



## Clinical And Etiological Profile of Congestive Heart Failure: Observations From A Prospective Study

### KEYWORDS

Congestive Heart Failure, Clinical and Etiological Profile, Chronic Rheumatic Heart Disease

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**ABSTRACT** Background: Congestive heart failure (CHF) remains as one of the leading causes of death. In contrast to Western countries where HF is predominantly a disease of the elderly, in India affects relatively younger age group the most. Though in recent decades ischemic heart disease (IHD) is the commonest cause for HF, rheumatic heart disease (RHD) still remains a significant cause for HF in India due to its over population and low socioeconomic status. There is minimal recent data available on clinical and etiological profile of the CHF in India. Hence, this study was carried out to evaluate the same in Indian patients.

**Materials and Methods:** The study was prospective observational. After obtaining an informed consent, a detailed history was taken, and then the study patients underwent thorough physical examination and detailed investigations. The study included a total of 140 patients aged more than 15 years, admitted to a teaching hospital with clear symptoms and signs suggestive of CHF and satisfying the Framingham criteria for diagnosis of HF.

**Results:** The predominant age group affected was 41-70 years and 15-30 years. Male:female ratio in our study was 2.18:1. Majority of our study patients had most of the symptoms of CHF like breathlessness, palpitations, edema, easy fatigability and chest pain. About 67% of the patients were in NYHA class IV and the most frequent physical findings were rales, S3/S4, apical impulse abnormality, murmurs and raised JVP. All patients satisfied the Framingham criteria for diagnosis of definite CHF. Anemia and hyponatremia were the predominant laboratory abnormalities and poor prognosticators. Congestive heart failure triad, ST elevation/ LV strain and atrial fibrillation were the predominant ECG abnormalities. Cardiomegaly was the most frequent chest X-ray abnormality. Ischemic cardiomyopathy (28%) and Chronic Rheumatic heart disease (CRHD) (24%) were the most frequent Etiologies of HF on 2D ECHO Cardiography. About 42% of the patients received digoxin+ACEI+furosemide as treatment.

**Conclusion:** Although IHD is the predominant cause of HF, still chronic RHD continues to be the second most important etiological factor and hypertension stands third. In the current study, the highest frequency of HF was observed in the age groups 41-70 years and 15-30 years. Chronic rheumatic heart disease was more common in females and in younger age groups while CAD occurred exclusively in males and in older age groups. 2-D Echocardiography is essential for diagnosis and assessment of prognosis of HF. Most of the study patients (83%) recovered within 1-2 weeks and mortality rate was found to be 5%.

### INTRODUCTION

Although survival after heart failure (HF) has improved due to advancement in diagnosis and treatment, it is still one of the leading causes of death causing approximately 30,000 deaths per year.<sup>1</sup> Epidemiological studies have estimated that 1.5% to 2% population experience HF and it is the main reason for hospital admission of elderly patients.<sup>2</sup> In contrast to western countries where HF is predominantly a disease of the elderly, in India it affects relatively younger age group the most. The leading causes of HF in India include coronary artery disease (CAD), diabetes, hypertension, rheumatic valvular heart diseases and primary cardiac muscle diseases. Rheumatic heart disease (RHD) is still a common cause of HF in India, where the prevalence ranges from 6.0 to 11.0/1000.<sup>3,4</sup> Though there has been a significant decline in the prevalence of RHD in developed countries mainly due to improved socioeconomic conditions rather than any modern treatment methods, it

is still very much prevalent in all parts of India and other developing and underdeveloped nations of the world. It has been observed that amongst cardiovascular diseases, RHD accounts for 12-65% of all admissions in developing countries.<sup>5</sup>

