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Baseline Characteristics and Outcome of Patients with Heart Failure and Preserved Ejection Fraction Included in an Algerian Cohort

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Abstract

Background: *Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disease with a complex pathophysiology. Clinical presentation depends on comorbities and dominant etiology. This work aims to describe the baseline characteristics and outcome of an Algerian cohort of patients with HFpEF.*

Patients and methods: *A prospective observational study from April 2018 to April 2020, including patients aged 18 and over, referred to the echocardiography laboratory for HFpEF as defined according to the ESC 2016 criteria. Comprehensive Doppler echocardiography was performed at admission and levels of N-terminal Pro B-type Natriuretic Peptide (NT-proBNP) and Growth Differenciation Factor 15 (GDF 15) were measured. The outcome of the study was a composite endpoint of death from any cause, rehospitalization for HF or stroke at 1 year.*

Results: *153 patients were enrolled. The mean age was 73 ±11 years, and 67% were female. Patients were very frequently hypertensive (86%) and diabetic (64%) with a history of atrial fibrillation (46%), anemia (42.48%), chronic renal insinsufficiency (CRI) (38.56%), and obesity (35.76%). Among the echocardiographic parameters, left atrial dilatation was found in 80% of cases, Left ventricular hypertrophy (LVH) in 74% of cases and an E/é ratio > 13 in 69% of cases. Sixty-three percent of patients had an impaired global longitudinal strain (GLS < 16%) despite preserved LVEF (59% ±7%).*

*The median value of NT-proBNP was 1284 (Interquartile range **[**IQR**]**: 442-3109) with extremes ranging from 133 to 35000 pg/ml. The median value of Growth Differentiation Factor 15 (GDF 15) was 2530 (IQR: 1492-3929) with extremes ranging from 400 to 25632 pg/ml, and 87% of patients had a GDF 15 level > 1200 pg/ml.*

At one year follow up, rate of rehospitalization for heart failure and mortality were 5.9% and 13.7% respectively. Nearly half of deaths (45%) were from non-cardiovascular causes. The independent prognostic factors associated with one year outcome (composite endpoint of rehospitalization for HF, death from any cause or stroke) were: signs of peripheral venous congestion, anemia, and pulmonary artery systolic pressure at admission (all p<0.05). GDF 15 and NT-proBNP were associated with outcome in univariable but not in multivariable analysis.

Conclusion: *The patients included in our cohort are mainly elderly and hypertensive women, and more than half were diabetic. Majority of patients had impaired longitudinal strain with increased LV mass, impaired diastolic function, and high levels of GDF 15. The independent prognostic factors associated with one year outcome were: signs of peripheral venous congestion, anemia and PASP.*

Keywords: *Heart failure with preserved ejection fraction; Echocardiography; comorbidities, outcome.*

Abbreviations

ACE:	Angiotensin conversion Enzym
AF:	Atrial fibrillation
ARB:	Angiotensin Receptors Blockers
ARNI:	Angiotensin Receptors Neprilysin Inhibitors
BMI:	Body Mass Index
BNP:	Brain Natriuretic Peptide
CI:	Confidence intervall
CR:	Chronic renal insufficiency
COPD:	Chronic obstructive pulmonary disease
Cor:	Pearson's product-moment correlation
EF:	Ejection fraction
ESC:	European Society of cardiology
GDF:	Growth Differentiation Factor
GLS:	Global longitudinal strain

HF: Heart failure

HFpEF: Heart failure with a preserved ejection fraction

HFrEF: Heart failure with a reduced ejection fraction

LA: Left atrium

LAV: Left atrial volume

LV: Left ventricle

LVEF: Left ventricular ejection fraction

LVH: Left ventricular hypertrophy

LVM: Left ventricular mass

MACE: Major acute cardiovascular events

6M-WT: 6 Minutes' Walk Test

NT-proBNP: N terminal pro Brain Natriuretic Peptide

Pg: Picograms

Rho: Spearman's rank correlation

SD: Standard deviation

Introduction

Heart failure (HF) is a global public health issue because of its high prevalence, morbidity and socio-economic impact on the health system. Due to the sudden rise in prevalence and hospitalizations between the 1970s and 1990s, it is commonly referred to as an "epidemic". **[**1,2**]**

HF with preserved ejection fraction (HFpEF) accounts for 40 -70% of heart failure cases. **[**3,4**]** It is one of the leading causes of morbidity and mortality with a significant impact on quality of life, comparable to that of heart failure with reduced ejection fraction (HFrEF). **[**5**]** The prevalence of HFpEF increases with population aging, with a simultaneous increasing prevalence of co-morbidities including hypertension, obesity and diabetes. Labeled as an "orphan disease", many uncertainties remain about it. The perception of the HFpEF as a heterogeneous and complex entity, depending on the dominant etiology and the various comorbidities, could largely explain the failures of the clinical

trials. [6,7] In this report, we describe the clinical aspects, echocardiographic characteristics and the outcome of an Algerian cohort of patients with HFpEF. The description is based on the definitions and threshold values published by the European Society of Cardiology in 2016 on the HFpEF.

Methods

This is a single-center prospective observational study conducted between April 2018 and April 2020, which consecutively included adults patients (≥ 18 years) referred to the echocardiography laboratory of the cardiology department A2 of Mustapha Bacha University Hospital (Algiers, Algeria), in whom the diagnosis of HFpEF was retained according to the criteria of European society of cardiogy (ESC) 2016. Namely, the presence of signs and/or symptoms of heart failure , a rate of N-terminal (NT)-pro B-type natriuretic peptide (NT- proBNP) > 125 pg/ml or BNP > 35 pg/ml with at least one ultrasound criterion of structural heart disease (left ventricle mass ≥ 115 g/m² in men and ≥95 g/m² in women, indexed left atrial volume > 34 ml/m²) or functional abnormality (E/é ≥ 13 and e' septal and lateral mean < 9 cm/s). Patients were excluded from the study if they had more than moderate valvulopathy, World Health Organization (WHO) class 1, 3, 4, or 5 Pulmonary arterial hypertension, right ventricular arrhythmogenic dysplasia, congenital heart disease, right ventricular infarction, pericardial disease: Tamponnade, constrictive pericarditis or specific cardiomyopathy: viral, inflammatory (Sarcoidosis), genetic (Hypertrophic Cardiomyopathy), restrictive cardiomyopathy. Comprehensive Doppler echocardiography was performed at admission (GE vivid 7) and blood samples were drawn. Patients were followed up to 1 year. The primary endpoint of the study was a composite of death, rehospitalization for heart failure or stroke at 1 year.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or n (%) unless otherwise specified. Dichotomous variables were analyzed using chi-square test and continuous variables using Kruskal-Wallis rank sum test. Cox proportional hazard analysis was used to determine the independent prognostic power of each variable to predict the outcome. For all tests, a p-value ≤ 0.05 was considered statistically significant. All statistical analyzes were carried out using R 4.0 software.

