International Journal of Research in Medical Sciences
*Palkhiwala NB et al. Int J Res Med Sci. 2020 Aug;8(8):2753-2760*
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20203099

**Original Research Article**

# Clinical profile of patients presenting with heart failure with preserved ejection fraction

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**Received:** 16 June 2020
**Revised:** 06 July 2020
**Accepted:** 10 July 2020

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## ABSTRACT

**Background:** Evaluate the clinical profile of patients presenting with heart failure having normal or preserved ejection fraction and to determine the prevalence of comorbid illnesses in these patients.
**Methods:** The study was carried out on patients that presented with heart failure at the Vadilal Sarabhai hospital, Ahmedabad between September 2014-2016. Heart failure patients with normal ejection fraction (>50%) were selected. Socio-demographic, vital signs, data of 2D Echocardiography and Tissue Doppler study were collected. The patients were classified as per the Echocardiographic study into four categories. Different laboratory parameters were compared in patients with respect to (a) grade of Hypertension (b), grade of anemia (c), HbA1c levels. Statistical analysis was done using the SPSS software v20. Mann-Whitney and Kruskal-Wallis tests were performed to compare the means between different study groups.
**Results:** Out of the 70 patients, a majority (47%) belonged to the Grade 2 (pseudo-normalized) group of diastolic dysfunctions with most of them having only dyspnea and pedal edema (33%). 58.6% patients required intensive care for at least one day. Regarding co-morbidities 27 (38.6%) had hypertension, 34 (48.6%) were diabetic and 49(70%) had anemia. Patients with higher grade of dysfunction had higher HbA1c (p=0.023) and worsening anemia (p=0.003).
**Conclusions:** Authors concluded that it is of prime importance to find, prevent and treat the comorbidities along with targeted therapies for HFpEF. Further evaluation can be done for clinical applicability of different markers including HbA1c and U.ACR for renal dysfunction in HFpEF.

**Keywords:** Diastolic dysfunction heart failure, Diastolic heart failure, Heart failure, Heart failure with a normal EF, Heart failure with normal systolic function, Preserved ejection fraction

## INTRODUCTION

Twenty-five years ago, heart failure (HF) was understood as a clinical syndrome due to left ventricular (LV) systolic dysfunction apparent as reduced ejection fraction (HFrEF).[1] Finding a reduced EF in a patient with clinical signs and symptoms of HF provides objective documentation of cardiac dysfunction, thus making it almost certain that the patient does indeed have HF. However, in large randomized controlled trials, positive

inotropic agents proved to be detrimental in such patients with HF, which led to the challenging thoughts of the possibility of something beyond the understanding of HF then.[2-4]

As demonstrated by Kitzman et al in 1991, on invasive cardiopulmonary exercise testing, the patients failed to improve their end-diastolic volume with increasing filling pressures leading to a marked increase in the pulmonary capillary wedge pressures and a reduction in the exercise tolerance. This inability to follow the frank-starling principle demonstrated the presence of diastolic dysfunction in patients who were subjected to exercise.[5] A variety of terms have been used to describe patients with what is now called heart failure with a preserved ejection fraction (HFpEF). These terms include heart failure with a normal EF, heart failure with normal systolic function, diastolic heart failure, and diastolic dysfunction heart failure. These patients do not necessarily have an absolute normal systolic function (longitudinal mid-wall strain) nor do they have isolated diastolic dysfunction, hence the term heart failure with a preserved ejection fraction (HFpEF) is the preferred one.[6]

Majority of patients (more than 50% in many studies), who are diagnosed or hospitalized with heart failure have HFpEF (Heart Failure with Preserved Ejection Fraction).[2,7] Regardless of ejection fraction status (EF value), patients with HFpEF have the clinical syndrome of heart failure. In addition, many features are similar to the patients with HFrEF (heart failure with reduced ejection fraction), including abnormal left ventricular (LV) filling dynamics, elevated LV diastolic pressure, LV systolic and diastolic dysfunction, neuro-hormonal activation, impaired exercise tolerance, frequent hospitalizations, and reduced survival.[1,8-10]

Patients with HFpEF have a devastating 5-year mortality rate (approaching 60%), high-cost morbidity (6-month hospitalization rate of 50%), and debilitating symptoms (maximum myocardial oxygen consumption (MVO2) averaging 14 mL/g/min).[11,12] There is a substantial rise in the prevalence of this syndrome with increased longevity and increase in the co-morbid conditions such as hypertension, diabetes mellitus and obesity. Standard heart failure therapy is unable to reduce the morbidity and mortality associated with HFpEF, hence leaving a vast area for future research.[3]

In this study, the clinical profile of seventy patients has been studied in terms of clinical presentation and morbidity with respect to Echocardiographic grades of diastolic dysfunction and their associated co-morbidities such as hypertension, diabetes mellitus, obesity, thyroid dysfunction, anemia and chronic kidney disease.