Epidemiological data have also shown that approximately one-half of patients who develop HF have a normal or preserved ejection fraction (EF) (>40-50%) i.e., diastolic HF.<sup>6</sup> More than 400,000 new cases of HF are diagnosed each year in the United States; about 3 to 5 million people have Stage-B (A symptomatic ventricular dysfunction) and 2-3 million persons have Stage-C (symptomatic) HF.<sup>7,8</sup> Though it is claimed that ischemic heart disease (IHD) is the most important cause for HF in India in recent decades, RHD also continues to be a significant cause, due to its high prevalence. This has been due to low socioeconomic conditions, with overcrowding, poor housing conditions,

bad hygiene, and illiteracy leading to increased Group A  $\beta$ -hemolytic streptococcus infections, rheumatic fever, RHD and CHF.<sup>5</sup>

In comparison to the Global data and the increasing globalization and urbanization, it appeared to us whether clinical and etiological profile for congestive heart failure (CHF) has changed over the past few decades in India. However, there is very limited recent data available. Hence, we carried out the current study to evaluate the clinical and etiological profile of CHF in Indian subjects with CHF.

## MATERIALS AND METHODS

The study included a total of 140 patients aged more than 15 years admitted to King George Hospital (a teaching hospital), Visakhapatnam, India from Jan 2007 to Oct 2008 with clear symptoms and signs suggestive of CHF and satisfying the Framingham criteria for diagnosis of HF.

The study inclusion criteria were as follows: (i) patients aged  $\geq 15$  years, diagnosed as having CHF, (ii) clear symptoms (breathlessness, easy fatigability, edema, chest pain, palpitation, syncope, cough, hemoptysis, cyanosis), (iii) presence of S3/ S4 gallop, rales or neck vein distension, (iv) ECG abnormalities like arrhythmias, bundle branch block, chamber hypertrophy, ischemia, infarct, CHF triad, low voltage complex, (v) chest X-ray abnormalities correlating to HF like cardiomegaly, pulmonary edema and pleural effusions and (vi) 2D Echo Doppler abnormalities like depressed or preserved ejection fraction (EF), E/A flow ratio abnormalities, global or focal hypokinesia, (regional wall motion abnormality-RWMA), valvular lesions, intra and extra cardiac shunts.

### Exclusion Criteria

We excluded pregnant and lactating women and children below 15 years from our study. Additionally, patients who were not willing to give informed consent were also excluded.

### Study Design

The study was a prospective observational study. After obtaining an informed consent and detailed history, the study patients underwent a thorough physical examination and detailed investigations as follows: CBC complete blood biochemistry (Carbohydrate Profile, Lipid Profile, RFT, Serum Electrolytes, Serum Proteins, LFT), and wherever necessary, thyroid profile, prothrombin time- international normalized ratio (PT-INR), antistreptolysin O (ASO), C-reactive protein (CRP), X-ray chest, 12 lead electrocardiogram (ECG), 2D Echo Doppler and ultra sound scan abdomen.

After arriving at an etiological diagnosis, appropriate treatments were instituted for all the patients and monitored closely for multiple variables including the outcome, response to therapy and time for recovery [taken as improvement in (NYHA) class], during their inpatient stay and the data of all the 140 patients was closely studied and statistically analyzed.

## RESULTS

During the 20 month study period, a total of 140 patients with HF were analyzed for multiple variables. In our study, 69% (N=96) of patients were males, while only 31% (N=44) were females with a male: female ratio (M:F) 2.18:1, which was statistically significant ( $p < 0.001$ ). Among the study patients, females predominated in younger age groups, whereas males predominated in older age group (Fig. 1). Majority of the study patients had most of the symptoms

of CHF, and most common symptom was breathlessness (Fig. 2). As depicted in Fig. 3, 100% of the ischemic CMP cases occurred in males, While 61.8% of CRHD cases occurred in females and 38.2% in males.

Among the study patients, 67% of the patients were in NYHA class 4 (Table 1). Further categorizing the percent of males, and females in each NYHA class, 61% of male patients were in NYHA class 4, while 81.8% of female patients were in NYHA Class 4, which was not statistically significant ( $p < 0.05$ ). All the patients satisfied the criteria for diagnosis of Definite CHF, based on the Framingham criteria for diagnosis of CHF (Table 2).