Results

One hundred fifty-three consecutive patients were enrolled with a follow-up of one year. The mean age of the study population was 73 ±11 years (ranging from 42 to 91 years) and the majority of patients were female (67%). Baseline characteristics of the study population are presented in Table 1.

Co-morbidities, risk factors and clinical presentation

Patients were predominantly hypertensive (86%) and diabetic (65%) with a history of atrial fibrillation in 46% of them. 36% of patients were obese, 39% had chronic renal insufficiency (CRI), defined by glomerular filtration rate <60ml/min/1.73m², 26% had coronary artery disease (CAD), and 20% had chronic obstructive pulmonary disease (COPD) . Anemia (HB< 13 g/dL in men and < 12g/dL in women according to the World Health Organization (WHO) definition, was present in 42% of the population .

Clinical Characteristics (N=153)	
Age (year)	73 ± 11
Female (n, %)	101 (67)
Hypertension (n, %)	133 (87)
Diabetes (n, %)	100 (65)
Obesity (n, %)	54 (36)
Chronic renal insufficency* (n, %)	59 (39)
Anemia (% prevalence)	65 (42)
Chronic obstructive pulmonary disease (n, %)	31 (20)
Smoking (n, %)	6 (4)
Coronary artery disease (n, %)	39 (26)
Atrial fibrillation (n, %)	70 (46)
Doppler Echocardiography characteristics	
Left ventricular ejection fraction (%)	59 ± 7
Indexed left ventricular mass (g/m²)	121 ±38
Indexed volume of left atrium (ml/m²)	48 ± 19
Average E/E' (ratio)	16 ± 5
Systolic pulmonary arterial pressure (mm Hg)	43± 13
TR peak velocity (m/s)	2.86 ± 0.43
Global longitudinal strain (%)	14.3 ± 4.6
Biochemical characteristics	
NT- Pro BNP (mediane [IQR]), pg/m	1284 [442-3109]
GDF 15 (mediane [IQR]), pg/m	2530[1492-3929]
Functional Capacity	
6-minute walking distance (Mean ±SD), m	265 ±149
Treatments	
Diuretics (n, %)	125 (82)
Angiotensin II Receptor Antagonists (ARA II) (n, %)	102 (67)
Converting enzyme inhibitors (ACE inhibitors) (n, %)	35 (23)
AIIB or ACE inhibitors (n, %)	137 (90)
Beta-blockers (n, %)	97 (63)
Calcium inhibitors (n, %)	47 (31)
Platelet antiaggregants (n, %)	59 (39)
Statin (n, %)	71 (46)
Spironolactone	36 (24)
Digoxin (n, %)	9 (6)

Table 1. Baseline characteristics of the population study.

TR: Tricuspid regurgitation, NT-proBNP: N-Terminal pro B-type natriuretic Peptide, GDF-15: Growth differentiation factor, IQR: interquartile range.

*: glomerular filtration rate < 60ml/min/1.73m²SC.

The majority of our patients had signs of isolated left heart failure (71%), ranging from dyspnea on exertion to orthopnea. Signs of peripheral venous congestion were noted in 29% of patients. 19% of patients were hospitalized for primary acute heart failure or worsening signs of congestive HF despite a therapeutic adjustment in the ambulatory setting, and the remaining (81%) were managed in the outpatient setting.

When comparing these factors and comorbidities according to gender (Table 2), we noted a statistically significant difference by gender in terms of smoking, Coronary artery disease, and the presence of CRI with a clear male predominance. On the other hand, the comparison of these comorbidities according to age (Table 3) showed a significant increase in COPD with age.

Doppler Echocardiographic measurements

Left ventricular ejection fraction (LVEF) varied from 50 to 77% with an average of 59% ±7%. The average indexed LV mass was 121± 38 g/m² with extremes ranging from 55 to 331 g/m². The prevalence of left ventricular hypertrophy (LVH) was 74% with eccentric type in 51% of patients. Isolated left ventricular remodeling with normal left ventricular mass was noted in 11% of cases, while normal left ventricular geometry was present in 15% of cases.

The average indexed left atrium volume(LAVI) was 48± 19 ml/m² with extremes ranging from 18 to 150 ml/m². 81% of patients had left atrial (LA) dilatation defined by a LAVI > 34ml/m².

The value of the average mitral E/e' ratio (Sepal and lateral) varied from 6 to 37 with an average of 15.8 ± 5. 61% of patients had an E/e' ratio > 14 while 94% of patients had an E/e' ratio > 9.

The peak velocity of tricuspid regurgitation (TR) ranged from 1.94 to 4.18 m/s with an average of 2.86 ± 0.43 m/s. 53% of patients had a TR peak velocity > 2.8 m/s.

The mean pulmonary artery systolic pressure (PASP) was 43mmHg with extremes ranging from 20 to 84 mmHg. 68% of patients had SPAP > 35mmHg.

The mean value of the global longitudinal strain (GLS) was 14.3% ±4.6) ranging from 3.2 to 24%. 63% of patients had an impaired longitudinal strain defined by a GLS ≤ 16%.

Comparaison according to gender showed a significantly higher E/e' ratio in women while the LV mass was significantly higher in men. That's expected since the two genders have different cut-offs. Note that there is no significant difference in prevalence of left ventricular hypertrophy.