The main aim of the study was to evaluate the clinical profile of patients presenting with heart failure with a normal or preserved ejection fraction and to determine the prevalence of comorbid illnesses in these patients.

Other objectives of this study were as follows:

- To evaluate the signs and symptoms and distribute them with respect to various grades of diastolic dysfunction.
- To evaluate the morbidity of the patients.
- Various changes in the electrocardiogram and chest roentgenogram with respect to grades of diastolic dysfunction
- The prevalence of associated morbidities and its distribution with respect to their grades that of diastolic dysfunction

## METHODS

This prospective observational study was conducted with Heart failure patients with EF >50% with 70 sample size in September 2014 to September 2016.

### *Inclusion criteria*

- Clinical presentation of heart failure (Framingham criteria)
- LV ejection fraction >50%
- Echocardiographic evidence of diastolic dysfunction

### *Exclusion criteria*

- Chronic pulmonary disease
- Pulmonary thromboembolism
- Systolic heart failure
- Dilated cardiomyopathy
- Valvular heart disease
- Peri-partum cardiomyopathy
- Sepsis
- Myocarditis
- Acute coronary syndrome

**Table 1: Grades of diastolic dysfunction.**

| Grades | Description |
|---|---|
| Grade 1 (Abnormal relaxation) | E/A <0.8 |
| | DT >200 ms |
| | E/e' <= 8 |
| Grade 2 (Pseudo-normal) | E/A = 0.8-1.5 |
| | DT 160-200 ms |
| | E/e' 9-12 |
| Grade 3 (Restrictive reversible) | E/A >= 2 |
| | DT <160 ms |
| | E/e' >= 13 (This parameter reverses with valsalva or another preload reducing maneuver.) |
| Grade 4 (Irreversible restrictive) | Same as grade 3 but irreversible with with valsalva or another preload reducing maneuver. |

Out of all the patients attending the outpatient department and the emergency room with heart failure (fulfilling the criteria of heart failure according to the Framingham criteria) seventy patients with normal ejection fraction (>50%) were selected, preliminarily treated and stabilized.[13]

**Table 2: Grades of hypertension (JNC 7).**

| Class | Systolic blood pressure | Diastolic blood pressure |
|---|---|---|
| Normal | <120 | AND <80 |
| Pre-Hypertension | 120-139 | OR 80-89 |
| Grade 1 | 140-159 | OR 90-99 |
| Grade 2 | ≥160 | OR ≥100 |

After taking an informed written consent, socio-demographic and vital data were collected for these patients and they were subjected to Echocardiography and Tissue Doppler study.

Essential laboratory tests were performed, and special tests were conducted as and when required as per the patients' consent.

The patients were classified according to the Echocardiographic and tissue Doppler study into four categories. (Table 1) N-terminal Brain Natriuretic Peptide levels were measured. Patients were also grouped with respect to grade of hypertension (Table 2), grade of anemia (Table 3), HbA1c levels (Table 4).[14-16] Statistical analysis was carried out using the SPSS software version 20. Means and standard deviation were calculated for various parameters. Descriptive analysis was performed. Mann-Whitney and Kruskal-Wallis tests were performed to compare the means between different study groups. Following gradings were used for detailed analysis.

