e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(11); 1450-1455

Original Research Article

To Study Comorbidities in Heart Failure - Prevalence, Effect on Functional Status and Outcome in Indian Population

Nitinkumar Patel[1], Tejinder Singh Malhi[2], Bharat Singh Sambyal[3], Komal Patel[4]

[1]Assistant Professor, GMERS Medical College and Hospital Vadnagar, Gujarat, India

[2]Assistant Professor AIIMS Bathinda

[3]Surg Cdr, DM Cardiology, Assistant Professor Medicine, INHS Asvini, Mumbai, India

[4]Associate Professor, GMERS Medical College and Hospital, Vadnagar, Gujarat, India

Received: 21-08-2023 / Revised: 08-09-2023 / Accepted: 04-10-2023
Corresponding Author:Dr Komal Patel
Conflict of interest: Nil

Abstract:

Introduction: Heart failure (HF) is a complex clinical syndrome which results from structural and functional impairment of ventricular filling or ejection of blood. The prevalence of HF is about 1-2% in general population and 10% above the age of 80 years. HF has a high morbidity and reduced life expectancy, with 5 and 10 year survival rates. Heart failure may be associated with multiple concomitant diseases which may adversely affect outcomes.

Aims and Objectives: To study prevalence and prognostic impact of comorbidities in heart failure and also study impact of comorbidities on functional status and quality of life of patient along with association between comorbidities and outcome.

Materials and Methods: This study was prospective observational study conducted at RAMA Medical College, Hospital and Research Centre from feb 2014 to dec 2015.All patients > 18 years of age fulfilling the inclusion criteria were enrolled for the study. A detailed history taking and a general physical examination was carried out in all cases. Demographic data like age, gender, place of residence, race, ethnicity, clinical history and laboratory test were recorded.

All quantitative variables were estimated using measures of central location and measures of dispersion. Chi-square test was used to find out any statistical association between categorical variables. Independent T-test and Mann Whitney U test was used to compare various quantitative variables between two groups.

Result: Among 113 patient 70(61.9%) patients were male, 43(38.1%) patients were female with M: F ratio of 1.6:1. The mean age of patients enrolled in study was 60.3±12.5 years. In Total population mean age of male was 59±11.9 years and of female was 61±13.2 years respectively (p=0.3). The mean age of HFpEF group was significantly higher than HFrEF group (P value = 0.03). Between study group 54(47.8%) patients had preserved EF, 7(6.2%) mild LVSD 7(6.2%), moderate LVSD and 45(39.8%) severe LVSD. Mean EF of male was 38.4±14.4 and female was 45.9±13.5 in total population which was significant different (p value = 0.01). Mean EF of HFrEF and HFpEF was 29.6± 9.1, 54.4±5.1 respectively.

Conclusion: HFpEF was more common in older population with no sex preponderance. Whereas HFrEF was more common in males. HFrEF have greater burden of comorbidities as compared to HFrEF. Females bears greater burden of comorbidities as compared to males.

Keywords: Heart failure (HF), Heart Failure with reduced ejection fraction (HFrEF), Heart Failure with preserve dejection fraction (HFpEF), Ventricular systolic dysfunction (LVSD), Regional wall motion abnormality (RWMA).

Introduction

Heart failure (HF) is a complex clinical syndrome which results from structural and functional impairment of ventricular filling or ejection of blood. Although the clinical syndrome of HF may arise as a consequence of abnormalities or disorders involving all aspects of cardiac structure and function, most patients have impairment of myocardial performance, with findings ranging from normal ventricular size and function to marked dilation and reduced function [1]. Based on Ejection fraction heart failure is divided into two categories -HFrEF and HFpEF. The prevalence of HF is about 1-2 % in general population and 10% above the age of 80 years. HF has

a high morbidity and reduced life expectancy, with 5 and 10 year survival rates of 50% and 10% reported in epidemiologic studies [2]. Heart failure may be associated with multiple concomitant diseases which may adversely affect outcomes [3].

