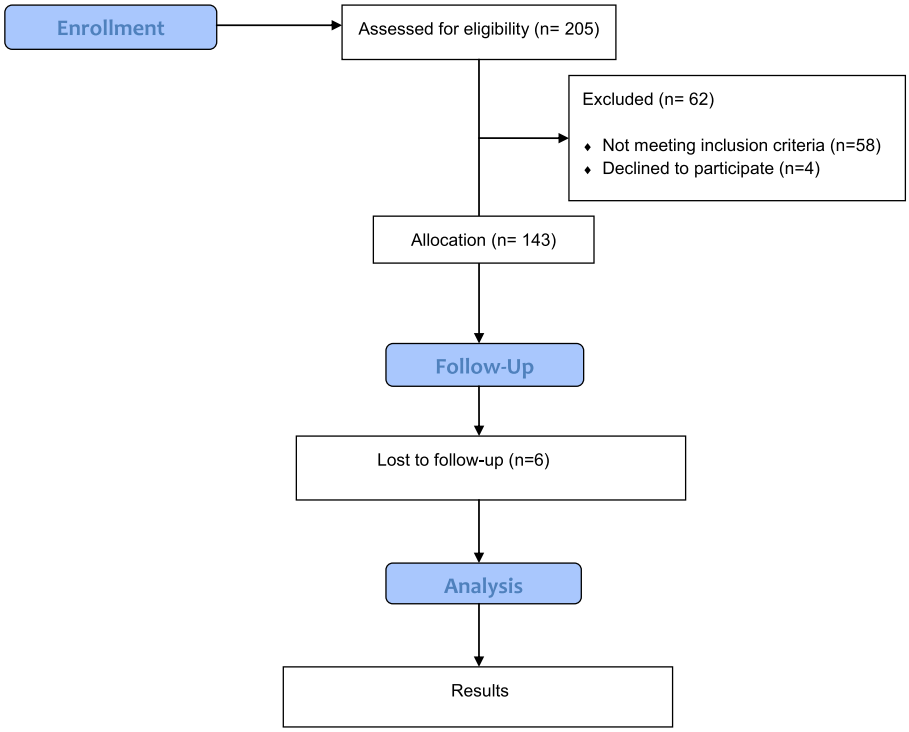
Demographical data

The mean age of the study population was 56.35 ± 14.36 years. Most of the study subjects (90.2%) were treated as inpatients during the initial visit at the time of enrolment, and the rest of the population were treated as outpatient. Male subjects accounted for 65.9% of the total study subjects.

Risk factors and aetiology

Hypertension was present in 45.5%, and diabetes was present in 36.4% of the study population. A history of smoking was present in 41.3% of which 16.8% were current

Figure 1 Flow diagram showing study disposition.



smokers. Dyslipidaemia was noted in 36.4%, peripheral vascular obstructive disease in 10%, and chronic kidney disease in 5.3%. The baseline characteristics have been summarized in *Tables 1* and *2*. The commonest aetiology for HF was ischemic (66.4%), the rest being non-ischemic. The major causes of non-ischemic left ventricular dysfunction were valvular heart disease and dilated cardiomyopathy (DCM; *Figure 2*).

Heart failure treatment

All the patients received some form of diuretics, and the most often prescribed HF medications were loop diuretics, aldosterone antagonists, ACEI/ARB beta blockers, and digoxin (*Table 2*). One fifth of patients were on anticoagulants due to various reasons. Eight subjects were on ivabradine.

Outcomes

The patients were followed up for a period of 1 year for the occurrence of MACE, which included rehospitalization for HF or death. A total of 137 patients were followed up until study completion of which 11 patients died and 95 patients were rehospitalized at least once after the index hospitalization. Almost a third of patients (32.8%) had an improvement in NYHA functional class by at least one Class. More than half of patients (54%) who died during follow-up were in NYHA functional class IV and the rest in NYHA III during the index

