The Open Cardiovascular Medicine Journal
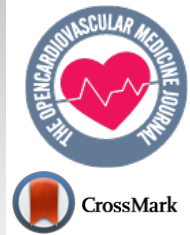
RESEARCH ARTICLE

Clinical Characteristics, Comorbidities, and Prognosis in Patients with Heart Failure with Unknown Ejection Fraction

Steven J. Lavine[1,2,*], Ghulam Murtaza[1], Zia Ur Rahman[1], Danielle Kelvas[1] and Timir K Paul[1]

[1]*East Tennessee State University - Quillen College of Medicine Mountain Home, TN 37684, USA*
[2]*Washington University of St. Louis 660 South Euclid Avenue Campus Box 8086 St. Louis , MO 63110, USA*

Abstract:

Background:

Heart Failure (HF) is a frequent cause of mortality and recurrent hospitalization. Although HF databases are assembled based on left ventricular (LV) ejection fraction, patients without LV ejection fraction determination are not further analyzed.

Objective:

The purpose of this study is to characterize patient attributes and outcomes in this group-HF with unknown Ejection Fraction (HFunEF).

Methods:

We queried the electronic medical record from a community-based university practice for patients with a HF diagnosis. We included patients with >60 days follow-up and had interpretable Doppler-echocardiograms. We recorded demographic, Doppler-echocardiographic, and outcome variables (up to 2083 days).

Results:

There were 820 patients: 269 with HF with preserved Ejection Fraction (HFpEF), 364 with HF with reduced Ejection Fraction (HFrEF), of which 231 had a LV ejection fraction=40-49% and 133 had a LV ejection fraction<40%, and 187 with HFunEF. As compared to patients with HFunEF, HFpEF patients were younger, had a higher coronary disease and hyperlipidemia prevalence. Patients with HFrEF had more prevalent coronary disease, myocardial infarction, and hyperlipidemia. Patients with HFunEF were more likely to be seen by non-cardiology providers. All-cause mortality (ACM) was greater in HFunEF patients than patients with HFpEF (Hazard Ratio (HR)=1.60 (1.16-2.29), p=0.004). Furthermore, HF readmission rates were lower in HFunEF as compared to HFpEF (HR=0.33 (0.27-0.54), p<0.0001) and HFrEF (HR=0.30 (0.028-0.50), p<0.0001).

Conclusion:

Patients with HFunEF have greater ACM and lower HF re-admission than other HF phenotypes. Adherence to core measures, including LV ejection fraction assessment, may improve outcomes in this cohort of patients.

Keywords: Heart failure, Ejection fraction, Mortality, Heart failure re-admission, Heart failure phenotypes, Heart failure verification.

1. INTRODUCTION

HF is the leading cause of morbidity, mortality and recurrent hospitalization. It is most common in the elder population accounting for 875,000 admissions each year [1] with prevalence increasing further with age. The prevalence of the HF in the elderly population has been increased due to improved survival following myocardial infarction and increased prevalence of co-morbidities including hypertension, diabetes, metabolic syndrome, valvular heart disease and coronary artery disease [2 - 4]. HF databases are usually assembled based on LV ejection fraction. Within the patient population, there may exist a group of patients (<20%) who do not have a LV ejection fraction determination and are not further analyzed or a previous assessment of LV function obtained several years in the past has been used [5 - 7]. There is sparse data available in the literature about patient

* Address correspondence to this author at Washington University of St. Louis, 660 South Euclid Avenue, St. Louis, MO 63110, USA; Tel/Fax: 314-454-7409, 314-362-4278; E-mail:Stevenjlavine@wustl.edu

characteristics and outcomes in this group of patients that we are defining as HFunEF. The purpose of this study is to characterize patient attributes and describe outcomes in this group as compared to patients with other HF phenotypes: HFpEF and HFrEF.

2. MATERIALS AND METHODS

This study received expedited approval by the Quillen College of Medicine Institutional Review Board. The Quillen College of Medicine clinical practice is contained in a single electronic medical record (Allscripts, Touchworks, Chicago, Ill) and was queried for HF diagnosis using ICD-9 codes (428.xx), HF admission, or HF on a problem list. There were 863 patients with HF that were identified. Only those patients who were followed at least 60 days, did not have a pericardial disease, or congenital heart disease were included. Excluded patients included those having a congenital disease with and without valve stenosis (8 patients), followed for <60 days (32 patients) and constrictive pericarditis (3 patients). Consequently, 820 patients were included in the study and were followed for a time period of 60 days to a maximum time period of 2113 days (through October 1, 2016) with a median of 1481 days.

A review of outpatient records was performed to determine the age, sex, and prevalence of the coronary disease, previous myocardial infarction, diabetes, hypertension, and hyperlipidemia. Body surface area, blood pressure, and heart rate at the time of the echocardiogram were recorded. Medications were reviewed at the time of 1st and subsequent visits to determine the use of angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, beta-blockers, aldosterone antagonists, nitrates, hydralazine, diuretics, calcium channel blockers, digoxin and statins. The coronary disease was defined as having evidence of >50% lesion in any coronary artery by coronary angiography, abnormal myocardial perfusion scan, ECG criteria evidence of an old myocardial infarction [8] or evidence of myocardial infarction using the universal definition [9]. Diabetes was defined as fasting glucose $\geq$126 mg%, postprandial blood glucose $\geq$200 mg%, hemoglobin A1C $\geq$6.5%, or taking anti-diabetic medications. Hypertension was defined as blood pressure >140/90 or taking anti-hypertensive medications. Hyperlipidemia was defined as total cholesterol >200 mg%, triglycerides>150 mg%, or taking lipid-lowering medications. Laboratory data was reviewed and the average brain natriuretic peptide (BNP), hemoglobin, creatinine values, percentage of patients with stage 3 chronic kidney disease as glomerular filtration rate <60 ml/min/1.73 m2 (CKD-EPI study equation [10], and troponin I were recorded. The prevalence of atrial fibrillation was determined by examining the EKG of each patient at each visit or hospitalization. The presence of more than mild aortic valve stenosis, aortic valve regurgitation, mitral, or tricuspid regurgitation was observed from medical records recording clinical assessments of patients. Evidence of verifiable HF was determined using the Framingham HF criteria requiring either 2 major criteria or 1 major and 2 minor criteria (CHF1 score>4) [11] or BNP>100 pg/ml.

