

ASSOCIATION BETWEEN COMMON CARDIOVASCULAR RISK FACTORS AND HEART FAILURE WITH NORMAL EJECTION FRACTION

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Contribution

All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: The objective of this study was to determine the association between common risk factors and heart failure with normal ejection fraction (HFNEF).

Methodology: This was a case control study conducted at Department of Cardiology, Lady Reading Hospital (LRH), Peshawar from March 2011 to November 2011. Patients having HFNEF, of both genders with age ≥ 40 years were taken as cases. Parents of children presented to Pediatric out patient department (OPD) of LRH Peshawar, of both gender with age ≥ 40 years were taken as control. Cases and controls were carefully scrutinized for the detection of common risk factors like obesity, hypertension, diabetes and coronary artery disease (CAD). Logistic regression was used to see the effect of risk factors in both the groups. Odds ratio and p-value was calculated for each risk factor in both the groups.

Results: A total of 139 patients each in cases and control groups were studied. In the cases and controls, males were 45.3% and 49.6% respectively. The average age was 56.64 ± 10 years for the cases and 48.92 ± 10 years for controls. Hypertension was noted in 54.7% and 29.5% of cases and controls respectively (OR = 3.543, p = 0.000), CAD in 34.5% and 6.5% of cases and controls (OR = 7.619, p = 0.000), Diabetes mellitus in 33.1% and 10.1% (OR = 4.416, p = 0.000), and Obesity in 15.1% and 20.1% cases and controls (OR = 0.706, p = 0.271).

Conclusion: CAD, hypertension, and diabetes mellitus are strongly associated clinical risk factors in patients with HFNEF.

Key Words: Heart Failure With Normal Ejection Fraction (HFNEF), Risk Factors, Diastolic Dysfunction, Transthoracic Echocardiography, Tissue Doppler Imaging (TDI)

INTRODUCTION

Heart failure (HF) is a complex syndrome, resulting from structural or functional cardiac disorders that impair the ability of the cardiac pump to support a physiological circulation.¹ Congestive heart failure affects about 2% of the western population, with prevalence increasing sharply from 1% in 40 years to 10% above age 75 and it is the most common cause of hospitalization in patients over 65 years of age.² Patients with an ejection fraction of 50 percent or higher were classified as having heart failure with normal ejection fraction (HFNEF), whereas those with an ejection fraction of less than 50 percent were classified as having heart failure with reduced ejection fraction (HFREF).³ The proportion of patients with HFNEF is about 50% in the general heart failure population.² The symptoms of heart failure may be identical whether failure is secondary to systolic or diastolic dysfunction, however, there are differences in the prognosis, characteristics of the patients, pathophysiology and treatment between the two conditions.⁴ Compared to patients with a low ejection fraction, those with preserved ejection fraction are older, more often women and are more likely to have a hypertensive aetiology.⁵ Hypertension is the most common cause of diastolic dysfunction and diastolic heart failure that is about 60%.⁶ Recent data suggested that coronary artery disease is a cause of diastolic dysfunction in approximately 1/3rd of patients.⁶ Obesity alone is the cause of 11% cases of cardiac failure in men and 14% of cases in women in United States.⁶ Many reports have shown a prevalence of about 30-60% of diastolic dysfunction even in well controlled diabetics.⁶ A history of coronary artery disease was associated with the greatest risk of heart failure (29.1% vs 11.86% OR 3.05, 95% CI) followed by diabetes (18.5% vs 7.89%, OR 2.65, 95% CI), obesity (24.5% vs 9.28%, OR 2.00, 95% CI) and hypertension (61.2% vs 57.62%, OR 1.44, 95% CI) with the p value of less than 0.001 for each.⁷

The most useful clinical tools for the assessment of left ventricular diastolic function is Conventional Doppler Echocardiography, not only utilized for diagnostic purposes but also for establishing prognosis and evaluating the effect of treatment.⁸ Tissue Doppler imaging (TDI), including the transmitral flow velocity to annular velocity ratio (E/E' index), which measures myocardial velocities during the cardiac cycle, is considered more reliable for diagnosing diastolic dysfunction.⁹