Presence of more than 2 comorbidities is defined as Multimorbidity. As the number of comorbidities increases, there is increased risk of decline in functional status, adverse drug effects, prescription non-adherence, conflicting medical advice, unnecessary hospitalizations, and mortality [4]. Multimorbidity in heart failure may precipitate acute decompensation, greater healthcare burden and increases the risk of morbidity and mortality[5]. Major proportion of hospitalization in HF patients is due non-cardiovascular causes, rather than cardiovascular cause. Therefore, comorbidities play a prominent role in the prognosis of patients with heart failure [6].

Renal dysfunction, anemia, and diabetes mellitus are the three most prevalent comorbidities occurring in patient with heart failure as per European society of cardiology [7]. About quarter of patient with heart failure suffered from pulmonary and renal disease leading to increased burden of mortality and morbidity.

Aims and Objectives

1) To study prevalence and prognostic impact of comorbidities in heart failure (both HFpEF and HFrEF patient).

2) To study impact of comorbidities on functional status and quality of life of patient.

3) To study impact of comorbidities on NYHA functional class

4) To study association between comorbidities and outcome in term of hospital admission (all cause and HF related) and mortality (all cause and HF related) in (both HFpEF and HFrEF patient).

Materials and Methods

This study was conducted at RAMA Medical College, Hospital and Research Centre from Feb. 2014 to dec 2015.

All patients > 18 years of age fulfilling the inclusion criteria will be enrolled for the study. This is a single center prospective observational study.

Inclusion Criteria are Age above 18 years and All patients of heart failure.

Exclusion Criteria are Refusal to give informed consent, Pregnant and postpartum patient.

i e within 42 days, Patients not fulfilling the age criteria i.e. Age less than 18 years.

Methodology

An informed consent will be obtained from all patients enrolled in the study. A detailed history taking, and a general physical examination will be carried out in all cases. Patient will be divided into two groups: HFpEF and HFrEF. Demographic data like age, gender, place of residence, race, ethnicity, clinical history and laboratory test will be recorded. LVEF will be measured by 2 D ECHO by Simpson method. LV systolic dysfunction will be graded as mild (EF-41-45%), moderate (36-40%) or severe (EF-35% or lower). All clinical data will be noted. Quality of life will be calculated by NYHA class.

Heart failure: Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria: Paroxysmal nocturnal dyspnea, Neck vein distention, Rales, Acute pulmonary edema, S3 gallop, Increased central venous pressure (>16 cm H2O at right atrium), Hepato-jugular reflux, Weight loss >4.5 kg in 5 days in response to treatment.

Minor criteria: Bilateral ankle edema, Nocturnal cough, Dyspnea on ordinary exertion, Hepatomegaly, Pleural effusion, Decrease in vital capacity by one third from maximum recorded, Tachycardia (heart rate>120 beats/min.)

Heart failure with preserved ejection fraction - According to Heart Failure Society of America the diagnosis of HFpEF required signs or symptoms of HF, a LVEF>50%, a and evidence of diastolic LV dysfunction[8].

Heart failure with reduced ejection fraction- diagnosis of HFrEF required signs or symptoms of HF, a LVEF<50%.

Diabetes-Diabetes will be taken as either FBS > 126, or RBS > 200 with symptoms of hyperglycemia, 2 hour post prandial glucose > 200 mg/dl in Oral glucose tolerance test or HbA1c > 6.5 in accordance to ADA guidelines.

Hypertension- HTN will be included as per JNC VIII criteria. Anyone already diagnosed or on treatment will be taken as hypertensive [9].

Obesity- Patients will be divided into different groups as per BMI classes for Indian patients. BMI categories as per Asian classification are < 18.5 kg/m underweight, 18.5-22.99 kg/m normal, 23.0-27.49 kg/m as overweight and > 27.5 kg/m as obese.

OSA - The patient reports daytime sleepiness, unrefreshing sleep, fatigue, insomnia, and/or unintentional sleep episodes during wakefulness. The patient awakens with breath holding, gasping, or choking. The patient's bed partner reports loud snoring, breathing interruptions, or both during the patient's sleep [10].

Dyslipidemia: Complete lipid profile will be done, and patients classified as having dyslipidemia if they have raised LDL > 100 mg/dl, HDL < 40 mg/dl in males and <50 mg/dl in females, triglycerides > 150 mg/dl or total cholesterol > 200 mg/dl. T3, T4 and TSH will be done for thyroid dysfunction.