Inpatient and outpatient records were examined to

determine if patients were readmitted for HF after the initial contact with the health care system by assessing each admission to determine if HF was the reason for admission as opposed to chronic pulmonary disease, pneumonia, or other diagnoses. ACM was determined from medical records, conversation with family, and examining obituaries and/or the national death index. Time from being 1st seen to HF or ACM was determined. The type of specialty caring for the patient was recorded: family medicine, internal medicine, or cardiology. If cardiology was involved in the care of the patient, the patient was assigned to cardiology even if family or internal medicine were seeing the patients.

Patients were assigned to HF phenotypic groups based on LV ejection fraction determined by Doppler echocardiography. LV ejection fraction $\geq$50% was HFpEF (n=269). LV ejection fraction <50% was termed HFrEF (HFrEF, n=364). HFrEF was subdivided into HF with mid-range ejection fraction if the ejection fraction was 40-49% and HF with low ejection fraction if the ejection fraction was <40%. Patients without echocardiography performed or other modalities for determination of LV ejection fraction were termed HFunEF (n=187).

2.1. Echocardiography

All images were digitally obtained from 3-5 (5 if atrial fibrillation) consecutive cardiac cycles using a Phillips iE 33 (Cleveland, Ohio) with a 2.5 mHz broadband transducer (X5) at end-expiration. Doppler echocardiography was obtained from multiple ultrasonic windows to provide views of all cardiac chambers and valves. Transmitral pulsed Doppler was obtained from 1-2 x 1-2 mm sample volume placed at the tips of the mitral leaflets. Using a 1-2 x 1-2 mm sample volume, LV outflow tract pulsed Doppler was obtained from the apical 3 or 5 chambers approximately 3-5 mm from the aortic valve annulus. Spectral tissue Doppler was obtained from the septal and lateral mitral annuli using a 3x3 mm pulsed Doppler sample volume. All measurements are the average of 3-5 (5 if atrial fibrillation) consecutive cardiac cycles at end-expiration and were performed according to the recommendation of the American Society of Echocardiography guidelines [12]. We calculated LV end-diastolic and end-systolic volumes (using Simpson's rule), LV mass, and left atrial volumes and indexed these measures to body surface area. The ejection fraction was calculated in the usual manner. End diastolic basal right ventricular basal dimension and tricuspid annular plane systolic excursion were measured as described by the American Society of Echocardiography guidelines [12]. From the LV outflow tract pulsed Doppler recordings, we determined the peak velocity and velocity-time integral. The LV outflow tract area was calculated as the product of 0.785*LV outflow tract diameter^{2,} assuming circular geometry. The stroke volume index was calculated as the product of the velocity-time integral and LV outflow tract area and indexed to body surface area. From transmitral Doppler, E, A, E/A were obtained based on the American Society of Echocardiography guidelines [13]. Spectral Doppler of the septal and lateral mitral annulus e' was analyzed and averaged. The E/e' was calculated [13]. Tricuspid regurgitation velocity was obtained from a continuous wave Doppler transducer using multiple windows. Using the

modified Bernoulli equation, right ventricular systolic pressure was estimated with the addition of an estimate of right atrial pressure based on respiratory variations of the inferior vena cava dimension using the American Society of Echocardiography recommendations [13].

2.2. Statistics

Data were expressed as mean+standard deviation for continuous normally distributed data as determined by the Kolmogorov-Smirnov test. For data that were not normally distributed, median and interquartile ranges were computed. Categorical data was expressed as a percentage of the group having that attribute. Differences between the groups were determined using 1-way analysis of variance or 1-way analysis of variance on ranks. If the F value was <0.05, the differences between individual groups were determined by Dunn's test. Differences in percentages among groups were determined using chi-square. If p<0.05, then a multi-comparison technique was utilized to determine where the significant differences existed. (COMPROP-SAS, Cary, NC). P values <0.05 were considered significant. Multiple logistic regression was performed to determine the independent correlates of ACM and readmission using univariate statistics with p<0.10 for each phenotype. Cox proportional analysis was utilized to assess the relation of HF phenotype to ACM and readmission for HF taking into account the variables derived above. Adjusted

Kaplan-Meier curves were subsequently constructed to determine HR's for ACM and readmission for HF. Landmark analysis was performed on all patients already admitted once to determine HR's for ACM and re-admission a 2nd time for HF. Log-rank testing was performed to determine significance. Statistics were calculated with Sigma Stat 4 (SYSTAT, San Jose, CA) and SAS (Cary, NC).

3. RESULTS

Baseline patient characteristics are summarized in Table **1**. The prevalence of HFunEF, HFpEF, and HFrEF was 22.8%, 32.8%, and 44.4%, respectively. The percentage of patients with HFunEF followed by family medicine was 70.2% (p<0.001 vs Cardiology), 27.8% by internal medicine (p<0.001 vs family medicine and p=0.041 vs cardiology), and 2.0% by cardiology. For the entire database, the percentage of patient care was provided by cardiology (14.6%), internal medicine (26.8%), and family medicine (58.6%). *As compared to patients with HFunEF*, HFpEF patients were younger, had a greater prevalence of the coronary disease, and hyperlipidemia. *As compared to HFunEF patients*, patients with HFrEF had a greater prevalence of coronary disease, myocardial infarction, hyperlipidemia, beta-blocker use, aortic regurgitation, mitral and tricuspid regurgitation, lower diastolic and mean blood pressures, greater BNP levels, and lower hemoglobin.

Table 1. Baseline Characteristics.

-	HFunEF (n=187)	HFpEF (n=269)	HFrEF (n=364)
Age (years)	73+16	66+17***	75+13^^
Sex (M/F)	101/130	165/104	187/177
Coronary Disease (%)	47.2	60.0*	66.1*
Myocardial Infarction (%)	20.0	26.0	41.0**^
Diabetes Mellitus (%)	54.1	59.9	46.1^
Hypertension (%)	82.3	91.0	88.5
Hyperlipidemia (%)	60.6	75.8*	77.1*
Aortic Stenosis (%)	5.2	12.6	15.2
Aortic Regurgitation (%)	2.6	3.1	13.0*^
Mitral regurgitation (%)	11.8	19.3	32.4***^
Tricuspid Regurgitation (%)	16.1	24.5	31.6**
ACEI/ARB (%)	62.2	68.0	65.4
Atrial fibrillation (%)	22.1	21.6	24.9
Beta Blockers (%)	59.4	59.2	72*^
Diuretics (%)	78.2	72.9	80.7
Aldosterone blocker (%)	9.4	18.6	12.2
Nitrates (%)	6.2	7.4	9.5
Hydralazine (%)	3.5	6.7	6.4
Digoxin (%)	7.4	7.4	9.5
Calcium Channel Blockers (%)	17.6	19.0	24.6
Systolic BP (mm Hg)	132.5+26.1	131.8+23.2	128.2+23.1
Diastolic BP (mm Hg)	73.4+12.2	71.1+12.5**	71.3+12.1*
Mean Arterial BP (mm Hg)	93.1+14.5	93.5+15.0	90.1+14.2*^
Heart Rate (beats/min)	79.1+16.4	78.6+15.5	76.4+14.2
BSA (m2)	1.89+0.29	2.23+0.26***	1.79+0.17***^^
BNP (pg/ml)	677+910	477+739	818+1067*
Hemoglobin (g/dl)	12.7+2.2	12.7+2.2	12.0+1.9**^^^

(Table 1) contd.....