Table 1 Baseline characteristics

Variable	All cases (%) (n = 143)	Recurrent hospitalizations (%) (n = 95)	Mortality (%) (n = 11)
Sex: Male	65.9	60	46
Sex: Female	34.1	40	54
Smoker	16.8	14.7	18
Ex-smoker	24.5	82.1	27
DM	36.4	36.8	72.7
Hypertension	45.5	45.3	81.8
Dyslipidaemia	36.4	35.8	45.4
CKD	5.3	2.1	9
COPD	19.6	18.9	27.2
Anaemia	14	55.8	–
NYHA II	23.8	20	9
III	62.2	66	54.5
IV	14	3.1	45.4
Ischemic aetiology	66.4	57.9	90.9
Orthopnea	46.9	48.4	72.7
Bendopnea	21.2	12.6	45.4
PND	25.9	27.3	36.4
Biventricular dysfunction	30	22.1	45.4
Cardiomegaly	63	78.9	72.7
PAH	25.2	32.6	18
Electrocardiogram: wide QRS	23.7	17.4	18
Electrocardiogram: LVH	47.5	45.3	63.6

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Table 2 Baseline characteristics

Variable	All cases (n = 143)	Recurrent hospitalizations (n = 95)	Mortality (n = 11)
Age (years) (mean, SD)	(56.4, 14.4)	(56.4, 14.37)	(70.2, 14.45)
Heart rate (mean, SD)	(86, 14.8)	(85.7, 14.7)	(81.2, 14.8)
EF (mean, SD)	(42.6, 10.4)	(42.26, 11.5)	(35.9, 10.4)
Serum sodium (mmol/L) (mean, SD)	(129.5, 5.57)	(127.3, 5.58)	(131.5, 5.61)
Serum potassium (mmol/L) (mean, SD)	(4.5, 0.53)	(4.86, 0.52)	(3.67, 0.52)
Serum creatinine (mg%) (mean, SD)	(1.38, 0.38)	(1.46, 1.51)	(1.29, 1.52)
Medications (% of cases)			
Digoxin	48.2	55.8	45.4
Aldosterone antagonists	65.7	69.5	72.7
Loop diuretics	99.3	97.9	100
Beta blockers	72.7	69.5	45.4
ACEI	60.1	54.7	81.8
ARB	7.7	8.4	9
Statins	83.2	77.9	100
Antiplatelets			
Aspirin (Asp)	66.4	23.1	27.3
Clopidogrel (clop)	57.3	18.9	9
Dual (Asp plus clop)	40.5	38.9	63.6
Ivabradine	5.6	6.3	18
Vaptans (Tolvaptan)	3.5	2.8	0.7

Figure 2 Congestive heart failure (CHF) aetiology and age distribution.

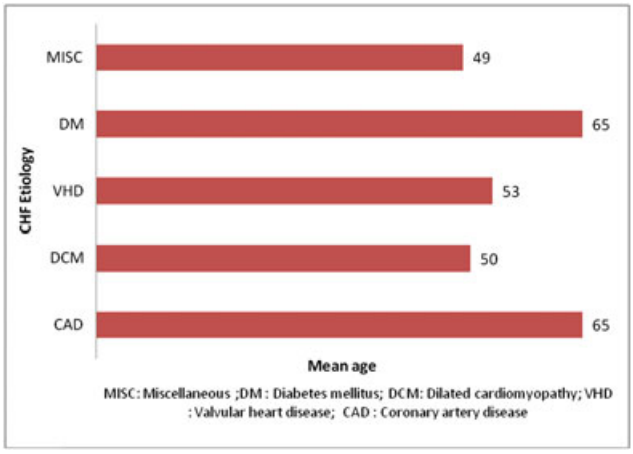


Table 3 Risk factors and mortality as outcome (univariate)

Variable	P value*
Age > 50 years	0.053
Sex	0.140
Hyponatraemia	0.176
Hypokalaemia	0.006
EF < 40	0.017
Ischemic aetiology	0.000
Smoker	0.924
Worsening NYHA class	0.002
Hypertension	0.012
T2DM	0.009
Dyslipidaemia	0.514
CKD	0.897
Haemoglobin < 10 gm%	0.091

*Significant at P = <0.05.

Table 4 Predictors of mortality as outcome (multivariate analysis by logistic regression)

Variable	Odds ratio (95% confidence interval)	P value
Hypertension	6.397 (0.692–59.156)	0.102
Worsening NYHA class	32.300 (3.733–276.532)	0.002
DM	1.571 (0.229–10.764)	0.646
Age category > 50 years	13.547 (2.034–90.238)	0.007
EF < 40	3.073 (0.429–21.997)	0.264
Hypokalaemia	7.524 (1.208–46.862)	0.031

enrolment. The majority had ischemia as the cause of HF (90%), and one-third of subjects (36%) had anaemia. Hyponatraemia was seen in 72% of patients who died, and a little over one-third (36%) had hypokalaemia. Features of biventricular dysfunction were seen in one-third of patients who expired during the study. The clinical and risk factor profiles of patients who died were worse than that of the rest of the study population.