Variable	Men, N= 52	Women, N= 101	p-value [1]	P value[2]
Age (classes), n (%)			0.7394	0.7251
40 - 54	5 (9.615)	8 (7.921)		
55 - 64	9 (17.31)	13 (12.87)		
65 - 74	17 (32.69)	25 (24.75)		
75-84	15 (28.85)	39 (38.61)		
85-94	6 (11.54)	16 (15.84)		
Type of heart failure, n / N (%)			0.9705	0.981
Global HF	11 (21.15)	24 (23.76)		
Right HF	3 (5.769)	7 (6.931)		
Left HF	38 (73.08)	70 (69.31)		
Comorbties and risk factors				
Diabetes, n (%)	35 (67.31)	65 (64.36)	0.9361	0.946
Hypertension, n (%)	43 (82.69)	90 (89.11)	0.5369	0.5197
Smoking, n (%)	6 (11.54)	0 (0)	**0.0023**	**0.0054**
Chronic renal insufficiency (CRI)*, (%)	27 (51.92)	32 (31.68)	0.0514	**0.0448**
Obesity, n (%)	13 (25)	41 (40.59)	0.1608	0.1529
Anemia, n (%)	26 (50)	39 (38.61)	0.4023	0.4078
Chronic obstructive Pulmonary Disease, n (%)	12 (23.08)	19 (18.81)	0.8243	0.8051
Coronary artery disease, n (%)	24 (46.15)	15 (14.85)	**0.0001**	**0.0004**
Atrial fibrillation, n (%)	21 (40.38)	49 (48.51	0.6331	0.6457
Echocardiographic findings				
LVEF, Mean± SD	58 ± 7	59.72±7	0.0950[x]	0.0959[y]
GLS, Mean ± SD	15 ± 4	14.02± 4	0.2372[x]	0.1942[y]
Indexed Left ventricular mass, Mean ± SD	133 ± 42	115± 33	**0.0083[x]**	**0.0059[y]**
Left ventricular Hypertrophy, n (%)	41 (78.85)	88 (87.13)	0.4106	0.4078
Type of LVH, n (%)			0.6578	0.6447
Eccentric LVH n (%)	20 (38.46)	38 (37.62)		
Concentric LVH n (%)	15 (28.85)	40 (39.6)		
Remodeing n (%)	7 (13.46)	10 (9.901)		
Normal geometry n (%)	10 (19.23)	13 (57%)		
E/E' ratio, Mean ± SD	14 ± 5	16.39±5	**0.0155[x]**	**0.0047[y]**
Left atrial dilatation, n (%)	42 (80.77)	81 (80.2)	0.9965	1
Left atrial volume, Mean± SD	51 ±23	46.7±15	0.2368[x]	0.3662[y]
Velocity of tricuspid regurgitation, Mean ± SD	2.85±0.44	2.84 ±0.42	0.8545[x]	0.5281[y]
Pulmonary arterial Systolic pressure,Mean ±SD	42 ± 13	41.89±13	0.80[x]	0.7549[Y]
Biomarkers				
NT-Pro BNP (pg/ml), Mean ± SD	2722 ±3422	3031±5704	0.677[X]	0.2558[Y]
GDF-15 (pg/ml), Mean ± SD	4184± 3969	3954 ±4637	0.7811[X]	0.6974[Y]
6 minutes walking distance (meter), Mean ±SD	322± 151	226±137	**0.0146[X]**	**0.0104[Y]**

1: Pearson's.Chi-squared_test with Yates' continuity correction ²:Fisher's Exact_Test for_Count_Data

x: Welch_Two_Sample_t-test; y: Wilcoxon_rank_sum_test_with_continuity_correction

HF: heart failure, LVEF: Left ventricle ejection fraction, GLS: Global longitudinal strain, LVH: Left ventricle hypertrophy, NT-proBNP: N-Terminal pro B-type natriuretic Peptide, GDF-15: Growth differentiation factor.

CRI: Chronic renal insufficiency *: glomerular filtration rate < 60ml/min/1.73m².

Table 2. Baseline characteristics of the population study by gender.

Variable	[40-64 y] N=35	[65-74 y] N= 42	[75-84 y] N= 54	≥85 y N= 22	p-value[1]	p-value[2]
Male	14(40)	17(40)	15(28)	6(27)	0.8428	0.8346
Type of HF, n (%)					0.402	0.3918
Global HF	7 (20)	8(19)	11 (20)	(41)		
Right HF	2(6)	5 (12)	1 (2)	2(9)		
Left HF	26(74)	29 (69)	42 (78)	11 (50)		
Diabetes, n (%)	19(54)	30(71)	38(70)	13(59)	0.7360	0.7626
Hypertension, n (%)	25(71)	38 (90)	52 (96)	18(82)	0.0509	0.0559
Smoking, n (%)	4 (11)	2(5)	0 (0)	0 (0)	0.2092	0.3013
CRI, n (%)	12(34)	15(36)	22(41)	10(45)	0.9870	0.9875
Obesity, n (%)	13(37)	14(33)	19(35)	8(36)	1	1
Anemia, n (%)	13(37)	22(52)	21(39)	9(41)	0.8795	0.8881
COPD, n (%)	0 (0)	7 (17)	16 (30)	8(36)	**0.0155**	**0.0049**
CAD, n (%)	13(37)	14(33)	11 (20)	1 (5)	0.1384	0.1049
Atrial fibrillation, n (%)	8(23)	21 (50)	27 (50)	14(64)	0.0907	0.0824
LVEF (%), Mean (sd)	58± 6.5	59± 7	60± 7	60± 7	0.7782[X]	0.8159[Y]
GLS (%), Moyenne (sd)	14± 4	14± 4.56	14± 3	16± 4	0.0672[X]	0.0777[Y]
ILVM, Mean (sd)	137± 46	112± 30	122± 35	110.6± 35.2	**0.0144[x]**	**0.0092[y]**
LVH, n (%)	31(89)	34(81)	45(83)	19(86)	0.9875[x]	0.9925[y]
Type of LVH, n (%)					0.4019	0.3558
Eccentric LVH	14 (40)	14(33)	22(41)	8 (36)		
Concentric LVH	17(49)	12(29)	19(35)	7 (32)		
Remodeling	0 (0%)	7 (17)	5 (9)	5 (23)		
Normal geometry	4(11)	9 (21)	8 (15)	2 (9)		
E/E' ratio, Mean (SD)	15± 6	16± 5	15± 5	17± 5	0.4628[x]	0.4144[y]
LA dilatation, n (%)	26(74)	31(74)	45(83)	21(95)	0.4881[x]	0.4573[y]
ILAV, Mean (sd)	45± 16	47± 24	49± 15	53± 17	0.381[x]	**0.0457[y]**
Velocity of TR (m/s), mean (sd)	2.73± 0.48	2.74± 0.36	2.91± 0.37	3.01± 0.51	**0.0201[x]**	**0.0123[y]**
PASP (mmHg), Mean (sd)	39± 14	39± 10	43± 12	49± 16	**0.0215[x]**	**0.0358[y]**
NT-Pro BNP (pg/ml), Mean (sd)	4066±7834	2445±3334	2669±4672	2664±212	0.5013[x]	0.1535[y]
GDF-15 (pg/ml), Mean (sd)	2332± 3821	3820 ± 3535	3916± 3587	8005± 6588	**0.0009[x]**	**0.0075[y]**
6-MWT(meters),Mean (sd)	378±120	263± 147	234±140	119± 37	**0.0001[x]**	**0.0006[y]**

1: Pearson's.Chi-squared test with Yates' continuitycorrection ²:Fisher's Exact Test for Count Data, X ANOVA; Y :Kruskal-Wallis rank sum test.