-	HFunEF (n=187)	HFpEF (n=269)	HFrEF (n=364)
Sodium (mmol/l)	138.2±4.6	137.4±3.2	137.3±3.3
Blood Urea Nitrogen (mg/dl)	24.0±14.1	23.0±13.5	24.1±13.7
Creatinine (mg/dl)	1.30±1.00	1.28±0.78	1.38±0.98
Troponin I (ng/ml)	0.188±1.244	0.724±4.512	0.354±2.112

Abbreviations: ACEI/ARB=angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BP=blood pressure; BSA=body surface area; BNP=brain natriuretic peptide;

Statistics: *p<0.05, **p<0.01, p<0.0001 vs HF with mid-range ejection fraction; ^p<0.05, ^^p<0.001, HFpEF vs HFrEF

Table **2** summarizes differences between patients with HF and mid-range ejection fraction (40-49%) and patients with HF and low ejection fractions (<40%). Patients with ejection fraction<40% comprised 36.5% of the HFrEF group. As compared to HF with mid-range ejection fraction, patients with HF and ejection fraction <40% had a lower prevalence of coronary disease but a more left anterior descending disease with apical akinesis, less hypertension and hyperlipidemia, and lower creatinine.

Table 2. Baseline characteristics, Doppler echocardiographic and outcome variables.

-	HFmrEF (n=231)	HFlowEF (n=133)
Age (years)	74±12	76±14
Sex (M/F)	101/130	65/68
Coronary disease (%)	64.9	54.1**
Myocardial Infarction (%)	32.9	24.0
Left anterior descending disease (%)	39.2	59.1*
Apical akinesis (%)	32.3	47.7*
Diabetes Mellitus (%)	46.8	44.4
Hypertension (%)	92.2	85.0*
Hyperlipidemia (%)	81.0	69.9*
ACEI/ARB (%)	64.5	63.2
Atrial fibrillation (%)	19.5	26.3
Beta blockers (%)	72.3	71.4
Diuretics (%)	79.4	83.1
Aldosterone blocker (%)	10.0	14.3
Nitrates (%)	9.0	9.8
Hydralazine (%)	9.8	6.8
Digoxin (%)	10.8	15.0
Calcium channel blockers (%)	23.8	25.6
Systolic Blood Pressure (mm Hg)	127.3±23.0	128.3±23.7
Diastolic Blood Pressure (mm Hg)	71.3±11.9	71.3±12.1
Mean Arterial Pressure (mm Hg)	90.0±14.1	90.3±14.1
Heart Rate (beats/min)	75.9±14.2	76.5±13.8
Body surface area (m2)	1.88±0.09	1.62±0.14***
BNP (pg/l)	803±1069	825±1080
Hemoglobin (g/dl)	12.0±1.9	11.9±2.0
Creatinine (mg/dl)	1.47±1.13	1.20±0.73*
LVEDVI (ml/m2)	58.0±25.0	55.4±19.2
LVESVI (ml/m2)	32.9±22.5	34.6±16.3
Ejection Fraction (%)	46.5±2.3	37.4±4.5***
Left atrial volume index (ml/m2)	35.4±17.3	37.0±14.3
E (cm/s)	101.8±35.2	110.6±37.9*
E/e'	14.3±6.5	15.4±7.3
Stroke volume index (ml/m2)	37.2±14.5	41.3±17.8
Tricuspid Regurgitation velocity (m/s)	2.86±0.6	2.93±0.6
CHF1 score>4 or BNP>100 pg/ml	60.3	56.3
1st Readmission rate (%)	44.6	45.1
2nd Readmission rate (%)	23.3	23.3
2nd Readmission rate- previously readmitted (%)	51.5	53.1

(Table 2) contd.....

-	HFmrEF (n=231)	HFlowEF (n=133)
ACM rate (%)	32.4	38.9

Abbreviations: See previous tables; CHF1score=Framingham HF score; HFmrEF= HF with mid-range ejection fraction; HFlowEF=HF with low ejection fraction<40
Statistics: *p<0.05, **p<0.01, ***p<0.0001 vs HFmrEF

Table 3. Echo-Doppler parameters.

-	HFpEF (n=269)	HFrEF (n=364)
LVEDVI (ml/m2)	51.9+20.5	57.1+23.2**
LVESVI (ml/m2)	29.3+19.4	31.3+20.2*
Ejection Fraction (%)	55.2+4.0	41.3+20.6***
LV Mass Index (g/m2)	98.3+30.8	100.1+31.0
Left atrial volume index (ml/m2)	32.7+14.3	38.7+18.6**
E (cm/s)	100.3+33.8	74.6+58.9*
E/A	1.26+0.65	1.33+0.74
Deceleration time (msec)	223.1+73.2	216.9+74.7
E/e'	13.3+6.0	14.8+6.9
Stroke volume index (ml/m2)	35.0+14.1	36.7+15.9
TR velocity (m/s)	2.78+0.59	2.88+0.60
RAP (mm Hg)	7.2+4.4	7.7+4.7
TAPSE (mm)	13.9+6.1	14.0+5.3
RV base (cm)	3.9+0.9	3.8+0.8

Abbreviations: LVEDVI=LV end-diastolic volume index; LVESVI=LV end-systolic volume index; E=peak rapid mitral filling velocity; E/A=peak rapid mitral filling velocity/peak atrial filling velocity; E/e'=peak rapid mitral filling velocity/peak early diastolic mitral annular velocity; TR=tricuspid regurgitation; RAP=right atrial pressure;; TAPSE=Tricuspid annular plane systolic excursion; RV base=Right ventricular end-diastolic basal dimension
Statistics: *p<0.05, **p<0.01, p<0.0001 *vs* HFpEF

Table 4. Heart failure readmission and all-cause mortality.