Prognostic predictors

Various risk factors were studied as predictors of outcome by univariate and multivariate analyses (*Tables 3* and *4*). By univariate analysis, male sex (P = 0.042) and cardiomegaly (P = 0.035) were predictors of rehospitalization, whereas the univariate predictors of mortality were ischemic aetiology (P = 0.000), age > 50 years (P = 0.053), hypertension (P = 0.012), worsening NYHA class (P = 0.003**)**, diabetes mellitus (P = 0.009), and hypokalaemia (P = 0.006). A multivariate analysis was performed, which showed age > 50 years

[*P*= 0.007; OR (CI) = 1.571 (0.229–10.764)], worsening NYHA class [*P* = 0.002; OR (CI) = 32.300 (3.733–276.532)], and hypokalaemia [*P* = 0.031; OR(CI) = 7.524 (1.208–46.862)] as significant predictors of mortality during long-term follow-up.

Discussion

Heart failure is an important clinical problem and one of the leading causes of morbidity and mortality worldwide. Epidemiological studies on HF have played a major role in the detection of risk factors, their prevention, and establishment of path breaking treatment strategies.[2] The prevalence of HF is found to increase with age,[3] and women have a greater propensity to develop HF than men as age increased. Similar findings were noted in our study also (*Figure 3*). The mean age of subjects with HF in our study was younger. Epidemiological studies have showed that among the HF population, 50% has reduced EF,[4] and the prevalence of diastolic dysfunction is on the rise.[5] Our study population included patients with reduced EF only (50%) and has not included HF with preserved EF. Considering the aetiology, almost half the cases of HF were due to coronary artery disease (CAD), with diabetes mellitus contributing significantly to HF (*Figure 4*). Among those who died during the study period, more than 90% of the population had CAD as the aetiological factor. Valvular heart disease predominated by rheumatic heart disease still continues to be an important cause of HF in our population. The mean age of presentation was also found to be younger in those with valvular heart disease when compared with the western data.[6] Other leading causes of HF in our population were DCM, which included both primary and secondary DCM, which was similar to other studies from this part of the world.[7,8] Peripartum cardiomyopathy and left ventricular non-compaction were also important causes of HF in the study. It is in fact very difficult to determine which variable is prognostically most important to predict individual patient outcomes in HF. Established risk factors for the development of HF in men and women include age, CAD, hypertension, diabetes, obesity, and smoking[9–11] apart from other prognostic variables which are the area of intense ongoing research.[12] The subjects involved in our study also had similar risk factor profile. Heart failure registries have shown the prevalence of hypertension as two-thirds, CAD as one half, and dyslipidaemia as more than one third in HF. In our study, the percentage of hypertension was close to half, CAD was noted in two-thirds, and dyslipidaemia in one third.[13,14] Various risk factors were studied as prognostic predictors of HF outcomes by both univariate and multivariate analyses (*Tables 3* and *4*). The outcomes studied were rehospitalization and mortality. By univariate analysis, male sex (*P*= 0.042) and cardiomegaly (*P* = 0.035) were predictors of rehospitalization, whereas the univariate predictors of mortality were ischemic aetiology (*P*= 0.000), age > 50 years (*P* = 0.053), hypertension (*P*= 0.012), worsening NYHA class (*P* = 0.003), diabetes mellitus (*P* = 0.009), and hypokalaemia (*P* = 0.006). Multivariate analysis performed showed age > 50 years, NYHA class, and hypokalaemia as significant predictors of mortality during long-term follow-up (*Table 4*). Age is one of the strongest predictors of adverse outcome in HF, and in our study, the mean age of the population who died was 70 years. Iron deficiency in patients with HF has been associated with worse outcomes in various trials, and correcting the same with intravenous iron has been found to improve HF-related outcomes.[15,16] In our study, however, anaemia was not found to be a prognostic predictor. Similarly, renal insufficiency is very commonly seen in HF and is associated with poor outcomes.[17] But the same could not be established in our study and probably the low number of chronic kidney disease patients (only 5%) may have failed to establish the association. Discussing the role of HF symptoms in the prediction of prognosis, patients with EF less than 40% presented with the classical features of HF—orthopnea, pulmonary oedema, paroxysmal nocturnal dyspnoea, increased jugular venous

Figure 3 Age and sex distribution of congestive heart failure cases.