**Table 3: Grades of anemia (WHO).**

| Population (>15 years of age) | Non-anemia hemoglobin (g%) | Anemia - hemoglobin (g%) | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| Non-pregnant Females | ≥12 | 10-11.9 | 8-10.9 | <8 |
| Pregnant Females | ≥11 | 10-10.9 | 7-9.9 | <7 |
| Males | ≥13 | 11-12.9 | 8-10.9 | <8 |

## RESULTS

Total data of 70 patients was collected. The mean age of patients was 53.33+/-14.3 years. 35 were male and 35 were female. The mean body mass index was 24.9±3.2 with only 6 patients in the obese category (<10%) whereas, 27 were pre-obese. (38.5%)

**Table 4: According to HbA1c levels.**

| Class | HbA1c (%) |
|---|---|
| Normal or well-controlled | <5.7 |
| Pre-diabetic or Impaired glucose tolerance | 5.7-6.4 |
| Diabetes Mellitus or Uncontrolled | >6.4% |

### *Clinical presentation*

The mean systolic blood pressure was 138.9 mmHg±25.8 and mean diastolic blood pressure was 79.6 mmHg±11.5. 7 patients presented with accelerated hypertension with a blood pressure of >160/100 mmHg, 5 of whom had S3 gallop and pulmonary rales and all of whom had significant LV hypertrophy, confirmed later by 2D-Echocardiography and had a raised NT-pro BNP level.

All 70 patients had dyspnea on exertion. Distribution of patients according clinical picture with respect to grades of diastolic dysfunction is as follows:

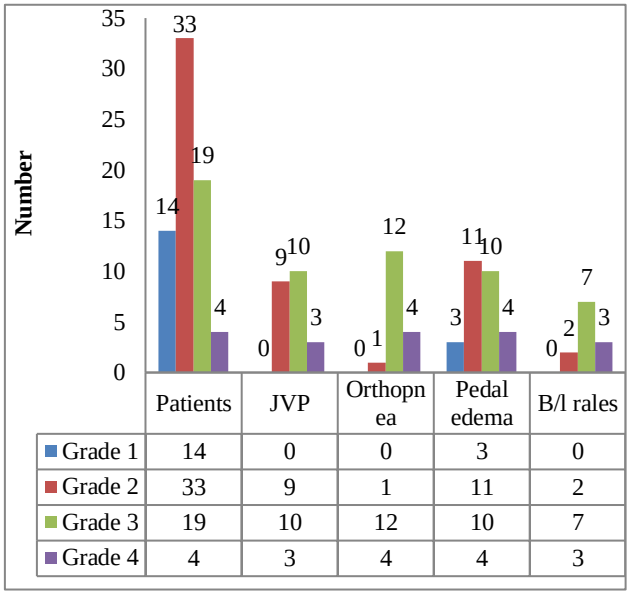


**Figure 1: Distribution according to grades of diastolic dysfunction.**

Out of the 70 patients, 22 patients had raised JVP (31%), 12 patients (17%) had pulmonary edema (auscultatory rales), 13 patients had S3 gallop (18%) and 4 patients had S4 gallop (5.7%). Chart 1 also depicts that a majority (47%) of patients belonged to Grade 2 (pseudo-normalized), with most of them having only dyspnea and pedal edema (33%) as complaints. All patients belonging to Grade 4 (restrictive irreversible pattern) diastolic dysfunction had orthopnea and pedal edema and 75% have raised JVP and bilateral pulmonary rales suggestive of pulmonary edema (Figure 1).

***Morbidity data with respect to hospital and ICCU stay***

All 70 patients were indoor patients with distribution of hospital stay and need of ICCU admission as follows:

**Table 5: Distribution of patients based on their hospital stay.**

| Days | In hospital | | In ICCU | |
|---|---|---|---|---|
| | Number | Percentage % | Number | Percentage % |
| 0-1 | 7 | 10% | 52 | 74.3 |
| 2-3 | 27 | 38.5 | 15 | 21.5 |
| 4-5 | 19 | 27.2 | 1 | 1.4 |
| 6-7 | 10 | 14.2 | 1 | 1.4 |
| >7 | 710 | 9.9 | 1 | 1.4 |
| Total | 70 | 100 | 70 | 100 |
| Mean with SD | 4.3±3.8 | - | 1.2±2.1 | - |

Almost 30% of patients were stabilized and discharged on the third day of admission, but another 58.6% patients required intensive care for at-least one day. Only 2 patients required intensive care for more than a week and were discharged after a successful management. Mortality data is not available due to non-enrollment of patients who died in the ICCU. 41.4% patients never required ICCU admission and were treated in the ward. Almost all the patients in ICCU required non-invasive Bi-level positive airway pressure (Bi-PAP) therapy.