-	HFunEF (n=187)	HFpEF (n=269)	HFrEF (n=364)
Verifiable HF: CHF1 score>4 or BNP>100 pg/ml	30.9	57.9**	58.9**
1st HF Readmission rate (%)	16.0	40.1***	45.1***
1st HF readmission (days)	1864+1935	1372+1190***	1431+1699**
2nd HF readmission rate based on previous readmission rate (%)	25.0	42.6*	53.1**
2nd HF readmission based on previous readmission (days)	156+449	316+540***	285+521**
ACM (%)	43.4	26.7*	34.2
ACM (Days)	1668+1046	1668+1045	1674+1668

Abbreviations: see previous tables
Statistics: *p<0.05, **p<0.01, ***p<0.001 vs HFunEF

Table **3** summarizes the Echo-Doppler parameters for HFpEF and HFrEF. Patients with HFunEF did not have echocardiograms performed. Patients with HFrEF had greater LV and left atrial volume indexes and a lower LV ejection fraction.

Table **4** summarizes HF readmission and ACM for all 3 HF phenotypes. *As compared to HFunEF, patients with HFpEF* were greater in number with verifiable HF, higher HF readmission rate in a fewer number of days, a higher 2nd HF readmission rate for patients admitted once for HF in a fewer number of days, and a lower ACM. *As compared to HFunEF,* patients with HFrEF demonstrated a greater percentage of patients with verifiable HF, higher HF readmission rate in a fewer number of days, and a higher 2nd HF readmission rate for patients admitted once for HF in a fewer number of days.

Table **5** summarizes the multiple logistic regression analysis for HF readmission, 2nd HF readmission for patients already readmitted once, and ACM for all phenotypes. For *HFunEF*, diabetes and ACM were independently related to HF readmission. Age, diabetes, and HF readmission were independently related to ACM. For *HFpEF*, ACM was independently related to HF readmission. For 2nd HF readmission for patients previously readmitted, BNP>100 pg/ml was independently related. For ACM, HF readmission, age, mitral regurgitation, and hemoglobin were independently related. For *HFrEF*, BNP>100 pg/ml and beta-blocker use (inverse relation) were independently related to HF readmission. BNP>100 pg/ml was independently related to the 2nd HF readmission for patients previously readmitted. BNP >100 pg/ml, hemoglobin, and age were independently related to ACM.

Table 5. Predictors of heart failure readmission, all-cause mortality, and 2nd readmission in patients previously readmitted.

-	HF with *Unknown Ejection* Fraction	HFpEF	HFrEF
HF Readmission	**Diabetes** OR:3.29(1.38-8.25),p=0.011	**ACM** OR:2.46(1.23-4.91),p=0.011	**BNP>100pg/ml** OR:4.78(2.99-7.57),p<0.001
-	**ACM** OR:2.40(1.01-3.78), p=0.049	-	**Beta blocker use** OR:0.47(0.25-0.88),p=0.019
2nd HF Readmission for patients previously readmitted	**none**	**BNP>100 pg/ml** OR:1.81(1.03-2.89),p=0.032	**BNP>100 pg/ml** OR:1.78(1.01-3.52),p=0.041
ACM	**Age** OR:1.06(1.02-1.76),p=0.007	**HF Readmission** OR:2.98(1.62-5.51),p<0.001	**BNP>100 pg/ml** OR:2.27(1.38-3.73),p<0.001
-	**Diabetes** OR:2.44(1.19-4.98),p=0.015	**Age** OR:1.07(1.03-1.92),p<0.001	**Hemoglobin** OR:0.80(0.71-0.91),p=0.006
-	**HF Readmission** OR:1.48(1.01-1.67),p=0.046	**Mitral regurgitation** OR:2.52(1.09-5.82),p=0.031	**Age** OR:1.03(1.01-1.05),p=0.017
-	-	**Hemoglobin** OR:0.88(0.75-0.99),p=0.049	-

Abbreviations: See previous tables

Fig. (**1A**) depicts the adjusted Kaplan-Meier curves for ACM for each phenotype over the length of follow-up and indicates that HFunEF had significantly greater ACM than HFpEF (HR=1.60, p=0.004), and HFrEF had significantly greater ACM than HFpEF (HR=1.84, p=0.043). When HFrEF is subdivided (Fig. **1B**), there was no significant difference in ACM between subgroups with LV ejection fraction <40% and LV with mid-range ejection fraction=40-49%.
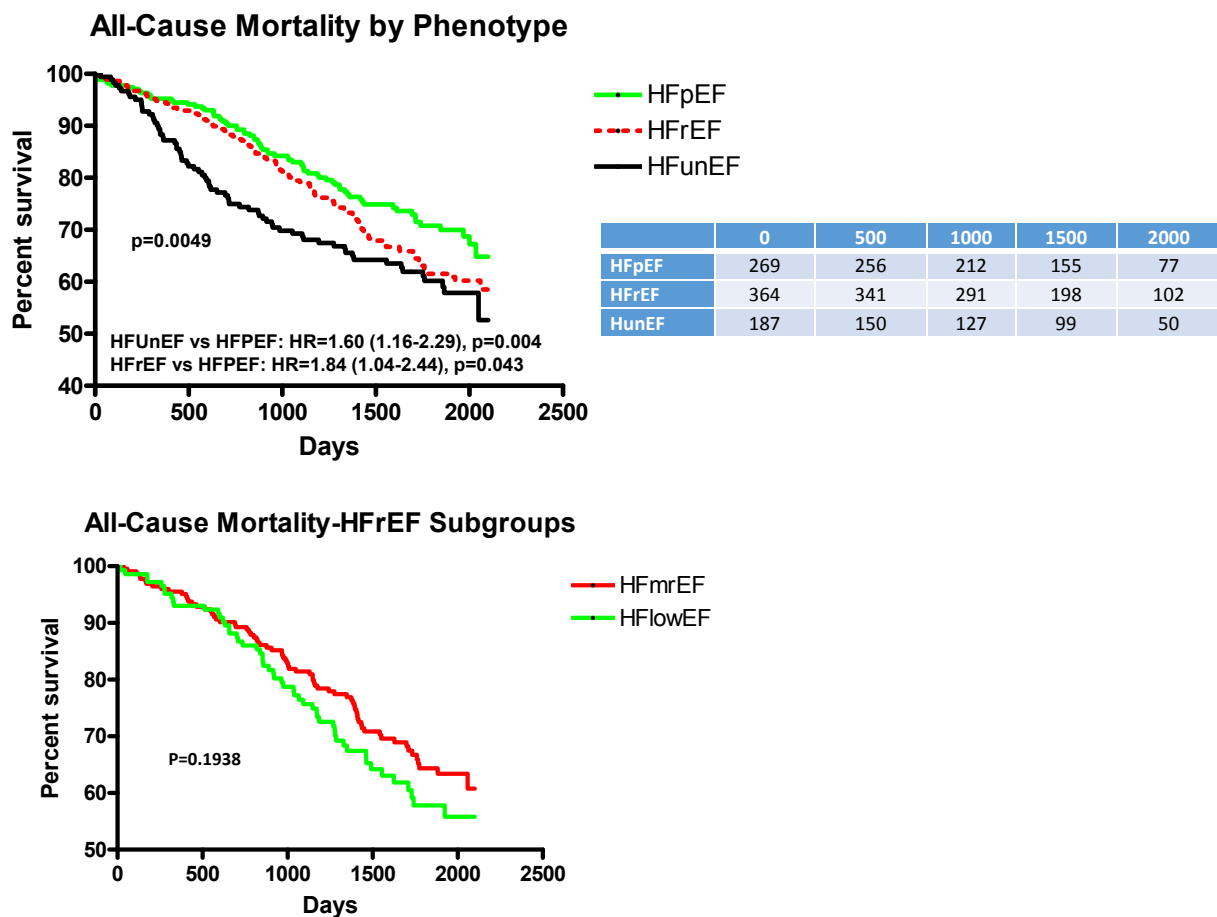