Y: years, HF: heart failure, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CRI: Chronic renal insufficiency, (*: glomerular filtration rate < 60ml/min/1.73m²). LVEF: Left ventricle ejection fraction, ILVM: Indexed left ventricular mass, SD: standard deviation, GLS: Global longitudinal strain, LVH: Left ventricle hypertrophy, LA: Left atrium, ILAV: Indexed left atrial volume, TR: Tricuspid regurgitation, PASP: Pulmonary artery systolic pressure, NT-proBNP: N-Terminal pro B-type natriuretic Peptide, GDF-15: Growth differentiation factor, 6-M. WT : 6-Minutes walking test.

Table 3. Characteristics of the study population by âge

Studies	Region	HFP EF	Age Years	Women %	LVE F %	Control Group	Monitoring
Wang and La [i]	USA	20	63+/-16	35%	≥50%	yes	no
Liu et al [ii]	Taiwan	26	68+/-13	31%	≥50%	yes	no
Phan et al [iii]	UK	40	67+/-10	73%	>50%	yes	no
Tan et al [iv]	UK	56	72+/-7	69.6%	>50%	yes	no
Kasner et al [v]	Germany	21	51+/-4.2	52%	≥50%	yes	No
Morris et al [vi]	Germany	119	70+/-10	44%	>50%	yes	No
Yip et al [vii]	China	112	74+/-12	**64%**	≥50%	yes	No
Abe et al [viii]	USA	10	65+/-12	30%	≥50%	yes	Undeclared
Obokata et al [ix]	Japan	40	77+/-13	**65%**	>50%	yes	No
Pillicori &al [x]	UK	138	78+/-10	37%	≥50%	yes	28months
Kraighkrain & al [xi]	International	219	71+/-9	**61%**	≥45%	yes	No
Menet et al [xii]	France	40	70+/-13	77%	≥50%	yes	No
Luo et al [xiii]	China	58	70+/-10	40%	≥50%	yes	No
Donal et al [30]	France.Swede	356	76+/-9	55.9%	>45%	no	28months
Wang et al [xiv]	China	80	66+/-8	37%	>50%	no	36months
Stamperhi &al [xv]	USA	100	60+/-1	76%	≥50%	no	12 months
Shah et al [xvi]	International	447	70.3+/-9.8	53.7%	≥45%	yes	31months
Kosmala et al [xvii]	Australia	207	63.7+/-8.6	73%	≥50%	yes	No
Morris et al [xviii]	Japan, Germany	218	72+/-10.5	52.3%	>50%	yes	No
Toufan &al [xix]	Iran	126	57.5+/-10	**69.8%**	≥50%	yes	No
Freed et al [xx]	USA	308	65+/-13	**64%**	≥50%	no	13 months
Carluccio et al [xxi]	Italy	46	75+/-8	52%	≥50%	yes	No
Iwano et al [xxii]	Japan, USA	50	59+/-16	70%	≥50%	yes	No
Hung et al [xxiii]	Taiwan	58	64.3+/-12.4	53.4%	>50%	yes	No
Obokata &al [xxiv]	Japan	102	77+/-11	57%	≥45%	no	12 months
Devore et al [xxv]	USA, Canada	187	69+/-2.5	48.1%	≥50%	no	06months

Huang & al [xxvi]	Singapore	129	75.1+/-10.7	58%	≥45%	no	36months
Lo et al [xxvii]	Taiwan	74	73.8+/-17	**60.8%**	≥50%	yes	No
Bosch et al [xxviii]	Singapore	159	68+/-11	52%	≥50%	yes	24months
Our study	**Algeria**	**153**	**73+/- 11**	**67%**	**≥50 %**	**no**	**12 months**

Table 4. General Characteristics of Individual HFpEF Patient Studies

On the other hand, comparison according to age, showed a significant increase in the indexed LA volume with age, while the increase in the peak velocity of TR and PASP were significant from the age of 75 years. Indexed LV mass was higher in patients between 40 and 64 years old and 75-84 years old.

Blood biomarkers

Regarding blood biomarkers, the mean value of the NT- pro BNP was 2995 ± 5148 pg/ml with extremes ranging from 133 to 35000 pg/ml. Plasmatic concentration of Growth Differentiation Factor 15 (GDF 15) was available in 111 (73%) patients only. The mean GDF 15 value was 4102±4274 pg/ml with a range of 400 to 25632 pg/ml. 70% of patients had values > 1800 pg/ml and 13% had values between 1200 and 1800 pg/ml, while only 13% had values < 1200 pg/ml. High levels of GDF 15 were significatively associated with age (P=0.004, cor= 0.27) , diabetes (p=0.01, rho=0.24), CRI (P=0.0034, rho=0.44), anemia (P=0.003, rho=0.27), left atrial volume (P=0.002, cor=0.29), atrial fibrillation (P=0.001, rho=0.30), PASP(P=0.032, cor=0.37), NT-ProBNP (P= 0.001, cor=0.49), and 6 minutes walking distance (P=0.0006, cor=-0.47)

GDF-15 was also sigificatively associated with the use of ACE inhibitors (P=0.02, rho= -0.21) , ARBs (P=0.20, rho= 0.210), and treatment with insulin (P-0.20, rho-0.21).

The 6-minute walking test: The 6-minute walking distance was performed in only 43% of our patients. The average walk distance was 265 ± 146 m, ranging from 100 to 512 m, with a walking distance < 300 meters in 53% of patients. Walking distance decreased inversely with age, especially in women.