The most frequent physical findings observed in the study were rales in 89% of patients, S3/S4 in 87%, apical impulse abnormality in 77%, murmurs in 72%, parasternal lift in 70%, raised JVP in 65% of patients. Only 9% of patients were obese and the mean BMI of the study group was within the normal range. As per Joint National Committee (JNC)-7 criteria for hypertension, a total of 26 (18%) patients were categorized as hypertensive. Among the study patients, the minimum systolic blood pressure (SBP) was found to be 70 mmHg and maximum SBP 250 mmHg. About 69% of the study population had SBP between 70 and 110 mmHg while 77% of the patients had diastolic blood pressure (DBP) between 41 and 80 mmHg, and 17% of the patients had DBP between 81 and 120 mmHg.

About 31% of the patients were found to be anemic, 20% had hyponatremia, which were poor prognosticators, 18% of the patients were diabetic and another 2.13% were hypothyroid. Table 3 depicts the 2D-Echo Doppler wise classification of HF of study patients, i.e., systolic HF(HF with depressed EF) and Diastolic HF(HF with preserved EF). The most frequent ECG abnormality was found CHF Triad (28%) and on chest X RAY examination 35% of the patients had cardiomegaly of biventricular contour. The 2D-Echo Doppler test showed that 57% of the patients were having diastolic HF and only 43% of patients had systolic HF, which was statistically significant ( $p < 0.001$ ). In the study, ischemic cardiomyopathy was found to be the leading cause of HF constituting 28%, followed by chronic rheumatic heart disease (CRHD) in 24%, hypertension- acute left ventricular failure (LVF) 18% and dilated cardiomyopathy in 14%, corpulmonale in 8%, Congenital Heart Disease in 4%, constrictive pericarditis in 2%, acute myocarditis in 1% and non-Rheumatic valvular heart disease in 1% of the patients.

About 36% of HFs in the study constituted of acute HF (which includes acute hypertensive LVF, acute MI and acute myocarditis), while 45% constituted of chronic HF and the remaining 19% was acute decompensation on chronic stable HF. Depending on the underlying etiological condition, the patients were treated appropriately (Table 4). The most frequent (42%) combination therapy used in the study patients was digoxin+furosemide+angiotensin converting enzyme inhibitor (ACEI), followed by digoxin and diuretics (27%), and ACEI+angiotensin receptor blocker (ARB)+-blocker (BB) (18%). With the treatment, the shortest recovery time was observed to be 3 days and the longest to be 23 days. There was no significant co-relation between NYHA class and recovery time, and the mortality was observed in 8 (5%) patients.

## DISCUSSION

In our study, 60% of the patients belonged to the 41-70 years age group, while in western studies most of the HF cases occurred above the age of 65 years. This predomi-

nance of HF among the lower age group in our study is due to<sup>6,9</sup> Rheumatic heart disease which usually occurs in children and adolescents. And In India, it can be found in infants and even among the middle aged and elderly though in lesser frequency.<sup>5</sup> This was similar to our study findings, where CRHD predominantly occurred in younger age groups while CAD occurred predominantly in older age groups.

In our study, the M:F ratio was found to be 2.18:1. This was due to CAD exclusively occurring in males and uncommon in females, while the chronic RHD (which manifests as HF at relatively younger age group compared to IHD) was less common in males (38.2%) and more common in females (61.8%).<sup>10</sup> Whereas in the western studies, the M:F ratio has been found to be 2:1, which was due to CAD predominantly occurring in males and half of the cases of HF occurring in females due to their longevity of life.<sup>11</sup> Though the M:F ratio of our study and western studies is similar, the etiological factors are varying with IHDs being predominant in western studies while IHD and CRHDs were predominant in our study. These results go in line with another study, which noted that IHD was more common than RHD. The M:F ratio 2.18:1 in our study was due to 100% of ischemic cardiomyopathy and some percent of CRHD-CHF occurring in males, while in females only CRHD-CHF occurred, though more frequently compared to males. With westernization and improved lifestyle, infections ought to reduce in India, thereby reducing the incidence of Group A Beta Hemolytic streptococcal infection, Acute Rheumatic fever, CRHD leading to HF, still CRHD remains the second most common cause of HF although, in one of the studies conducted in a developing country, it was found that incidence of CRHD was more common than IHD.