	0	500	1000	1500	2000
HFpEF	269	256	212	155	77
HFrEF	364	341	291	198	102
HunEF	187	150	127	99	50

Fig. (1). Kaplan-Meier plots of all-cause mortality (**A**) for HFpEF, HFrEF, and HFunEF. There was greater all-cause mortality for both HFunEF and HFrEF than HFpEF. Kaplan-Meier plots of all-cause mortality for HFrEF subgroups (**B**): HF with mid-range ejection fraction (HFmrEF) and HF with ejection fraction< 40% (HFlowEF). There were no difference between the subgroups.

Fig. (**2A**) depicts the adjusted Kaplan-Meier curves for HF readmission for all HF phenotypes over the length of follow-up. There was a significantly lower rate of readmission for HFunEF as compared to both HFpEF and HFrEF with HR's of 0.28 (p<0.0001) and 0.30 (p<0.0001), respectively, with similar HF readmission between the 2 HFrEF subgroups (Fig. **2B**).

Fig. (**3A**) depicts the adjusted rate of 2nd HF readmission for patients previously readmitted for HF. There was a lower rate of 2nd HF readmission over the length of follow-up for patients with HFunEF as compared to HFrEF and HFpEF with HR of 0.40 and 0.56, respectively, but the curves are superimposable for the 2 subgroups of HFrEF (Fig. **3B**).

Fig. (**4A**) demonstrates increased ACM in patients with HFpEF and HFrEF who have been previously readmitted. There was only a trend for patients with HFunEF with increased ACM with prior HF readmission. When HFrEF was divided into subgroups, increased HRs were noted with both subgroups (Fig. **4B**)
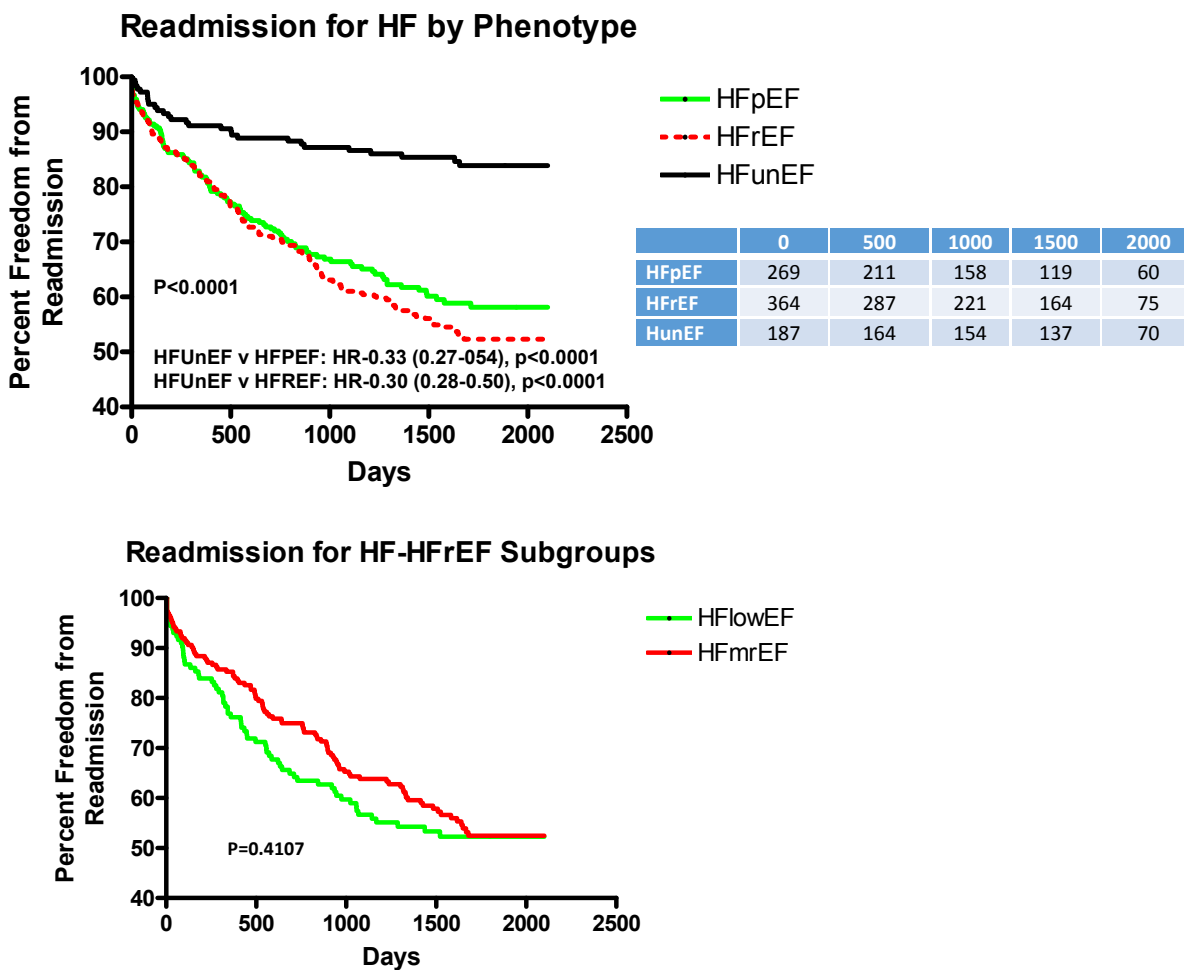