Stroke/Cva: Stroke will be defined as focal neurological deficit of vascular origin lasting more than 24 hours and confirmed by computed tomogram scan[11].

Atrial Fibrillation: Atrial fibrillation (AF) is a supraventricular arrhythmia characterized electrocardiographically by low-amplitude baseline oscillations (fibrillatory or f waves) and an irregularly irregular ventricular rhythm. The f waves have a rate of 300 to 600 beats/min and are variable in amplitude, shape, and timing. Standard ECG machine will be used for recording ECG.

Coronary Artery Disease –all patients with stable angina, unstable angina, STEMI, NSTEMI and previous history of revascularization are included in CAD.

Anemia - The WHO defines anemia as: <130 g/L (13 g/dL) in men older than age 15 years and <120 g/L (12g/dL) in non-pregnant women older than age 15 years [12].

Chronic Kidney Disease- The presence of chronic kidney is determined by an estimated glomerular filtration rate less than 60/min /1.73 mA2 calculated by MDRD method [13].

Peripheral Arterial Disease - defined as history of claudication or ankle-brachial index < 0.8.

Chronic Obstructive Pulmonary Disease- Defined as presence of dyspnea, chronic cough with sputum production, and history of exposure to risk factor for disease (smoking, smoke from home cooking and occupational dust) along with presence of post bronchodilator FEV1/FVC ratio < 70% measured by spirometry [14].

Statistical Analysis

Sample size (n) will be 100 based on effect size and alpha error consideration. Data will be explored for any outliers, typing errors and missing values. All quantitative variables will be estimated using measures of central location (mean, median and mode) and measures of dispersion (standard deviation and standard error). Qualitative or categorical variables will be described as frequencies and proportions. Chi-square test will be used to find out any statistical association between categorical variables. Independent T-test and Mann Whitney U test will be used to compare various quantitative variables between two groups. Multivariate analysis will further be carried out to find significant predictors for the outcome of interest in both groups separately and comparison of outcomes will be done. All tests will be two-tailed and p-value < 0.05 will be taken as significant.

Result

Demographic Profile

Among 113 patient 70(61.9%) patients were male, 43(38.1%) patients were female with M: F ratio of 1.6:1. In HFrEF group 43(72.9%) patients were male, 16(27.1%) patients were female (M: F ratio - 2.6: 1). In HFpEF group 27(50%) patients were male, 27(50%) patients were female (M: F ratio 1:1). There was statistically significant difference among groups (P value-.01). The mean age of patients enrolled in study was 60.3±12.5 years. In Total population mean age of male was 59±11.9 years and of female was 61±13.2 years respectively (p=0.3). The mean age in HFrEF group was 57±13.4 years. In HFrEF group mean age of male was 57.56±12.7 years and of female was 59±15 years respectively (p value=0.7).The mean age in HFpEF was 62.9±11 years. In HFpEF group mean age of male was 62.41±9.9 years and of female was 63.48±12.1 years (p value = 0.7). The mean age of HFpEF group was significantly higher than HFrEF group (P value = 0.03).

Clinical Features The most common symptoms observed were dyspnea (94.3%), chest pain (72%), edema (32.7%), orthopnea (31.9%), PND(30.9%) and palpitation(28.3%). In HFrEF group, most common symptom were dyspnea (100%), chest pain (72.6), orthopnea (59%), PND (59%), palpitation (42.4%), edema (40.7%). In HFpEF group, most common symptoms were dyspnea (94.4%), chest pain (72%), edema (32.7%), orthopnea (31.9%), PND (30.9%) and palpitation (28.3%). Chest pain, orthopnea, PND, palpitation and edema were significantly (P value=0.02) more common in HFrEF than HFpEF. The most common clinical finding among patient were tachypnea (37%), raised JVP (36.3%), Tachycardia (30.1%), crepitation (30.1%) Hypoxia (28.3%), murmur (8.5%). Among study group hypotension (35.6% vs1 .9%), Tachycardia (45.8% vs 13%), tachypnea (55.9% vs 16.9%), hypoxia (40.7% vs 14.8%), raised JVP (59.3%vs 11.1%), murmur (8.5% vs 0%), crepitation (47.5%-11.1%) were statistically more common in HFrEF group as compared to HFpEF group (P value = 0.02). The most ECG finding among patients were ST elevation (44.2%), ST depression (26.5%), Tinversion(23%), Q wave(17%), LBBB(11.5%) and CHB. Between study group 54(47.8%) patients had preserved EF, 7(6.2%) mild LVSD 7(6.2%), moderate LVSD and 45(39.8%) severe LVSD. Between study group RWMA (78%vs42.6%) and MR (54.2%vs 42.1%) were statistically more common in HFrEF (P value-0.02). Mean EF of male was 38.4±14.4 and female was 45.9±13.5 in total population which was significant different (p value = 0.01). Mean EF of HFrEF and HFpEF was 29.6± 9.1, 54.4±5.1 respectively.