In contrast to this, a study conducted in India claims that RHD is the fourth leading cause of HF, which is more prevalent in age groups between 16 to 25 years, with a M:F ratio about 1:2.5.

Majority of our study patients had most of the symptoms of CHF like breathlessness in 100%, and the least common symptom was hemoptysis in 14%, which is in line with available studies. Our study patients had physical findings like raised JVP in 65% S3/ S4 in 87%, which is consistent with data from the other study. As per the Framingham criteria for the diagnosis of CHF, the major criteria made out in our study population were paroxysmal nocturnal dyspnea (PND) or orthopnea in 54%, neck vein distension 65% and the minor criteria made out were night cough in 72%, dyspnea on exertion in 80% and hepatomegaly in 72% and ankle edema 69%, and all the patients satisfied the Framingham criteria for a diagnosis of Definite CHF. Whereas in the western studies, the predominant major criteria are S3 gallop, rales, PND or orthopnea and acute pulmonary edema and the predominant minor criteria are night cough, dyspnea on exertion (DOE) and pleural effusions and all the patients satisfy the criteria for diagnosis of definite CHF.

In our study, 69% of the patients had SBP between 70-110 mmHg and 16% had SBP of 111-150 mmHg and the highest recorded SBP was 230 mmHg, indicating that low output cardiac failure was predominant. The DBP was between 41-80 mmHg in 77% and between 81-120 mmHg in 17% and only in 6% the DBP was >120 mmHg. The pulse pressure (difference between SBP and DBP) was narrow, once again indicating that low output cardiac failure was

predominant in our study. As per the JNC-7 criteria for diagnosis of hypertension, 18% of our study patients were diagnosed to be hypertensive, 69% had less than normal BP and 13% were in the normotensive range. This is in contrast to the western data where among patients with a clinical diagnosis of HF, 75% had hypertension and this was the sole cause for HF in 25% of the patients. This also concludes that Hypertension was not the most predominant cause of HF in our study.<sup>15</sup>

According to NYHA classification, 67% of the study patients were classified as NYHA Class 4, followed by 23% in to NYHA Class 3 and just 8% in class 2, indicating that most of our patients were getting hospitalized in advanced stage of HF i.e. stage C and D, thus adversely affecting the outcome. Sixty seven percent of the patients being in NYHA Class 4 is a typical setting in developing countries, with similar findings in India also. It was also observed that 61% of male patients were in NYHA class 4 and 81.8% of female patients were in NYHA Class 4, which was statistically significant ( $p < 0.05\%$ ). This also indicates that women's health is getting lesser priority in developing countries.

The most frequent ECG abnormalities observed in the descending order of frequency were ST elevation and LV strain in 30%, CHF Triad in 28%, atrial fibrillation in 15% and right ventricular strain in 9% of patients. It may be remembered that no ECG feature is characteristic of CHF and they may only reflect a cause of CHF and our data is consistent with the same. The chest X-ray abnormalities that were seen in our study were cardiomegaly (bi-ventricular contour) in 37%, left ventricular contour in 29% of patients, right ventricular contour in 18% of patients, and there was no cardiomegaly in 16% of patients, which is again consistent with the statement that "CHF is no longer synonymous to cardiomegaly."