	0	500	1000	1500	2000
HFpEF	269	211	158	119	60
HFrEF	364	287	221	164	75
HunEF	187	164	154	137	70

Fig. (2). Kaplan-Meier plots of HF readmission (**A**) for HFpEF, HFrEF, and HFunEF. There was greater HF readmission in patients with HFunEF than for the other 2 phenotypes. Kaplan-Meier plots of HF (**B**) readmission for the subgroups of HFrEF. There were no differences between the subgroups. Abbreviations: HF=heart failure and see Fig. (**1**) for abbreviations.
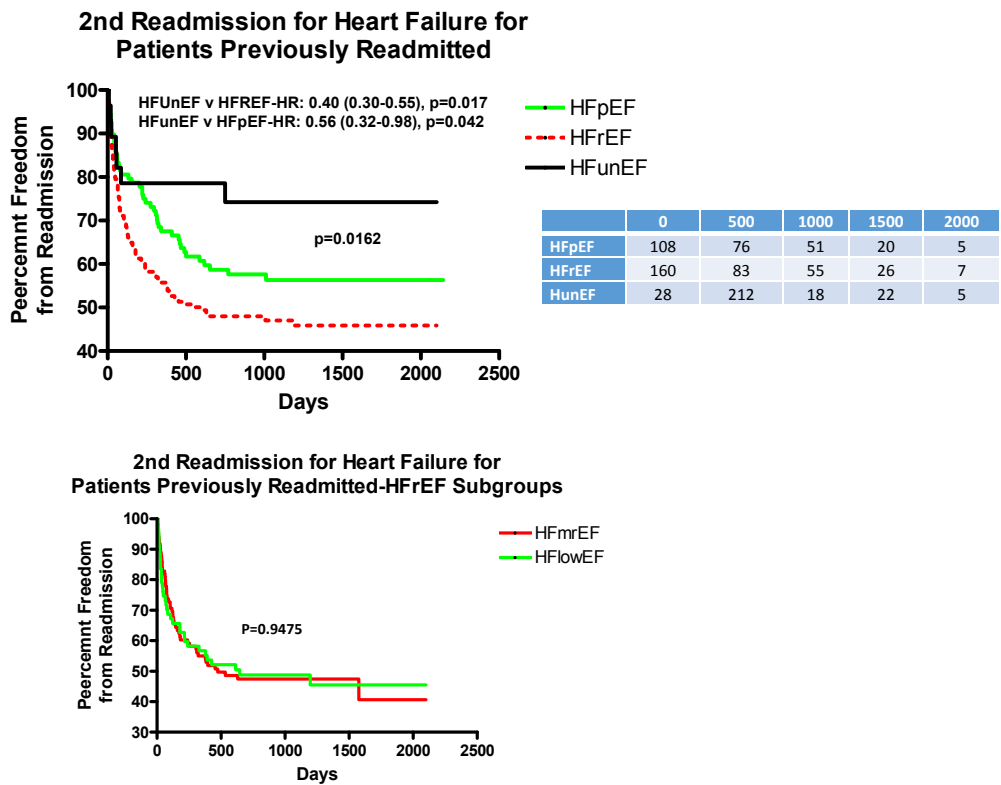
2nd Readmission for Heart Failure for Patients Previously Readmitted

	0	500	1000	1500	2000
HFpEF	108	76	51	20	5
HFrEF	160	83	55	26	7
HunEF	28	212	18	22	5

2nd Readmission for Heart Failure for Patients Previously Readmitted-HFrEF Subgroups

Fig. (3). Kaplan-Meier plots (**A**) for 2nd HF readmission for patients previously readmitted for HFpEF, HFrEF, and HFunEF. There was greater 2nd HF readmission in patients with HFunEF than the other 2 phenotypes. Kaplan-Meier plots (**B**) for 2nd HF readmission for patients previously readmitted for HF for the subgroups of HFrEF. There were no differences between subgroups. See Fig. (**1**) for abbreviations.
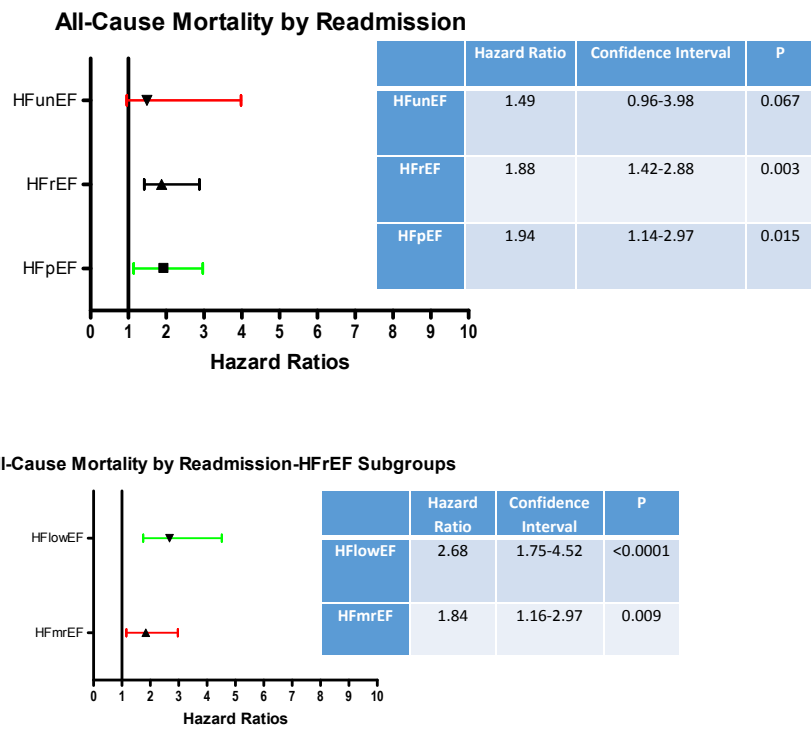
All-Cause Mortality by Readmission

	Hazard Ratio	Confidence Interval	P
HFunEF	1.49	0.96-3.98	0.067
HFrEF	1.88	1.42-2.88	0.003
HFpEF	1.94	1.14-2.97	0.015

All-Cause Mortality by Readmission-HFrEF Subgroups

	Hazard Ratio	Confidence Interval	P
HFlowEF	2.68	1.75-4.52	<0.0001
HFmrEF	1.84	1.16-2.97	0.009

Fig. (4). Forest plots (**A**) for all-cause mortality by the previous readmission are shown for HFpEF, HFrEF, and HFunEF. Both HFpEF and HFrEF demonstrate increased all-cause mortality by the previous readmission. Only a trend is noted for HFunEF. Forest plots (**B**) for all-cause mortality by the previous readmission are shown for the subgroups of HFrEF. Both subgroups demonstrate increased all-cause mortality by previous readmission.