Two patients required invasive mechanical ventilation and were successfully extubated later. There was no significant difference between various grades of dysfunction (p=0.158) (Table 5).

***Changes observed on ECG and chest X-Ray***

On electrocardiography, 3 patients showed atrial fibrillation - AF (4.3%), 21 showed Left Ventricular Hypertrophy (LVH) (30%), 2 showed QS pattern (2.9%) while 46 patients had a Normal Sinus Rhythm (NSR) with no significant abnormalities (65.7%). On CXR, 5 patients showed pulmonary edema (7.1%) in the form of fluffy opacities and 5 patients showed pleural effusion (7.1%). Majority of the patients had no CXR findings (CXR NAD).

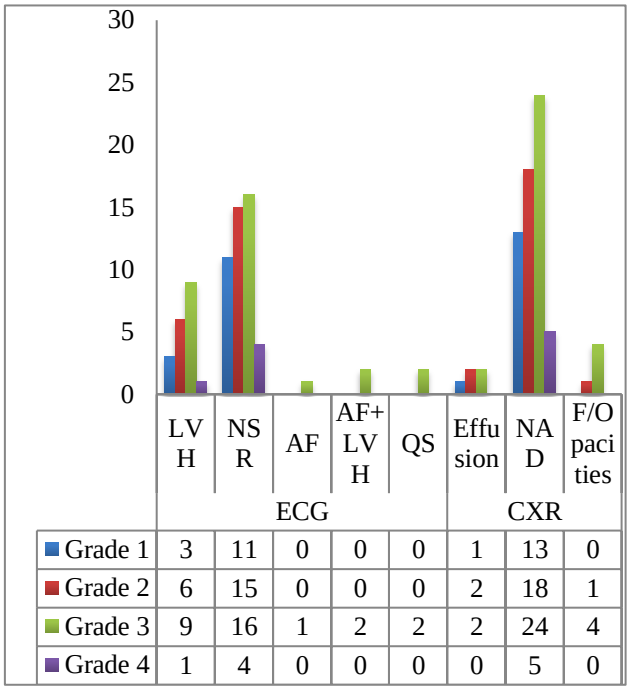


**Figure 2: Distribution based on the grades of diastolic dysfunction.**

As noted, majority of patients did not show significant changes in the ECG and Chest X-Ray. Those who did show significant changes belonged to the Grade 3 diastolic dysfunction subgroup. Based on this results, we felt that ECG and Chest X-Ray might not be helpful in the diagnosis of underlying diastolic dysfunction in patients who present with dyspnea on exertion (Figure 2).

***Prevalence and association of hypertension in diastolic dysfunction***

In this study, 27 patients had hypertension (38.6%) and 7 patients were pre-hypertensive (10%).

**Table 6: Distribution of patients according to grades of diastolic dysfunction.**

| Grade of hypertension | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
|---|---|---|---|---|---|
| Normal | 8 | 12 | 14 | 2 | 36 |
| Pre-Hypertension | 1 | 3 | 3 | 0 | 7 |
| Grade 1 | 3 | 0 | 5 | 3 | 11 |
| Grade 2 | 2 | 6 | 8 | 0 | 16 |
| Total | 14 | 21 | 30 | 5 | 70 |

Out of 30 patients of grade 3 diastolic dysfunction, 13 (47%) had hypertension. No significant association was found between hypertension and worsening grades of diastolic dysfunction (p=0.431) (Table 6).

***Prevalence and association of diabetes mellitus with HFPEF***

In this study, 34 patients were diabetic (48.6%), out of which 6 had Type I DM while 28 had Type II DM. The distribution of diabetic patients with respect to the grades of diastolic dysfunction is as follows: (Figure 3)