In our study, the investigation of choice for the anatomical, pathological and etiological diagnosis for CHF has been 2D-Echo Doppler. Now-a-days, the CHF is no longer classified as low output failure/ high output failure, right HF/ left HF, forward failure/ backward failure and the present day CHF classification with respect to etiology is in terms of CHF with depressed ejection fraction ( $EF < 40\%$ ) (systolic HF) and CHF with preserved  $EF > 40-50\%$  (diastolic HF). Presently in the community studies it has been shown that about half of the HFs are diastolic in nature,<sup>16</sup> whereas in our study it was slightly high i.e., 57% of HFs were diastolic in nature i.e.  $EF > 40-50\%$ . Ejection fraction-wise etiology in our study was consistent with standard text book description i.e. concordance in 87% discordance in 6.5% and equivocal 6.5%, which is acceptable by any standards.

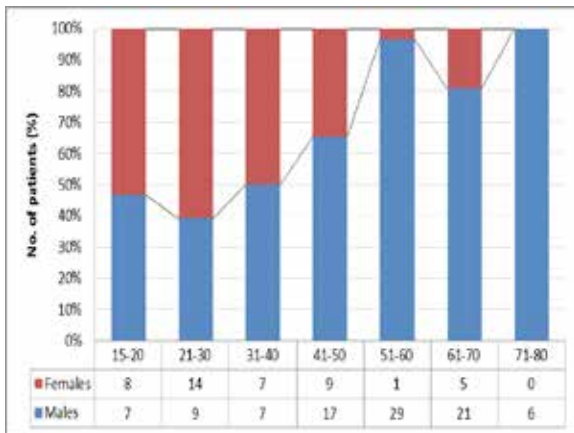
The most frequent abnormalities detected on 2D-Echo Doppler were evidence of CAD like RWMA or Global hypokinesia in 28%, CRHD in 24%, LVH in 18%, evidence of cor-pulmonale including IPAH 8%, DCM including peripartum cardiomyopathy in 14%, which was not in concordance with global data, which show the predominant cause for CHF as CAD followed by hypertension and cardiomyopathies.<sup>17-22</sup> The above said diagnosis was made after detailed symptom and sign evaluation, thorough laboratory investigations like ECG, Chest X-Ray and 2D-Echo Doppler. Because the most common causative factor was ischemic cardiomyopathy, majority of the study patients (42%) were treated with digoxin+diuretic+ACEI, and most of the patients (83%) recovered well within 1-2 weeks. The mortality rate was found to be 5%.

**CONCLUSION**

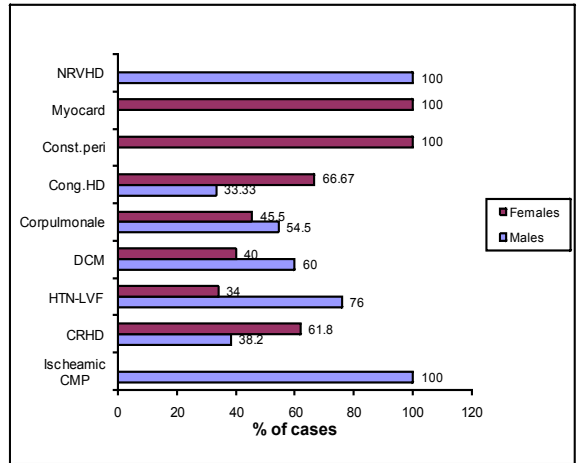
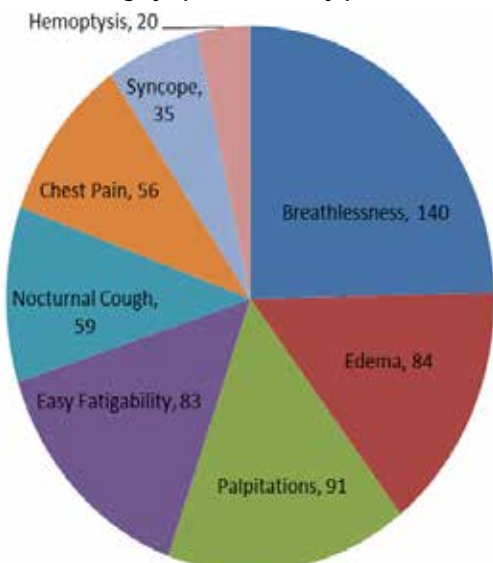
Despite many recent advances in the evaluation and management of HF, the development of symptomatic HF still carries a poor prognosis. Although IHD is the predominant cause of HF, CRHD is also a very important cause of HF and hypertension being third most frequent etiology. In our study, the predominant age group affected was 41-70 years and 15-30 years. Chronic rheumatic heart disease predominantly occurred in females and in younger age groups while CAD occurred exclusively in males and in older age groups. Though the male female ratio of our study and western studies is similar, the etiological factors were varying with IHDs being predominant in western studies while IHD and CRHDs were predominant in our study. 2-D Echocardiography is essential for diagnosis and assessment of prognosis of HF. Most of the study patients (83%) recovered within 1-2 weeks and mortality rate was found 5%. Chronic rheumatic heart disease can be effectively handled by taking some steps to eradicate group A -hemolytic streptococcus infection, which may include community awareness to seek medical attention early, also medical community education to pick-up cases early and promptly institute appropriate therapies.