Medication

With regard to the medical treatment, nearly 90% of patients were under angiotensin receptor antagonists or Angiotensin converting enzyme inhibitors, and 81% were under diuretics. 63% were on

beta-blockers, 46% were on statins, 38% were on anti-platelet agents, 31% were on calcium channel blockers, 25% were on Spironolactone, and 6% were on digoxin.

One year outcome

A total of 58 major adverse cardiac events (MACE) including death from any cause, hospitalization for heart failure or stroke were recorded during one year of follow-up, representing a rate of 38%. One year mortality was 13.73%, with nearly hal of cases (45%) from non cardiovascular cause. The rehospitalization rate for heart failure was 5.9%.

In univariable analysis, factors that were associated with the occurance of MACE at one year were: signs of peripheral venous congestion, chronic renal failure, anemia, obesity, atrial fibrillation (All $P<0.05$), indexed left atrial volume ($P= 0.031$), systolic arteriel pulmonary pressure ($P= 0.0003$), the levels of NT-ProBNP ($P=0.033$), GDF 15 ($P= 0.006$), as well as the 6 minutes walk-distance ($p<0.05$). After multivariate adjustment, the independent prognostic factors associated with one year outcome were: signs of peripheral venous congestion ($P=0.003$, Odds ratio **[**OR**]**=8.49), anemia ($P=0.026$, OR=2.53), and PASP($P=0.024$, OR=1.04 per 1 mmHg increase).

Discussion

Our study prospectively included a population of patients with HFpEF as strictly defined by the criteria of the European Society of Cardiology of 2016. We discuss here in the findings of present study in the light of previous studies dealing with patients with HFpEF (Table 4).

Clinical, echocardiographic and blood biomarkers characteristics

The risk factors and co-morbidities of the patients included in our study were as described above, including patients with HFpEF with predominantly female, and a high prevalence of hypertension, diabetes, and atrial fibrillation. **[**9,10**]**

Despite a disparate distribution of co-morbidities with variations by study type (Registry, Randomized Controlled Trial, or community-based study), study population, and geographic region, the most common co-morbidities are hypertension, atrial fibrillation, chronic kidney disease, and diabetes with significant variability between studies.**[**8**]**. On the other hand, I PREFER study which included a population of patients with HFpEF from Latin America, the Middle East, and North Africa including Algeria, showed that the population of patients with HFpEF was older, with a predominance of women,

obesity, hypertension, and atrial fibrillation compared to patients with reduced LVEF (HFrEF).[9] Our results highlight the high prevalence of hypertension among other risk factors [11,12, 13, 14, 15].

The prevalence of diabetes among patients with HFpEF varies widely, with extremes ranging from 5 to 60% depending on the series. [16 ,17] In our series, 66% of patients were diabetic, slightly exceeding the high prevalence series of diabetes. Its prevalence in other Algerian series varies from 45% in patients hospitalized for acute HF regardless of LVEF [18] to 49% in hypertensive patients with normal LVEF. [19] Regional variations in co-morbidities, lifestyle, nutritional patterns, activity, and genetic predisposition can explain these variations worldwide. Despite this high prevalence, diabetes does not appear to be a predictor of new cases of HFpEF, according to Ho and colleagues [20].

The prevalence of anemia in our series was 42%, in line with the results of some published reports indicating that anemia is also very common in this population of patients, with a prevalence varying according to studies and definition of anemia, ranging from 42% to 70%. [21].

The prevalence of chronic renal insufficiency (CRI) was 31%, 49% and 35% in the I-PRESERVE, DIG-PEF, and CHARM-preserved trials, respectively. Our results are in line with these data, since 39% of our patients had CRI.

Obesity was common in our series with a prevalence of 36%, which is consistent with data from previous studies [8, 9]. Obesity (BMI>30 kg/m2) is one of the most common co-morbidities in patients with heart failure and is one of the risk factors for the development of HFpEF. [22] It is common in both types of heart failure, but most studies show that it is more common in HFpEF than in HFrEF with a prevalence of 39% in HFpEF patients versus 27% in HFrEF patients [8]. Its prevalence also shows regional variability with a rate of 40-45% in the Middle East and North Africa, and 31% in Latin America. [9]

The prevalence of atrial fibrillation (AF) in our series was 46% at the time of diagnosis of HFpEF, similar to previous studies [23, 24, 25] which reported that atrial fibrillation is common in HFpEF with variability depending on study design and diagnostic methods (clinical diagnosis vs. Holter screening). In a meta-analysis of 66,357 patients, the prevalence of permanent AF appears to be slightly higher in patients with HFpEF compared to those with HFrEF (48 vs 44%). [26] The prevalence of Coronary artery disease (CAD) in patients with HFpEF is variable according to registries, definitions, and validation methods, ranging from 20% to 76% with an average of 41% [27]. A history of coronary artery disease (history of an acute coronary syndrome, revascularization, or significant coronary artery stenosis) was found in 26% of our patients.

Compared with men, women had lower prevalence rates of coronary artery disease and chronic kidney disease which is consistent with previous studies: PURSUIT-HFpEF [Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction] [28], and APOLLON study [29].

Regarding baseline blood biomarkers, levels of GDF-15 were elevated (> 1200 pg/ml) in 87% of our patients and were found to be associated with 1-year outcome in univariable but not in multivariable analysis. Previous studies including larger number of patients have shown that higher GDF 15 levels were associated with worse outcome (all-cause mortality) in patients with HfpEF. [30] Thus GDF15, may provide complementary pathophysiological information supporting an independent role of inflammatory cytokine release (GDF15) in the pathophysiology of HFpEF, whereas NT-proBNP, reflects haemodynamic wall tension or stress. [31] Another finding in our study is the association of baseline levels of GDF-15 and the use of angiotensin-converting enzyme (ACE) inhibitors, which can support the hypothesis that GDF 15 may be an interesting biomarker for treatment responsiveness, by reduction of cardiac stress due to treatment leading to down-regulation of GDF15 levels. [32]

Treatment

In the absence of pharmacological treatment that have been shown to be really effective in patients with HFpEF, treatment is based primarily on agressive control of risk factors and co-morbidities and the treatment of signs of congestion by diuretics. According to the medication prescribed to patients included in our study, beta-blockers, diuretics, aldosterone antagonists, and other blockers of the renin-angiotensin system were prescribed in similar proportions to that of previous reports. [33, 34] The majority of our patients received diuretics (82%) and renin-angiotensin-aldosterone system inhibitors (89%). However, our series is distinguished by higher use of angiotensin receptor blockers (ARBs) over ACE inhibitors (67% vs 22%) and may reflect the potential benefit of this therapeutic class as suggested by the results of CHARM-Preserved and I-Preserved trials in patients with HFpEF.