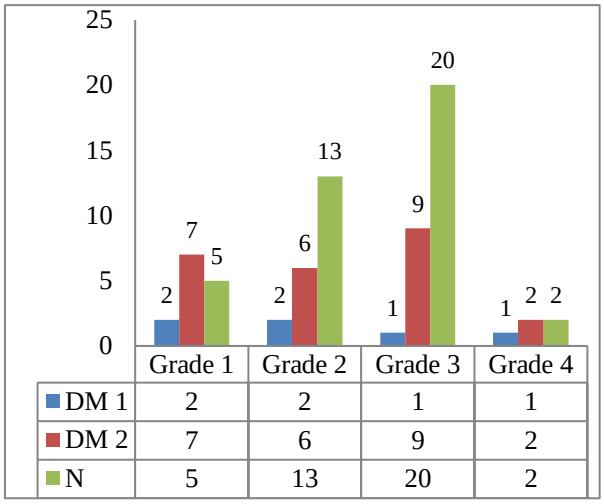


**Figure 3: Distribution according to the grades of diastolic dysfunction.**

The distribution of the patients is as follows with respect to HbA1c:

**Table 7: Distribution in various grades of diastolic dysfunction according to HbA1c.**

| Diastolic dysfunction | Number | Mean (HbA1c) | Standard deviation (HbA1c) |
|---|---|---|---|
| Grade 1 | 10 | 7.7 | 2.75 |
| Grade 2 | 9 | 7.2 | 0.83 |
| Grade 3 | 12 | 9.6 | 2.14 |
| Grade 4 | 3 | 10.33 | 52 |

HbA1c was significantly elevated in higher grades of dysfunction. (p=0.023) (Table 7).

In this study, 14 (20%) patients had Diabetic Retinopathy and 11 (15.7%) patients had Diabetic Neuropathy.

***Prevalence and association of anemia with HFpEF***

In this study, 60 patients had Anemia (85.7%) and they were distributed in the various grades of diastolic dysfunction as follows.

Figure 4 depicts the prevalence (as percentage %) of different grades of anemia on X-axis in patients of different diastolic dysfunction grades on Y-axis. All (100%) patients of grade 4 diastolic dysfunction had moderate anemia while in grade 3, 66.7% patients had moderate anemia. None of the patients in this study had severe anemia. On application of the Kruskal-Wallis test, significant difference was observed in the 4 grades of diastolic dysfunction (p=0.019).

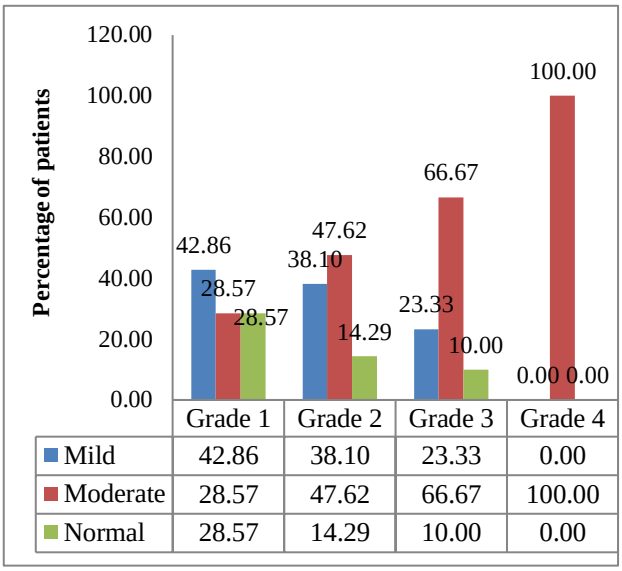


**Figure 4: Distribution according to the grade of diastolic dysfunction in percentage %.**

Figure 4 also shows a trend of increasing prevalence of moderate anemia as grade of diastolic dysfunction increases. Hence, a causal relationship can be studied, and significant results may be achieved with larger sample sizes. (Figure 4)

***Prevalence and association of intrinsic kidney disease with HFpEF***

Authors used Urinary Albumin ratio for association of IKD with respect to HFpEF. Urinary albumin to creatinine ratio was tested for 35 patients who had a history of diabetes mellitus or kidney disease. Out of those, 14 patients had albuminuria (using 30mg/g as the cut-off), and 21 patients had a ratio <30 mg/g. On using Mann-Whitney test for comparison, it was found that patients with albuminuria tend to have higher grade of diastolic dysfunction. (p=0.037)

***Prevalence of acute coronary syndrome***

In this study, only 10 patients (14.3%) had a history of acute coronary syndrome. 7 of them had been re-vascularized in the past by PTCA. Out of these 10 patients, 7 had grade 3 diastolic dysfunction while 3 had grade 2 diastolic dysfunction and all these patients were hypertensive.