**FIGURES**

**Fig. 1: Age sub group and male and female distribution of study patients**



**Fig. 2: Presenting symptoms of study patients (n)**



**Fig.3: Gender distribution on etiological basis of study patients**

**TABLES**

**Table 1: Classification of study patients according to NYHA**

Functional Capacity	Male	Female	Total	%
Class I	0	0	0	0
Class II	10	2	12	9
Class III	27	6	33	23
Class IV	59	36	95	68
Total	96	44	140	100

**NYHA: New York Heart Association**

**Table 2: Diagnosis of CHF in study patients according to Framingham's criteria**

Criteria	Parameter	No. of Patients (%)
Major Criteria	PND or Orthopnea	76 (54)
	Neck Vein Distension	92 (65)
	Rales	123 (87)
	Cardiomegaly	114 (81)
	Acute Pulmonary edema	35 (25)
	S3 Gallop	112 (80)
	JVP >16 cms H2O	92 (65)
Minor Criteria	Hepatojugular Reflex	66 (47)
	Ankle Edema	97 (69)
	Night cough	101 (72)
	DOE	112 (80)
	Hepatomegaly	102 (72)
	Pleural Effusion	31 (22)
	Tachycardia (HR>120)/min	42 (30)
Major or Minor Criteria	Weight Loss>4.5 kg on Rx	95 (67)

**PND: Paroxysmal nocturnal dyspnea; JVP: Jugular Venous Pressure; DOE: Dyspnea on Exertion; HR: Heart Rate; Rx: Medication**

**Table 3: Study patients had following 2D-Echo Doppler wise classification of HF**

	EF<40% Systolic HF	EF>40-50% Diastolic HF	Total N	%
Male	51	45	96	69
Female	8	36	44	31
Total	59	81	140	100
Percentage	43	57	***	***

**HF: Heart Failure****Table 4: Treatment allocation among study patients**

Treatment	Numbers
Digoxin, Diuretics	38 (27)
Digoxin, Furosemide, ACEI	59 (42)
ACEI, Furosemide	6 (5)
Others (Amlodipine, Aspirin, Antibiotic, Streptokinase)	5 (3.5)
Streptokinase, Nitroglycerine, Furosemide, CCB	5 (3.5)
Streptokinase, Nitroglycerine, Furosemide	1 (0.7)
ACEI + ARB + BB	26 (18.3)
Total	140

**ACEI: Angiotensin Converting Enzyme Inhibitors; CCB: Calcium Channel Blocker; ARB: Angiotensin Receptor Blocker; BB: Beta-Blocker**