Echocardiographic caracteristics

Left ventricular hypertrophy (LVH): Our cohort is characterized by a high prevalence of LVH, which was present in 74% of patients similar to other trials and registries such as the European PEP-CHF (Europe) [35] study and the American ARIC registry. [36]

Very few studies have distinguished LVH from ventricular remodeling. [8,37]. Fourty-seven percent of our patients had a relative wall thickness ≥0.42, similar to the data from the North African cohort of I-PREFER study which reported a prevalence of relative wall thickness > 0.44 of 40% [9], and those from the TOPCAT study [Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function], which reported concentric remodeling in 34% of cases, while the Latin American and Middle Eastern cohorts of the I-PREFERE study reported a higher prevalence of 66% and 61% respectively. [9]

Left atrial dilatation: Our series is characterized by a higher prevalence of left atrial (LA) dilatation (81%) compared to TOPCAT (53%) [38] and I-PRESERVE (66%) studies [39]. The CHARM-Preserve ultrasound substudy reported a left atrial indexed volume > 32 ml/m² in 71% of patients [40]. This high prevalence could be explained by the fact that left atrial hypertrophy increases with age, especially in patients with co-morbidities such as hypertension, diabetes, obesity, and atrial fibrillation,[41] which were common in our series.

Although the relationship between LA dilatation and LVH is not yet clear, it is possible that this high prevalence of LA dilatation is also related to the high prevalence of LVH. Indeed, Gavin et al, in their analysis of the TOPCAT sub-study, found that patients with high LV mass had a significantly higher LA volume than patients with low LV mass and low LVH prevalence.[42]

Diastolic dysfunction: In our study, approximately 60% of patients had an average E/e' ratio > 14 at rest, 69% had an E/e' ratio > 13. Our data align with those of the TOPCAT trial [34] and the echocardiographic substudy of CHARME-Preserved [36] and I-PRESERVE [35], which report a prevalence of diastolic dysfunction of 66%, 67%, and 69% respectively.

Similar to data from the echocardiographic substudies of the HFpEF randomized controlled trials (TOPCAT, I-PRESERVEand CHARM Preserved) one-third of our patients had a normal diastolic function at rest at the time of echochardiography. [34, 35, 36]

As expected, echocardiographic findings demonstrated differences in diastolic function status at rest between male and female. Women had higher LV filling pressure as evaluated by E/e' ratio, and lower left ventricular mass than men, which is consistent with the findings of previous studies [31,43,44]. The PARAMOUNT trial (Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNi) with angiotensin receptor blockers (ARBs) on the management of heart failure with preserved ejection fraction) was the first investigation that provided a detailed sex-specific analysis of LV structure, function, and mechanics in HFpEF [45], and showed that indexed LV mass was significantly lower in women with HFpEF, with a significantly higher E/e' ratio.

Studies that have examined the correlation of this parameter to left ventricular filling pressures have shown that its use in routine clinical practice is subject to limitations, with a sensitivity of the algorithmic approach that vary very widely between 34% and 87% [45,46,47,48,49] according to the studies, which makes its use as the only echographic criteria for measuring the filling pressures of the LV not recommended.

Despite a preserved ejection fraction, 62% of our patients had an impaired global longitudinal strain (GLS < 16%) as previously described in a recent meta-analysis of 10 studies including 1810 patients with HFpEF and 462 asymptomatic controls [50]. The prevalence of longitudinal systolic dysfunction was significantly higher in patients with HFpEF with an average of 65% ranging from 37% to 95%, compared to only 13% (0% to 30%) in asymptomatic subjects. [48] We didn't find any difference in LV longitudinal strain between women and men with HFpEF as described in the PARAMOUNT trial.

Younger patients with HFpEF had higher indexed LV mass compared with older patients. Atrial size increased with increasing age. Older age was associated with similar rates of abnormal relative wall thickness and abnormal filling pressures. Our results join data published from patients with left ventricular ejection fraction ≥45% from 3 large HFpEF trials (TOPCAT, I-PRESERVE, and CHARM preserved [51]

Older age was also associated with higher PASP in our study. These finding correlate with data that demonstrate that pulmonary artery systolic pressure increases with advancing age in normal adults, suggesting that age-associated blood vessel stiffening may contribute to these differences in pulmonary artery systolic pressure.[52]

Outcome

The mortality and hospitalization of heart failure (HHF) rate vary in HFpEF population according to the design of studies, patient status (hospitalized vs ambulatory) , the threshold used to define a preserved LVEF, and the inclusion end exclusion criteria. [53] Accordingly, mortality was higher in studies that included only hospitalized patients. [54,55].

In-hospital mortality varies from 2,4 % to 4,9 % [50] in observational studies, with slightly higher mortality at 30 days (5 %) and, 60 and 90 days (9,5 %), while the one-year mortality varies from 20 % to 29%. [56]. Our results showed slightly lower one-year mortality as compared to data from other studies, with a rate of 13.7%. indeed, our study included both inpatients and outpatients, but the vast majority were outpatients. There is also a change in the distribution of the causes of death towards

non-cardiovascular causes in relation to an increase in non-cardiovascular comorbidities, [57] especially in HFpEF patients [58], emphasizing the key role of comorbidities in these patients [59]. In our study, 45% of deaths were from a non-cardiovascular cause.

Overall, 28-30% of hospitalizations in major HFpEF Randomized control trials [60] were related to HF, and patients with HFpEF seem to have an early risk of HF-specific hospitalization of ~10–30%. In our study, the global rate of Hospitalization of HF was 5.9% only, perhaps because of a large proportion of ambulatory patients included in our study.

Conclusion

The majority of patients in our cohort are elderly and hypertensive women, more than half of whom have diabetes. Patients had a high prevalence of alteration in longitudinal systolic function with an increase in LV mass, an alteration in diastolic function, and high levels of GDF-15. The independent prognostic factors of one year outcome were signs of peripheral venous congestion, anemia and PASP.