4. DISCUSSION

In this study, we demonstrated that in a rural community cohort, 22.8% of patients with a diagnosis of HF did not have an ejection fraction calculation and 70% were cared for by family medicine. Second, patients with HFunEF had a lower prevalence of coronary disease, hyperlipidemia and lower diastolic blood pressure. Third, adjusted ACM was increased as compared to HFpEF and HF readmission was reduced as compared to the other HF phenotypes possibly related to the increased ACM. Furthermore, the 2nd readmission in patients previously readmitted was also reduced as compared to the other HF phenotypes. Fourth, ACM based on prior readmission only showed a positive trend as compared to significant increases in HFpEF and HFrEF. Finally, although differences were noted in subdividing HFrEF into subgroups with HF with LV ejection fraction<40% or HF with LV ejection fraction between 40-49%, ACM and HF readmission were similar.

4.1. Previous Literature

HF is a chronic problem associated with high morbidity and mortality with higher prevalence and incidence in the elderly population due to increased survival from myocardial infarction and increased prevalence of co-morbidities with aging. Diagnosis can be easily missed due to non-specific symptoms that simulate respiratory conditions and lack of access to or use of echocardiography. Diagnosis of HF can be further substantiated and phenotyped with echocardiographic assessment characterized by either HFrEF or HFpEF. According to the European Society of Cardiology, HF is clinically defined as a syndrome in patients with typical symptoms (shortness of breath, fatigue and ankle swelling) and signs (elevated jugular venous pressure, pulmonary crackles, and displaced heartbeat) resulting from an abnormality in cardiac structure and function [14]. The diagnosis of HFrEF requires 3 criteria: symptoms, signs as stated above, and a reduced LV ejection fraction. The diagnosis of HFpEF needs 4 criteria: typical symptoms, signs, LV ejection fraction >50%, and structural heart disease including LV hypertrophy, left atrial enlargement and/or diastolic dysfunction. However, there are patients who are not "phenotyped" in administrative or even patient-level databases because an assessment of LV ejection fraction was not performed. This study addresses the characteristics and some of their outcomes from a single rural database in a community medical school without a specific HF service.

Explanations as to why patients without an ejection fraction determination should demonstrate increased ACM are at best speculative. Differences in clinical characteristics include a lower prevalence of coronary disease, hyperlipidemia, mitral and aortic regurgitation as compared to HFrEF. These differences, except for coronary disease, are small and unrelated to ACM by multiple logistic regression. The lower prevalence would not have an obvious mechanistic reason to increase ACM. Additionally, HF medication (angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, beta-blockers, and aldosterone antagonists) that is used to promote survival, was limited in this group and similar to the other groups. Of note, readmission for HF was

lower and consequently, attention to HF care may have been reduced in this group. We were unable to characterize the cause of ACM, whether it is non-cardiac or cardiac and the prevalence of sudden death.

Previous studies have reported an increased prevalence of ***unrecognized HF*** in elder populations referred to a cardiologist or to the hospital for echocardiography to confirm the diagnosis. Riet *et al*. [15], studied 585 patients >65 years old presenting to the primary care physician with dyspnea on exertion in the last 12 months but no confirmatory echocardiogram to determine the prevalence of HF in the elderly population. These patients underwent history examination, physical exam, electrocardiography and serum N-terminal pro-B-type natriuretic peptide testing with echocardiography performed only in patients with abnormal electrocardiography or serum N-terminal pro B-type natriuretic peptide >15 pmol/ml. Using European Society of Cardiology Guidelines, 92 patients had HF, 17/585 (2.9%) had HFrEF and 70/585 (12%) had HEpEF, while 5 (0.9%) had isolated right-sided HF. They also noted that HF was confused with chronic obstructive pulmonary disease and other respiratory problems in the primary care setting, which could lead to delay in diagnosis resulting in increased HF hospitalization, morbidity and mortality. Winter *et al*. [16], demonstrated the prevalence of unknown HF and LV dysfunction in patients >60 years of age with type 2 diabetes mellitus. Patients were diagnosed with HF on the basis of the European Society of Cardiology Guidelines. Of the 581 patients studied; 161 were diagnosed with HF: 28 (4.8%) had HFrEF and 133 (22.9%) had HFpEF. There was increased prevalence with age and a female sex preponderance. Barents *et al*. [17], reported the prevalence, misdiagnosis of chronic HF and the role of natriuretic peptides in 150 nursing home residents using the New York Heart Association classification and natriuretic peptides. HF diagnosis was confirmed in 24 residents, out of which, 15 had de-novo HF. Another important feature is that 13 out of 22, who were thought to have HF before screening, were rejected after the screening. Rutten *et al*. [18], reported the prevalence of HF in an elderly population with stable chronic obstructive pulmonary disease in whom patients had a detailed history, physical exam, chest radiography, ECG, echocardiography and pulmonary function testing. The diagnosis of HF was based on the European Society of Cardiology guidelines. Unrecognized HF was noted in 83 of 405 patients. Of the 83 patients, 42 had HFrEF and 41 had HFpEF. Most males who were younger had HFrEF, while HFpEF was common in elder women. Finally, Mosterd *et al*., included 5450 participants aged 55-95 years in the Rotterdam study to determine the prevalence of HF and symptomatic or asymptomatic LV systolic dysfunction. The overall prevalence of HF was 3.9%, with no difference between men and women, with an increased prevalence with age. The prevalence of LV systolic dysfunction was 3.7% and 2.5 times more common in men and most were asymptomatic. Most of the previous literature commented on the characteristics of populations screened for LV dysfunction or HF in variably symptomatic populations. ***There is little data characterizing patients with HFunEFand their outcomes,*** most likely due to national programs and core hospital measures advocating and requiring an assessment of LV

ejection fraction. Patient data and outcomes are often not evaluated in this subset of patients.