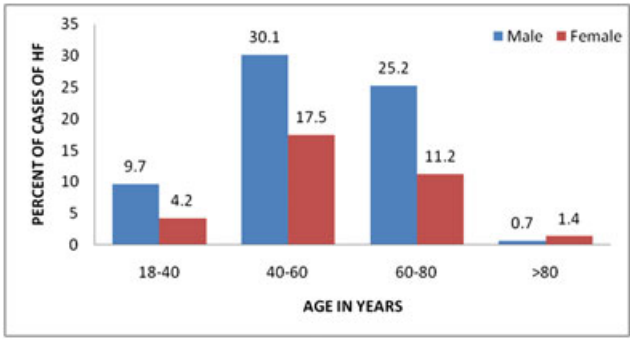
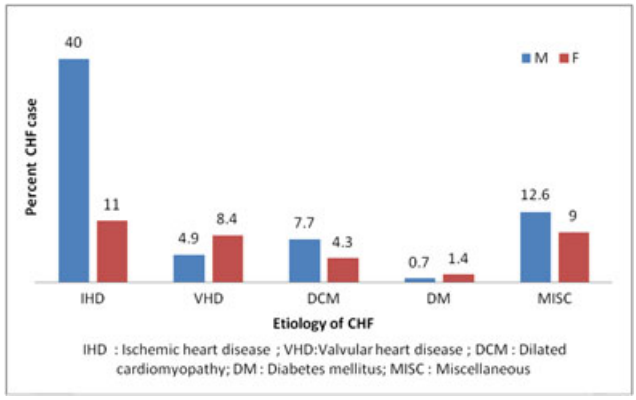


Figure 4 Distribution of congestive heart failure (CHF) cases according to aetiology (M, male; F, female).



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pressure, pedal oedema, and ascites. A particular mention should be made on bendopnea, which is a recently described symptom of HF.[18] In our study, around 21% had bendopnea on presentation and almost half of the subjects who died (45%) had bendopnea. Whether bendopnea will become a future surrogate of poor outcomes in HF needs further intense research. Dyselectrolytemia in HF, which includes both hyponatraemia and hypokalaemia, has been studied intensely in HF and has been associated with worse outcomes.[19,20] Hence, identifying and managing the same are very important in improving HF outcomes. In our study, although hyponatraemia was associated with HF outcomes, the level of significance could not be attained. But that does not negate the importance of hyponatraemia in HF. The concept of aquaresis in HF with euvolemic and hypervolemic hyponatraemia has opened newer insights in the pathophysiology and management of HF.[21–24] In our study, tolvaptan was used in a few patients for a short course with mixed results. Though tolvaptan corrected the hyponatraemia at the time of administration and improved symptoms, it was not associated with any long-term benefit as the same patients were rehospitalized later. Hypokalaemia, however, was associated with poor outcomes in both univariate as well as multivariate analysis.[25]

Limitations

The study design, which was observational, has *per se* limitations in the analysis of the results. Larger studies with longer follow-up will help to throw more light into the epidemiological pattern of HF. Our study had a follow-up period of 1 year only, and longer follow-up period could have increased the outcomes and better prognostication of risk factors in HF. Also, the role of biomarkers was also not studied due to technical limitations, which could have increased the understanding of the disease.

Conclusions

Congestive HF still continues in epidemic proportions and both incidence and prevalence increases with the ageing population in spite of medical advances. Identifying risk factors, their prevention, and effective treatment of patients remains the cornerstone of improving outcomes in HF. In our study, age, NYHA class, and hypokalaemia were found to be important prognostic predictors of HF. Studies assessing the importance of bendopnea in HF are very few, and the present study throws more light on the importance of bendopnea in HF. Epidemiological studies are still needed to decipher newer pathophysiological mechanisms and identification of risk predictors.

Conflict of interest

None declared.

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