References

1. Braunwald E. Shattuck reading—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med. 1997; 337(19):1360-1369. DOI: 10.1056/NEJM199711063371906
2. McCullough PA, Philbin EF, Spertus JA, Scott Kaatz, Keisha R Sandberg, and al. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. J Am Coll Cardiol. 2002; 39(1):60-69. DOI: 10.1016/s0735-1097(01)01700-4
3. Owan TE, Redfield MM. Epidemiology of diastolic heart failure.ProgCardiovasc Dis. 2005;47(5):320-332. DOI: 10.1016/j.pcad.2005.02.010.
4. Owan TE, Hodge DO, Herges RM, Steven J Jacobsen, Veronique L Roger, and al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N EnglJMed. 2006;355:251-259. DOI: 10.1056/NEJMoa052256
5. Braunwald E. Heart failure. JACC Heart Fail. 2013;1(1):1-20. DOI: 10.1016/j.jchf.2012.10.002

6. Sanjiv J. Shah, Daniel H. Katz, Senthil Selvaraj, Michael A Burke, Clyde W Yancy and al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation 2015. January 20(3): 269-279. DOI: 10.1161/CIRCULATIONAHA.114.010637
7. M. Galinier et al. Preserved Ejection Fraction Heart Failure - Status and Prospects. Cardiology-pratique.com /journal/article/0029203. November 27, 2019
8. 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 chronicheart failure of the European Society of Cardiology. Eur Heart J 2016;37:2129–2200.
9. M. Vaduganathan, A. Michel, K. Hall, C. Mulligan, S. Nodari and al. Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: a systematic review. European Journal of Heart Failure (2016) 18, 54–65 doi:10.1002/ejhf.442. DOI: 10.1002/ejhf.442.
10. José A. Magaña-Serrano, Wael Almahmeed, Efrain Gomez, Mostafa Al-Shamiri, Djamila Adgar, and al. Prevalence of Heart Failure With Preserved Ejection Fraction in Latin American, Middle Eastern, and North African Regions in the I PREFER Study (Identifification of Patients With Heart Failure and PREserved Systolic Function: An Epidemiological Regional Study). Am J Cardiol 2011;108:1289 –1296). DOI: 10.1016/j.amjcard.2011.06.044
11. S. Benkhedda, A. Chibane, A. Temmar, et al. Prevalence of cardiovascular risk factors associated to hypertension in the Algerian population. Report SAHA, J Hypertens, 23, Suppl. 2, 2005,"
12. Benkhedda, S; Chibane, A; Temmar, et al. Hypertension in Algeria: an epidemiological overview: P3. 377, Journal of Hypertension, 22, S396, 2004, LWW"
13. Benkhedda, S; Chibane, A; Atif, et al. Prevalence of cardiovascular risk factors associated with hypertension in the Algerian population. A national survey journal of hypertension, 23,s 188-s189,2005,"lippincott williams & wilkins 530 walnut st, philadelphia, pa 19106-3261 usa
14. Benkhedda, S; Chibane, A; Temmar, et al. HTA in Algeria: frequency and epidemiological characteristics-survey results SAHA1, Arch Mal Coeur Opinion 97, 51-52, 2004,"
15. Benkhedda, S; Chibane, A; Temmar, et al. Hypertension: Prevalence, awareness, treatment, and control in Algeria. Result of the national survey journal of hypertension, 23, s295-s295, 2005,""lippincott williams & wilkins 530 walnut st, philadelphia, pa 19106-3261 usa"""
16. Kelly McHugh , Adam D DeVore , Jingjing Wu, Roland A Matsouaka, Gregg C Fonarow, and al. Heart Failure With Preserved Ejection Fraction and Diabetes: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Feb 12;73(5):602-611. DOI: 10.1016/j.jacc.2018.11.033

17. A P. Ambrosy, G C. Fonarow, J Butler, O Chioncel, S J Greene, and al. The Global Health and Economic Burden of Hospitalizations for Heart Failure Lessons Learned From Hospitalized Heart Failure Registries. Journal of the American College of Cardiology Vol. 63, No. 12, 2014. DOI: 10.1016/j.jacc.2013.11.053
18. D. Djermane, M. Djouhri, F.Z. Amorouayeche, A. Azzouz, S. Ouabdeslem, and al.. Intra-hospital prognosis of acute heart failure: Preliminary results in an Algerian population, Archives of Cardiovascular Diseases Supplements, 11, 1.40, 2019, Elsevier". Doi : 10.1016/j.acvdsp.2018.10.085
19. N. Taleb-Bendiab, S. Benkhedda, L. Henaoui,N. Meziane-Tani. Assessment of the study of longitudinal systolic function by 2D strain in hypertensive patients with preserved LVEF, Archives of Cardiovascular Diseases Supplements, 10,1,109, 2018, Elsevier. Doi : 10.1016/j.acvdsp.2017.11.222
20. Jennifer E Ho, Asya Lyass, Douglas S Lee, Ramachandran S Vasan, William B Kannel, and al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. Circ. Heart Fail. 6, 279-286 (2013). DOI: 10.1161/CIRCHEARTFAILURE.112.972828
21. K. Okuno, Y. Naito, M. Asakura, M. Sugahara, T. Horimatsu, and al. Anemia has an impact on prognosis in heart failure with preserved ejection fraction with mild chronic kidney disease Heart & Vasculature 34 (2021) 100796. DOI: 10.1016/j.ijcha.2021.100796
22. KA Ammar, MM Redfield, DW Mahoney, M Johnson, S J Jacobsen, and al. Central obesity: association with left ventricular dysfunction and mortality in the community. Am Heart J. 2008 Nov;156(5):975-81. DOI: 10.1016/j.ahj.2008.06.018
23. M J Lenzen, W J M Scholte op Reimer, E Boersma, P J M J Vantrimpont, F Follath, and al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur. Heart J. 25, 1214-1220 (2004). DOI: 10.1016/j.ehj.2004.06.006
24. R S. Bhatia, J V Tu, D S. Lee, P C. Austin, J. Fang, and al. Outcome of heart failure with preserved ejection fraction in a population-based study. Engl. J. Med. 355, 260-269 (2006). DOI: 10.1056/NEJMoa051530
25. D S. Lee, P Gona, R S Vasan, M G Larson, E J Benjamin, and al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 119, 3070-3077 (2009). DOI: 10.1161/CIRCULATIONAHA.108.815944.