4.2. Limitations

As this was a retrospective evaluation of a community-based outpatient practice, it is limited by numbers and population diversity and the inherent nature of a retrospective study. Second, data abstraction was based on a chart review of both inpatient and outpatient recorded symptoms and medications. ACM was based on chart review, national death index, and obituary review and may not have reflected all mortality. Cardiovascular mortality could not be discerned nor medication compliance. Furthermore, optimal dosing was not evaluated in this study with regard to outcomes because of changing dosages in many patients for unclear reasons despite chart abstraction. Third, readmissions for HF may have occurred outside the East Tennessee area. The additional hospital system's records in the area were available and reviewed for admissions as patients may use both systems. Fourth, laboratory values were not available in all patients for BNP (7% missing), with non-significant differences among HF phenotypes ranging from 5-10%. Fifth, as there is inherent variability in the measurement of ejection fraction, this may lead to assigning patients to the wrong phenotype. As this was a retrospective study, there may be additional unknown differences among HF phenotype groups that were not accounted for.

4.3. Clinical Implications

Despite the requirement for hospital HF core measures for ejection fraction determination for all inpatients being observed in >90% cases, there are still patients with HF diagnosis who have do not have an assessment of ejection fraction. Furthermore, there appears to be an underutilization of guideline-based medications. The majority of such patients were seen by non-cardiovascular providers in this study, but is likely true in many populations. Unfortunately, these patients are readmitted less but have greater ACM. Demographic variables and laboratory variables, including brain natriuretic peptide, show little difference. Although this study portrays them as a separate phenotype, they clearly are not. More importantly, the lack of structural information afforded by echocardiography represents a lost opportunity and may have a role in their outcomes. It is also not inconceivable that non-cardiac causes may predominate their causes of death. The degree of detail and attention paid to ambulatory HF programs will need to be focused on all providers to afford patients' optimal care and outcomes.

CONCLUSION

In patients with HFunEF, ACM is increased and readmission for HF is reduced as compared to other phenotypes. The lack of structural information afforded by echocardiography may impact the care provided especially by non-cardiovascular providers in a rural community-based setting.

LIST OF ABBREVIATIONS

ACM	=	All-cause mortality
BNP	=	Brain natriuretic peptide
HFunEF	=	HF with unknown ejection fraction
HF	=	Heart failure
HR	=	Hazard ration
HFrEF	=	HF with reduced ejection fraction
HFpEF	=	HF with preserved ejection fraction
LV	=	Left ventricular

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This stude has been approved by East Tennessee State University, USA IRB-0515.18sw.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

The data in the manuscript can not be shared because the data despite being de-identified is obtained from a small rural area with a limited population using the University medical practice. The possibility of patient anonymity can not be guaranteed.

FUNDING

CONFLICTS OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

REFERENCES

[1]   Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992; 20(2): 301-6.
[http://dx.doi.org/10.1016/0735-1097(92)90094-4] [PMID: 1634664]

[2]   Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996; 275(20): 1557-62.
[http://dx.doi.org/10.1001/jama.1996.03530440037034] [PMID: 8622246]

[3]   Rich MW. Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. J Am Geriatr Soc 1997; 45(8): 968-74.
[http://dx.doi.org/10.1111/j.1532-5415.1997.tb02968.x] [PMID: 9256850]

[4]   Deedwania PC. The progression from hypertension to heart failure. Am J Hypertens 1997; 10(10 Pt 2): 280S-8S.
[http://dx.doi.org/10.1016/S0895-7061(97)00335-X] [PMID:

9366285]

[5]   Tsao CW, Lyass A, Enserro D, *et al.* Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. JACC Heart Fail 2018; 6(8): 678-85.
[http://dx.doi.org/10.1016/j.jchf.2018.03.006] [PMID: 30007560]

[6]   Shah KS, Xu H, Matsouaka RA, *et al.* Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol 2017; 70(20): 2476-86.
[http://dx.doi.org/10.1016/j.jacc.2017.08.074] [PMID: 29141781]

[7]   Caughey MC, Sueta CA, Stearns SC, Shah AM, Rosamond WD, Chang PP. Recurrent acute decompensated heart failure admissions for patients with reduced versus preserved ejection fraction (from the atherosclerosis risk in communities study). Am J Cardiol 2018; 122(1): 108-14.
[http://dx.doi.org/10.1016/j.amjcard.2018.03.011] [PMID: 29703442]

[8]   Burgess DC, Hunt D, Li L, *et al.* Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Eur Heart J 2010; 31(1): 92-9.
[http://dx.doi.org/10.1093/eurheartj/ehp377] [PMID: 19797259]

[9]   Bonaca MP, Wiviott SD, Braunwald E, *et al.* American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38). Circulation 2012; 125(4): 577-83.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.111.041160] [PMID: 22199016]

[10] Kilbride HS, Stevens PE, Eaglestone G, *et al.* Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis 2013; 61(1): 57-66.
[http://dx.doi.org/10.1053/j.ajkd.2012.06.016] [PMID: 22889713]

[11] McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971; 285(26): 1441-6.
[http://dx.doi.org/10.1056/NEJM197112232852601]   [PMID: 5122894]

[12] Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28(1): 1-39.e14.
[http://dx.doi.org/10.1016/j.echo.2014.10.003] [PMID: 25559473]

[13] Nagueh SF, Smiseth OA, Appleton CP, *et al.* Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016; 29(4): 277-314.
[http://dx.doi.org/10.1016/j.echo.2016.01.011] [PMID: 27037982]

[14] Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37(27): 2129-200.
[http://dx.doi.org/10.1093/eurheartj/ehw128] [PMID: 27206819]

[15] van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail 2014; 16(7): 772-7.
[http://dx.doi.org/10.1002/ejhf.110] [PMID: 24863953]

[16] Boonman-de Winter LJ, Rutten FH, Cramer MJ, *et al.* High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia 2012; 55(8): 2154-62.
[http://dx.doi.org/10.1007/s00125-012-2579-0] [PMID: 22618812]

[17] Barents M, van der Horst ICC, Voors AA, Hillege JL, Muskiet FAJ, de Jongste MJL. Prevalence and misdiagnosis of chronic heart failure in nursing home residents: the role of B-type natriuretic peptides. Neth Heart J 2008; 16(4): 123-8.
[http://dx.doi.org/10.1007/BF03086130] [PMID: 18427636]

[18] Rutten FH, Cramer MJ, Grobbee DE, *et al.* Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005; 26(18): 1887-94.
[http://dx.doi.org/10.1093/eurheartj/ehi291] [PMID: 15860516]