Table 1: Baseline comorbidities are listed in table.

Parameters	Total	HFrEF	HFpEF	P-value
Diabetes	59(52.2%)	30(50.8%)	29(53.7%)	0.09
Hb1ac	1.9	72.2	6.8	0.8
Hypothyroidism	17(15%)	9(15.3%)	8(14.8%)	0.9
TSH(uIU/ml)	4.0312.4	2.8	2.84.3	0.1
T3(ug/dl)	1.51.8 72.6	1.8□2.2	1.2□2.2	0.07
T4(ug/dl)		6.8□2.6	7.3□2.6	0.4
Dyslipidemia	84(74.30%)	40(67.8%)	44(81.5%)	0.09
Total cholesterol(mg/dl)	91.6□36	139□42	144□48	0.5
LDL(mg/dl)	38.5□10.5	93.3□36	89□37	0.5
HDL(mg/dl)	13651	38.6□10.7	38.4□11	0.9
Triglyceride(mg/dl)		137□46	134.54□55.2	0.7
CVA	6(5.3%)	2(3.4%)	4(7.4%)	0.4
PVD	2(1.8%)	1(1.7%)	1(1.9%)	0.7
Hypertension	70(61.9%)	28(47.5%)	42(77.8%)	0.01
Anemia	59(52.2%)	27(45.8%)	32(59.3%)	0.1
Hb(g/dl)	12.2□2.2	12.5□2.5	11.9□1.8	**0.04**
Iron deficiency	45(39.8%)	20(33.9%)	25(46.3%)	0.1
Iron(mcg/dl)	60.7□29	63.3□30	57.8□27.6	0.3
Ferritin(ng/ml)	365	491□1940	228.1□184	0.8
TIBC(mcg/dl)	332.6□91	339.2□90	325.3□92	0.4
%saturation (%)	19.7□9	20.5□9.8	18.85□8.2	0.3
Vitamin D deficiency	99(87.6%)	51(86.4%)	48(88.9%)	0.6
25 OH(ng/ml)	15.2	15.6	16.3	0.1
CKD	25(22.1%)	15(25.4%)	10(18.5%)	0.3
Urea(mg/dl)	49.9□35	59.9□39	42.3□29.3	**0.003**
Creatinine(mg/dl)	1.3□1.3	1.5□1.7	1.1□0.7	**0.01**
EGFR	78□38.3	72.2□37	84.9□39	0.08
Na(mEq/L)	136.2□7.1	136.6□8.6	136.1□4.8	0.9
OSA	2(1.8%)	1(1.7%)	1(1.9%)	0.7
Atrial Fibrillation	7(6.2%)	5(8.5%)	2(3.7%)	0.2
COPD	15(13.3%)	9(15.3%)	6(11.1%)	0.5
CAD	94(83.2%)	50(84.7%)	44(81.5%)	0.6
Obesity	25(22.1%)	13(22%)	12(22.2%)	0.9
All-Cause Mortality	19(16.8%)	13(22%)	6(11%)	0.1
HF Mortality	16(14.2%)	13(22%)	3(5.6%)	0.01
Non-HF Mortality	3(2.7%)	0(0%)	3(5.6%)	0.06
All Cause Readmission	24(21.2%)	16(27.1%)	8(14.8%)	0.1
HF Related Readmission	15(13.3%)	13(22%)	2(3.7%)	0.04
Non HF Readmission	9(8%)	3(5.1%)	6(11.1%)	0.2
NYHA	2.6±0.8	2.9±0.8	2.2±0.8	0.01

Discussion

Heart failure is a huge problem with overall prevalence of 2% in developed nations. Heart failure affect about 20 million people worldwide and is leading cause of mortality, morbidity and poor quality of life worldwide. Data on prevalence and clinical outcome of heart failure is limited in developing nation.