Heart failure with preserved ejection fraction becomes the most common form of heart failure, representing slightly more than half of all cases of heart failure.¹⁰ Its frequency increases dramatically with age underscoring the importance of this growing public health problem.¹⁰ One study indicates that the prognosis of patients with HFNEF is poor, and just as severe as in patients with reduced ejection fraction.¹⁰ Thus, both conditions have a severe prognosis

with 5 years mortality rates of almost 60%.¹⁰

The best strategy for avoidance of morbidity and mortality from HFNEF is prevention and control of risk factors. This study has important public health implication, and will help the physicians in suggesting that targeting specific and most commonly found risk factor on the basis of odds ratio may have the greatest impact on reducing the number of heart failure with normal ejection fraction cases in our population. The aim of this study was to know about the association of common and important risk factors leading to HFNEF.

METHODOLOGY

This was a Case Control study conducted at the department of cardiology, Post Graduate Medical Institute, Lady Reading Hospital Peshawar from March 2011 to November 2011. The study was conducted after approval from hospital ethical and research committee.

HFNEF was diagnosed on the basis of all of the following features:

1. History of shortness of breath on exertion.
2. Left ventricular ejection fraction of $\geq 50\%$ on Transthoracic Echocardiography.
3. E to A ratio of < 1 on Transthoracic Echocardiography.
4. $E/E' > 15$ on Transthoracic Echocardiography.

Our study cases included all patients of both gender and age 40 years and above with heart failure with normal ejection fraction (HFNEF). Controls were volunteered parents of children coming to paediatric out patient department (OPD) of Lady Reading Hospital Peshawar, of age ≥ 40 years and of both gender and no evidence of HFNEF.

Sample size was 139 in each group using 7.89% proportion of Diabetes in patients with normal echocardiography and no heart failure⁷, 18.5% probability of diabetes among patient with HFNEF⁷, 5% level of significance and 80% power of test and 2.65% of odds ratio under WHO software for sample size determination.

Patients with Congenital heart disease, Valvular heart disease, Rheumatic heart disease and technically difficult cases were excluded from the study.

All cases and controls were subjected to detailed history and clinical examination. Their clinical record was checked, BMI calculated and fresh ECG, Transthoracic echocardiography and lab investigation for blood sugars was done. Both cases and controls were carefully scrutinized for common risk factors including obesity (BMI 30 or more), hypertension (Patients taking antihypertensive medications or having blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic), diabetes (Random blood sugar > 200 mg/dl or subject already on anti diabetic medications) and coronary

artery disease (history of CAD or evidence of CAD on ECG/ echocardiography).

All the above mentioned information including name, age, and gender were recorded in a pre designed Performa. Strictly care was taken in selection of both cases and controls to avoid selection bias. Similarly care was taken during extraction of information to avoid responder bias.

The statistical analysis performed using the statistical package for social sciences (SPSS Ver. 15.0). Numerical variables like age were presented as mean \pm SD. Categorical variables like gender and common risk factors (Coronary artery disease, hypertension, Diabetes mellitus and obesity) were presented as frequencies and percentages. Logistic regression was used to see the effect of risk factors in both the groups. Although odds ratio was calculated for each risk factor in both the groups. Also chi square test was used to compare the age and sex in both the groups to see the effect modification.

RESULTS

The total number of study population was 139 in each group. In the cases, 45.3% (n=63) were male and 54.7% (n=76) were female, while in controls, 49.6% (n=69) were male and 50.4% (n=70) were female (Table 1). Gender was equally distributed with p-value=0.471. The mean age was 56.64 ± 10 years for cases and 48.92 ± 10 years for controls. Cases and controls were divided into two groups on the basis of age of 70 years. The cases and controls of less than 70 years of age were 87.1% (n=121) and 99.3% (n=138) respectively and the cases and controls of more than 70 years of age were 12.9% (n= 18) and 0.1% (n=1) respectively.