***Prevalence of hypothyroidism and obstructive sleep apnea***

In this study, out of the 70 patients, 20 patients had

hypothyroidism (28.6%) with only 3 patients having uncontrolled hypothyroidism with TSH values >40 IU/ml. Out of the 70 patients only 10 patients (14.3%) were diagnosed as Obstructive sleep Apnea. These individuals majorly belonged to the pre-obese or obese group.

**Table 8: Distribution in various grades of diastolic dysfunction according to NT-proBNP.**

| Diastolic dysfunction | Number | Mean NT-proBNP | Standard deviation NT-proBNP |
|---|---|---|---|
| Grade 1 | 4 | 136 | 107.2 |
| Grade 2 | 8 | 301.5 | 214.8 |
| Grade 3 | 30 | 324.3 | 149.2 |
| Grade 4 | 5 | 369.6 | 134.4 |

***Association of NT-proBNP with different grades of diastolic dysfunction***

Positive association was found between level of NT-proBNP and grades of diastolic dysfunction (Pearson co-efficient: 0.308, p=0.035) (Table 8).

## DISCUSSION

In this study, it is notable that male, obese and diabetic HFpEF patients present at a relatively younger age, highlighting the variability in the syndrome beyond the stereotypical profile of frail, elderly, hypertensive females. Mean age of this study population was (53.3+/14.3 years).

The number of males and females were equal in this study. (M=F=35), although it has been found in previous studies that females have a higher risk of HFpEF. Amongst different studies, Bhatia et al. observed that the majority of females presented with HFpEF (66%), while Abhayaratna et al. observed 50% co-dominance of males and females in their study.[7,17] Selma F. Mohammed et al also reported 66% females in their study.[18] It has been studied that females have increased vascular stiffness and, these differences also may result from reproductive hormone effects on LV structure and function and response to alterations in load.[19]

In terms of obesity, major portion of this patients (38.6%) belonged to the pre-obese group. Owan et al. reported a mean BMI of 29.7±7.8 with the obese population comprising 41.4% of their sample size, while Selma F. Mohammed et al. reported 42% patients belonged to the obese subgroup (i.e. BMI >29.9 kg/m$^2$).[2,18] Al Jaroudi W. et al. reported abnormal diastolic function in 61.9% patients, with stage 1 being the most common. As BMI increased, the prevalence of abnormal diastolic function increased (p<0.0001). In patients with normal LVEF, higher BMI was independently associated with worsening DD.[20] In this study, we had less number of patients belonging to obese criteria (<10%) on account of the overall lesser prevalence of obesity in the population presenting to this hospital.

Authors compared this patients in terms of clinical presentation with other studies. Majority of parameters are similar except the presence of orthopnea, pedal edema, raised JVP and a mean SBP. (Table 9) This variation may be due to the difference in the population size under study or selection bias.

**Table 9: Comparison of clinical presenting features with other study.**

| Parameters | This study (n=70) | Bhatia et al[2] (n=880) |
|---|---|---|
| Dyspnea on exertion | 100% | 94.9% |
| Orthopnea/PND | 24.3% | 42.5% |
| Acute Pulmonary edema i.e. bilateral rales | 17% | 17.3% |
| Pedal edema | 40% | 66% |
| Raised JVP | 31% | 57.5% |
| S3 gallop | 18% | 8.4% |
| S4 gallop | 5.7% | 3.8% |
| Mean SBP | 138.9 mmHg±25.8 | 156 mmHg |

In terms of Hypertension, mean SBP in this study was 138.9+/- 25.8 mm Hg. Selma F. Mohammed et al. has also reported a mean SBP of 132±23 mmHg, like this study. They have also reported prevalence of hypertension in 86% of all patients presenting with HFpEF.[18] Bhatia et al. reported a prevalence of hypertension in 55.1% of patients and a hazard ratio of 0.92 (p-value <0.001) for every rise of 10mmHg of SBP.[7] Abhayaratna WP. et al. reported a prevalence of 58% of hypertension and most patients (63.4%) belonging to the sub-group of moderate to severe diastolic dysfunction, had hypertension. As noted previously, hypertension works in multifactorial way to increase the vascular stiffness and ventricular remodeling and thereby dampening the diastolic properties of the ventricle and leading to elevated filling pressures. Control of hypertension is the single most important target in tackling HFpEF by preventing untoward effects on the cardiovascular physiology. Various trials such as CHARM, I-PRESERVE and DIG, for drugs like candesartan, irbesartan, digoxin respectively, have been conducted to search for an agent to reverse the HFpEF physiology, but are yet unsuccessful.[21-23]