The mean age of patients enrolled in our study was 60.3±12.5 years. The patient in HFpEF group was much older than HFrEF group (P value =0.03). Female were much older than men (p value=0.3). In similar study by Sameer Athar et al mean age in HFpEF group was 70±10.1 years and in HFrEF group was 69.5±10.3 years supporting our study[15]. In study by perez-calvo et al. mean age in HFpEF and HFrEF group was 81.6±9 and 78.7±13 years respectively which was in concordance with present study [16]. In Study by Frank Edelmann et al patient in HFpEF group (67±13years) was older than HFrEF group (63±14 years) [17]. In ADHERE Registry, OPTIMIZE –HF registry, GWTG registry, Alanna chamberlain et al and Olmsted county study HFpEF cohort was older than HFrEF cohort. In present study, Heart failure was more common in male in overall population with greater male preponderance in HFrEF group explained by greater prevalence of Coronary events in males in HFrEF group. In HFpEF group, incidence was equal among both male and female. In Ather Et al both HFrEF

(96.4%) and HFpEF (91.1%) cohort have higher proportion of males[15]. In study by perez-calvoetal. male population was predominant in HFrEF group and female were predominantin HFpEF group[16]. Similar finding were seen in Edelmann Et al, ADHERE Registry, OPTIMIZE –HF registry, GWTG registry and Olmsted county study [8].

Previous history of myocardial infarction was significantly higher in HFrEF group highlighting the role of ischemic cardiomyopathy in HFrEF. In Ather et al past history of myocardial infarction was more common in HFrEF (40.4%) as compared to HFpEF(27.1%) supporting present study [15]. Patients with HFrEF have higher prevalence of shock and increased sympathetic activity in form of tachycardia. HFrEF group have higher incidence of decompensation evident by greater incidence of shock, hypoxia (tachypnea, crepitation) in HFrEF group. In similar study by Edelmannn et. al dyspnea on exertion(87% vs 84%), orthopnea, (11.7% vs6.8%) raised JVP, (6.7% vs 2.4%) basal crepitation (11.4% vs 4%) was more common in patient with HFrEF as compared to HFpEF supporting our results [17].

Cardiac comorbidities were equally distributed among study group. Females have higher number of total and non-cardiac comorbidities in overall population and HFrEF group (p value= 0.001). In Ather et al patient with HFpEF had higher number of Non- cardiac comorbidities (4±1.7 vs 3.5±1.7). Similarly in Edelmann et al number of comorbidities in HFpEF (3.8±2.1) were higherthan HFrEF (3.2±1.9). In study by Alanna Chamberlain, burden of comorbidities were higher in HFpEF cohort (4.5±2.2) as compared to HFrEF (3.7±2.4) and number of comorbidities were equally distributed between both genders [18].

In Ather et al study diabetes mellitus, hypertension, anemia, COPD, Obesity were more common in HFpEF, whereas renal dysfunction was more common HFrEF. PVD, CVA and atrial fibrillation was equally distributed between both groups[15]. In Edelmann study diabetes mellitus, dyslipidemia, coronary artery disease, renal dysfunction, anemia, COPD, PVD, CVA, atrial fibrillation was more common in HFrEF, whereas hypertension and obesity was more common inHFpEF[17]. In Perez-Calvo et al hypertension, atrial fibrillation and COPD was more common in HFpEF and coronary artery disease was more common in HFrEF group whereas renal insufficiency and diabetes mellitus was equally distributed between both group[16]. This difference can be attributed to difference in demographics, sample size, population genetics and risk factors.

Conclusion

HFpEF was more common in older population with no sex preponderance whereas HFrEF was more common in males. HFrEF have greater burden of comorbidities as compared to HFrEF. Females bears greater burden of comorbidities as compared to males.