In this study, Diabetes mellitus (DM) was found in 33.1% (n=46) of the cases and 10.1% (n=14) of controls with odd ratio (OR) of 4.416 and p-value of 0.000. Obesity was found in 15.1% (n=21) of the cases and 20.1% (n=28) of controls. It was equally distributed in both cases and controls with OR of .706 and p-value of 0.271. Hypertension was significantly more common in cases 54.7% (n=83) compared to 29.5% (n=41) in controls, with odd ratio of

Table 1: Gender Wise Data Distribution in Case and Control Groups

Gender	Groups		Total	P-value	Odd ratio for gender (m/f) (95% confidence intervals)
	Cases	Control			
Male	N	63	69	.471	.841 (.525-1.347)
	%	45.3%	49.6%		
Female	N	76	70		
	%	54.7%	50.4%		
Total	N	139	139	278	

Table 2: Distribution of Risk Factors in Cases and Controls

Variable	Cases % (n)	Controls % (n)	P-value	Odd ratio (95% CI)
DM	33.1(46)	10.1(14)	.000	4.416(2.29-8.50)
OBESITY	15.1(21)	20.1(28)	0.271	.706(.379-1.315)
HTN	59.7(83)	29.5(41)	0.000	3.543 (2.154-5.826)
CAD	34.5(48)	6.5(9)	0.000	7.619 (3.561-16.303)

3.543 and p-value of 0.000. Coronary artery disease (CAD) was noted in 34.5% (n=48) of the cases and 6.5% (n=9) of controls. It showed that coronary artery disease was more common in patients with diastolic heart failure, odd ratio 7.619 and p-value of 0.000 (Table 2).

Of cases Sixty one (43.88%) patients had more than one risk factor contributing to diastolic dysfunction. Thirteen (9.35%) had hypertension and CAD, 8 (5.76%) had CAD and DM, 10 (7.19%) had DM and hypertension, 2 (1.44%) had hypertension and obesity, 2 (1.44%) had DM and obesity, 10 (7.19%) had hypertension plus CAD plus DM, 8 (5.76%) had HTN plus obesity plus DM, 4 (2.88%) had HTN plus CAD plus obesity, 2 (1.44%) had DM plus CAD plus obesity and in the last 2 (1.44%) had CAD, hypertension, DM and obesity (Table 3).

DISCUSSION

Heart failure with normal ejection fraction (HFNEF) or diastolic heart failure (DHF) is defined as failure of left ventricle to produce an adequate cardiac output at normal left ventricular filling pressure despite the presence of a normal left ventricular ejection fraction.¹¹ In the past, all the patients presented with cardiac failure were labeled as having systolic dysfunction, reason being that the diagnosis of diastolic dysfunction / diastolic heart failure was always been dubious before the advent of Doppler echocardiography. Results of early studies suggested that as many as 40% of patients with heart failure have isolated HFNEF.¹² However more recent data shows that the prevalence of diastolic dysfunction and Diastolic heart failure is dependent on age, sex, study setting (e.g Hospital vs. Community), methods used to make the diagnosis (Echocardiography vs Invasive techniques), LVEF cutoff 40% vs 50% and the underlying disease that contribute to diastolic dysfunction.¹³ One study indicates that the prognosis of patients with HFNEF is poor, and just as severe as in patients with reduced ejection fraction.¹⁰

In this case control study we found that most of our patients were female (52.5%) and of less than 70 years old. This