Regarding association of diabetes and HFpEf, Patil VC et al. also reported a higher incidence of diastolic dysfunction in asymptomatic diabetic individuals (p<0.001) with worse grades in disease of longer duration.[24] Bhatia et al. reported a prevalence of 31.7% of diabetes while Selma F. Mohammed et al. reported 35% prevalence in their study.[7,18] Based on similar findings in

different studies, we can say that diabetes mellitus can be considered a constant and an important factor in the progression of diastolic dysfunction, over and above its role in the causation of Ischemic Heart disease and consequently systolic heart failure. In this study, 14 (20%) patients had Diabetic Retinopathy and 11 (15.7%) patients had Diabetic Neuropathy.

**Table 10: Comparison with other studies with respect to anemia.**

| Study | Prevalence | Mean±SD |
|---|---|---|
| This study | 85.7% | 10.8±1.62 |
| Bhatia et al[2] | 21.1% | - |
| Selma F, Mohammed et al[29] | 56% | - |
| Owan et al[1] | - | 11.8±1.62 |

In this study, 85.7% patients had some severity of anemia and 70% patients had at-least moderate or severe anemia. Whereas in study of Bhatia et al, anemia was prevalent in only 21.1% population, Selma et al had 56% prevalence. We consider that the difference in the prevalence is because of the rampant nature of the disease in the population presenting to this hospital. Anemia can be considered a major health hazard by thrusting the early unmasking of diastolic dysfunction in this population as compared to the rest of the world. Whether anemia is the contributing risk factor for the lower mean age in this population as compared to the western studies, which focus more on hypertension, DM and obesity, needs further study to prove this hypothesis. Whether the established association of anemia with increased mortality in HFrEF is also valid and applicable to HFpEF patients requires further investigation. Importantly, anemia being a correctable risk factor should be addressed urgently to prevent decompensated heart failure and thus mortality (Table 10).

Renal function is dynamic in HF patients and a single point assessment may not reflect the chronic state. Nonetheless, renal dysfunction was associated with worse outcomes in HFpEF as described in various other studies. Shemirani H et al. did not find a positive correlation between Left ventricular Diastolic dysfunction and urinary albumin to creatinine ratio.[25] Whereas in a study by Katz et al. they concluded that increased U.ACR is an independent prognostic marker and is associated with increased RV and left ventricular remodeling and longitudinal systolic dysfunction.[26] As mentioned previously Smith et al. reported an increased mortality in patients in renal impairment.[27] Present study is limited because Urinary A/C ratio could not be checked for all patients. Whether similar association occurs in all patients with HFpEF needs further investigation. The role of various biomarkers should remain a major priority to predict the progression of HFpEF in patients with intrinsic renal disease.

In this study, authors saw that there was positive association between NT-proBNP and grades of diastolic dysfunction. Carsten Tscho¨pe et al. discussed similar results to this with a mean NT-proBNP of 189.54 pg/ml but with a positive correlation of NT-proBNP with worsening NYHA and diastolic dysfunction. NT-proBNP can reliably detect the presence of isolated diastolic dysfunction in symptomatic patients and is a useful tool to rule out patients with reduced exercise tolerance of non-cardiac origin.[28]

## CONCLUSION

Authors studied various clinical factors along with co-morbidities in patients presented with HFpEF to this hospital. We saw positive association between NYHA groups and diabetes as well as anemia. Hence, it can be concluded that it is of prime importance to find, prevent and treat the comorbidities along with specific targeted therapies for HFpEF. Novel markers that could be evaluated further are glycosylated hemoglobin for DM in HFpEF and U.ACR for Renal dysfunction in HFpEF, as indicated in the present study.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee of NHL Institutional Review Board*

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**Cite this article as:** Palkhiwala NB, Patel RP, Jani RT, Pandya JR, Jani CT, Parikh AP. Clinical profile of patients presenting with heart failure with preserved ejection fraction. Int J Res Med Sci 2020;8:2753-60.