Coronary artery disease, Dyslipidemia, Vitamin D deficiency, Hypertension were most common comorbidities. Type 2 diabetes, Dyslipidemia, CVA, Hypertension, Anemia, Iron deficiency, COPD were more prevalent in HFpEF group whereas Hypoalbuminemia, Hypothyroidism, Renal dysfunction, atrial fibrillation, Coronary artery disease were more prevalent in HFrEF group.

Renal dysfunction, diabetes mellitus, dyslipidemiahyp albuminemia, OSA,PVD, Hypertension, COPD, Vitamin D deficiency, renal dysfunction and Hypoalbuminemia have negative impact on quality of life.

Limitations:

Small sample size of study from single study therefore finding cannot beexplorated to general population. Multiple comparisons with limited data and increased probability of type 1 and type 2 errors, as we could not adjust to multiple hypothesis testing.

Bibliography

1. Brouwers FP, Hillege HL, van Gilst WH, van Veldhuisen DJ. Comparing newonset heart failure with reduced ejection fraction and new onset heart failurewith preserved ejection fraction: an epidemiologic perspective. Curr Heart Fail-Rep. 2012 Dec; 9(4):363-8.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al.2013 ACCF/AHA Guideline for the Management of Heart FailureA Report ofthe American College of Cardiology Foundation/American Heart AssociationTask Force on Practice Guidelines. J Am CollCardiol. 2013 Oct 15;62(16):0020e147-239.
3. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R, et al. Prevalenceof left- ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population basedstudy. Lancet Lond Engl. 2001 Aug 11; 358 (9280):439-44.
4. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most commonchronic condition--Multimorbidity. JAMA. 2012 Jun 20; 307(23):2493-4.
5. Lee TA, Shields AE, Vogeli C, Gibson TB, Woong-Sohn M, Marder WD, etal. Mortality rate in veterans with multiple chronic conditions. J Gen InternMed. 2007 Dec; 22 Suppl 3:403-7.
6. Lee TA, Shields AE, Vogeli C, Gibson TB, Woong-Sohn M, Marder WD, et al. Mortality rate in veterans with multiple chronic

conditions. J Gen Intern Med. 2007 Dec; 22 Suppl 3:403-7.
7. Van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L, et al. Comorbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail. 2014 Jan; 16(1):103-11.
8. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of theEuropean Society of Cardiology. Eur Heart J. 2007 Oct; 28(20):2539-50.
9. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5; 311(5):507-20.
10. Thorpy MJ. Classification of Sleep Disorders. Neurotherapeutics. 2012 Oct; 9(4):687-701.
11. Sacco RL, Kasner SE, Broderick JP, CaplanLR, Connors JJB, Culebras A, et al. An updated definition of stroke for the 21st century: a statement forhealthcare professionals from the American Heart Association/American Stroke Association. Stroke J Cereb Circ. 2013 Jul; 44(7):2064-89.
12. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968; 405:5-37.
13. Levey AS, Stevens LA, Schmid CH, Zhang Y (Lucy), Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann InternMed. 2009 May 5; 150(9):604-12.
14. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J RespirCrit Care Med. 2001 Apr; 163 (5):1256-76.
15. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in apredominantly male population with heart failure and preserved versus reduced ejection fraction. J Am CollCardiol. 2012 Mar; 59(11):998-1005.
16. Perez-Calvo JI, Josa-Laorden C, Rubio-Gracia J, Gimenez-Lopez I. Comorbidities in heart failure with mid-range ejection fraction. Vol. 41, European journal of internal medicine. Netherlands; 2017. p. e27-8.
17. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Dungen H-D, et al. Contribution of comorbidities to functional impairment ishigher in heart failure with preserved than with reduced ejection fraction. Vol. 100, Clinical Research in Cardiology.Berlin/Heidelberg; 2011. p. 755-64.82.
18. Chamberlain AM, St Sauver JL, Gerber Y, Manemann SM, Boyd CM, DunlaySM, et al. Multimorbidity in heart failure: a community perspective. Am J Med. 2015 Jan; 128(1):38-45.