**REFERENCES:**

- Devasia T, Nandibandi SD, Bhat R, Kareem H and Thakkar A. Clinical profile and treatment management of heart failure with preserved systolic function in rural setting of India. *Int J Clin Med.* 2014;5:171-176.
- Cowie M, Mosterd A, Wood D, Deckers J, Poole-Wilson P and Sutton G. The epidemiology of heart failure. *Euro Heart J.* 1997;18:208-225.
- Reddy S, Bahl A and Talwar KK. Congestive heart failure in Indians: How do we improve diagnosis & management? *Indian J Med Res.* 2010 Nov; 132(5): 549-560.
- Sainani GS and Sainani AR. Rheumatic Fever - How Relevant in India Today? *JAPI.* 2006;54:42-47.
- Lalchandani AD, Godara M and Mathiyalagan N. Section 10: Valvular Heart Disease. Chapter 106: Rheumatic Heart Disease: Epidemiology and Management. Available at: [http://www.csi.org.in/Cardio\\_pdf/SEC\\_10/Ch-106.pdf](http://www.csi.org.in/Cardio_pdf/SEC_10/Ch-106.pdf). Accessed on: 18 Jul 2015.
- Mosterd A, and Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;93:1137-1146.
- Goldberg LR and Jessup M. Stage B Heart Failure: Management of asymptomatic left ventricular systolic dysfunction. *Circulation.* 2006;113:2851-2860.
- Sinescu C and Axente L. Heart failure—concepts and significance. Birth of a prognostic model. *J Med Life.* 2010;3(4):421-429.
- Dec GW, Palacios IF, Fallon JT, Aretz HT, Mills J, Lee DC, et al. Active myocarditis in the spectrum of acute dilated cardiomyopathies: Clinical features, histologic correlates, and clinical outcome. *N Engl J Med.* 1985;312:885-890.
- Fauci AS, Braunwald E, Kasper ES, Hauser SL, Longo DL, Jameson JL, eds. In: *Harrison's Principles of Internal Medicine*, 17th Edition, McGraw Hill Education, 2008: Pages 1480,1444,14802092,2093,2094.
- Shiina Y, Igarashi M, Yoshioka K, Tanabe T and Handa S. Clinical profile and prognosis of hospitalized patients with congestive heart failure in Isehara, Japan. *Tokai J Exp Clin Med.* 2005;30(3):141-1418.
- Khan Z, Khan B, Hiader I, Khan I, Din J, Khan H, et al. Etiology of congestive heart failure at a tertiary care hospital. *RMJ.* 2010; 35(2):141-144.
- Ogah OS, Stewart S, Falase AO, Akinoyemi JO, Adegbite GD, Alabi AA, et al. Contemporary profile of acute heart failure in southern Nigeria: Data from the Abeokuta Heart Failure Clinical Registry. *JCHF.* 2014;2(3):250-259.
- Patel SN, Yeshwanth P and Rampure DM. A study on clinical and etiological profile of heart failure at Mamata General Hospital. *Sch. J. App. Med. Sci.*, 2014; 2(6G):3370-3374.
- Coronary heart disease (10-year risk). Framingham Heart Study. Available at: <https://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/10-year-risk.php>. Accessed on: 31 Mar 2015.
- Leeder S and Raymond S. A race against time: The challenge of cardiovascular disease in developing economies. Columbia University, City of New York, 2004.
- Cowie MR, Wood DA, Coats AJS, Thompson SG, Poole-Wilson PA,

Suresh V, et al. Incidence and aetiology of heart failure: A population-based study. *Euro Heart J.* 1999;20:421-428.

- Cubillos-Garzón LA, Casas JP, Morillo CA and Bautista LE. Congestive heart failure in Latin America: the next epidemic. *Am Heart J.* 2004;147(3):412-417.
- Effects of enalapril on mortality in severe congestive heart failure: The Consensus Trial Study Group. *N Engl J Med.* 1987;316:1429-1435.
- Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN, et al. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. *Circulation.* 1999;99:2658-2664.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293-302.
- Mackowiak PA, Jones SR and Smith JW. Diagnostic value of sinus-tract cultures in chronic osteomyelitis. *JAMA.* 1978;239:2772-2775.