Table 3: Data Distribution of Patients Having More Than One Risk Factor in Cases

Cases having more than one risk factors		
Risk Factors	No. of Pts	Percentage
HTN + DM	10	7.19
HTN + IHD	13	9.35
DM + IHD	8	5.76
HTN + OBESITY	2	1.44
DM + OBESITY	2	1.44
HTN + IHD + DM	10	7.19
HTN + OBESITY + DM	8	5.76
HTN + CAD + OBESITY	4	2.88
DM + IHD + OBESITY	2	1.44
HTN + IHD + DM + OBESITY	2	1.44

study indicates that coronary disease, hypertension, diabetes and obesity are common risk factors for diastolic heart failure in both men and women. The risk of heart failure is greatest for coronary disease and diabetes, while coronary disease and hypertension are responsible for the largest proportion of new diastolic heart failure cases in the population. Sex differences in the etiology of diastolic heart failure may exist with hypertension playing the greatest role in women and coronary disease in men and similar findings were noted by Dunlay et al.⁷

Hypertension was the most common risk factor of HFNEF i-e 59.7% of patients having diastolic heart failure had HTN and was most common in women (60.24%). Similar findings were reported by Jonathan et al, who reported that hypertension is the most common risk factor for the DHF.¹⁴ The Framingham study showed that 75 % of patients with DHF have hypertension.¹⁵ All the previous studies showed that hypertension is the most common cause of diastolic dysfunction / DHF and DHF is the most common cause of morbidity and mortality in hypertensive patients especially African American even more than IHD (62% vs. 44%).

In this study, coronary artery disease as a risk factor for HFNEF is the second most common risk factor i-e (34.5%). Limited data is available on the prevalence of cardiac failure with preserved systolic function in patients with coronary artery disease. Some studies suggested that the prevalence of cardiac failure with preserved systolic function after myocardial infarction was as high as 45 %.¹⁶ These studies however are mostly case series so their estimates of prevalence may be subject to selection bias. The exact prevalence of patients with cardiac failure and preserved systolic function with CAD in the community is not known. Hellermann et al, reported that 30% of patients after myocardial infarction with heart failure have preserved left

ventricular systolic function which is consistent with our study results.¹⁷ Other studies showed this prevalence rate between 27-45% for patients with heart failure and preserved systolic function (EF >50%) and coronary artery disease as the underlying condition and these results are also consistent with the current study results.¹⁶ Koren also reported that CAD is a contributing factor of diastolic dysfunction in heart failure patients in approximately one third of patients which coincide with our results.¹⁸

Obesity as a risk factor for HFNEF was noted in 15.1% in the cases (men=5.76, women=9.35) and 20.1% in controls with odds ratio of 0.706 and p-value of 0.271 which is not significant and it might be because of that our study population is small. Grossman et al, reported that obesity alone is the cause of 11 % cases of HFNEF in men and 14 % of cases in women.¹¹

In the current study, 33.1% of the cases and 10.1% of controls had diabetes mellitus, with an odd ratio of 4.416 and p-value of 0.00. Diabetes mellitus was more prevalent in the female study population (56.52% vs. 43.48%). The presence of isolated diastolic dysfunction in diabetic patients in the absence of hypertension and IHD was first described by Rubler et al.¹⁹ Braga et al, reported that diastolic dysfunction precedes the systolic changes in the diabetic heart even in the absence of CAD.²⁰ Many reports have shown prevalence of diastolic dysfunction from 30 - 60 % in diabetic persons and these results coincide with the current study. O'Connor et al, found that about 30 % patients with diastolic dysfunction / DHF also were suffering from diabetes mellitus in the absence of obstructive CAD and hypertension.²¹

There were certain study limitations. This was a small single centre study and therefore larger studies are recommended to validate and generalize the findings of this study. Majority of our study population was younger while HFNEF is a major cause of heart failure in elderly population.

CONCLUSION

Coronary artery disease, hypertension, and diabetes mellitus and obesity are commonly found risk factors in patients with heart failure with normal ejection fraction (HFNEF). There is strong association between Coronary artery disease, diabetes mellitus and arterial hypertension, and the development of diastolic dysfunction and heart failure with normal ejection fraction.

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