26. Z J Eapen, M A Greiner, G C Fonarow, Z Yuan, R M Mills, and al. Associations between atrial fibrillation and early outcomes of patients with heart failure and reduced or preserved ejection fraction. Am Heart J 2014; 167: 369-375. e2. DOI: 10.1016/j.ahj.2013.12.001
27. C S Lam, E. Donal, E Kraigher-Krainer, R S Vasan, and al. Epidemiology and clinical course of heart failure with preserved ejection fraction.Eur. J. Heart Fail. 13, 18-28 (2011). DOI: 10.1093/eurjhf/hfq121
28. Y. Sotomi, S.Hikoso, D. Nakatani, H. Mizuno, K. Okada, and al. Sex Differences in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. 2021;10:e018574. https://doi.org/10.1161/JAHA.120.018574
29. B Özlek, E Özlek, S Kahraman , M Tekinalp , H Zencirkıran Ağuş, and al. Gender disparities in HFmrEF and HFpEF. Anatol J Cardiol 2019; 21: 242-52. DOI:10.14744/AnatolJCardiol.2019.71954
30. A B Mendez Fernandez, A F Gregori, A G Osuna, S M Perez, M J P Buxo, and al. Growth differentiation factor 15 as mortality predictor in heart failure patients with non-reduced ejection fraction. ESC Heart Fail . 2020 Oct;7(5):2223-2229. doi: 10.1002/ehf2.12621
31. M M.Y. Chan, R.Santhanakrishnan, J P.C. Chong, Z. Chen, B C. Tai, and al. Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction European Journal of Heart Failure (2016) 18, 81–88 doi:10.1002/ejhf.431
32. M. Wesseling, J.H.C. de Poel and S. C.A. de Jager. Growth differentiation factor15 in adverse cardiacremodelling: from biomarker to causal player. ESC Heart Failure2020;7:1488–1501
33. E. Donal, LH Lund, E. Oger, C Hage, H. Persson, and al. New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: a subanalysis of the Ka (Karolinska) Ren (Rennes) Study. Eur J Heart Fail 2015; 17: 680–8. DOI: 10.1002/ejhf.291
34. R T. Campbell, PS Jhund, D. Castagno, NM Hawkins, MC. Petrie, and al. What have we learned about patients with heart failure and preserved ejection fraction from DIGPEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol 2012;60:2349—56. DOI: 10.1002/ejhf.291
35. JG. Cleland, M. Tendera, J. Adamus, N. Freemantle, L. Polonski, and al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006; 27(19):2338-2345. DOI: 10.1093/ eurheartj/ehl250
36. DK Gupta, AM. Shah, D. Castagno, M Takeuchi, L R Loehr, and al. Heart Failure with Preserved Ejection Fraction in African-Americans - The Atherosclerosis Risk in Communities (ARIC) Study. JACC Heart Fail 2013;1(2):156-163. DOI: 10.1016/j.jchf.2013.01.003

37. Gomez-Soto FM, Romero SP, Bernal JA, et al. a propensity-adjusted case-control study. Int J Cardiol 2010; 139 (3):276-282.
38. AM. Shah, S J. Shah, I S. Anand, et al. Cardiac Structure and Function in Heart Failure with Preserved Ejection Fraction: Baseline Findings from the Echocardiographic Study of the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circ Heart Fail. 2014 January ; 7(1): 104–115.
39. M. R. Zile, J. S. Gottdiener, S. J. Hetzel, et al. Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction Circulation. 2011; 124:2491-2501.
40. Persson et al. Diastolic Dysfunction in Heart Failure with Preserved Systolic Function: Need for Objective Evidence Results from the CHARM Echocardiographic Substudy-CHARMESJACC Vol. 49, No. 6, 2007. February 13, 2007:687-94
41. Rossi A, Gheorghiade M, Triposkiadis F, et al. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. Circ Heart Fail 2014; 7 1042-1049.
42. Gavin A. Lewis, Erik B. Schelbert, Simon G. Williams et al. Biological Phenotypes of HFpEF. JACC VOL. 70, NO. 17, 2017:2186 – 200
43. M. Tadic, C. Cuspidi, S. Plein, E. Belyavskiy, F. Heinzel, and al. Sex and Heart Failure with Preserved Ejection Fraction: From Pathophysiology to Clinical Studies. J. Clin. Med. 2019, 8, 792; doi:10.3390/jcm8060792
44. M. Gori., C.S. Lam., D.K. Gupta., A.B. Santos., S. Cheng, and al.Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur. J. Heart Fail. 2014;16:535–542. doi: 10.1002/ejhf.67.
45. Obokata M, Kane GC, Reddy YN, et al. A Simultaneous Invasive-Echocardiographic Study. Circulation. 2017; 135(9): 825-838.
46. Lancellotti P, Galderisi M, Edvardsen T, et al. results of the multicentre EACVI Euro-Filling study. Eur Heart J Cardiovasc Imaging. 2017;18(9):961-968.
47. Balaney B, Medvedofsky D, Mediratta A, et al. Invasive Validation of the Echocardiographic Assessment of Left Ventricular Filling Pressures Using the 2016 Diastolic Guidelines: Head-to-Head Comparison with the 2009 Guidelines. J Am Soc Echocardiogr. 2018; 31(1): 79-88.
48. Sato K, Grant ADM, Negishi K, et al. Reliability of updated left ventricular diastolic function recommendations in predicting elevated left ventricular filling pressure and prognosis. Am Heart J. 2017;189:28-
49. Andersen OS, Smiseth OA, Dokainish H, et al. Estimating Left Ventricular Filling Pressure by Echocardiography. J Am Coll Cardiol. 2017 Apr 18;69(15):1937-1948.

50. Morris DA, Ma XX, Belyavskiy B, et al. Left ventricular longitudinal systolic function analyzed by 2d speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. Open Heart 2017;4: e000630.
51. J Tromp, L Shen, P S. Jhund, I S. Anand, P E Carson, and al. Age-Related Characteristics and Outcomes of Patients With Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol 2019;74:601–12
52. G C Kane, A Sachdev, H R Villarraga, N M Ammash, J K Oh, and al. Impact of age on pulmonary artery systolic pressures at rest and with exercise. Echo Research and Practice. Vol: 53–61 (2016) DOI: https://doi.org/10.1530/ERP-16-0006 .
53. Somaratne, J. B. et al. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. Eur. J. Heart Fail. 11, 855–862 (2009).
54. Perez De Isla, L. et al. Diastolic heart failure in the elderly: in-hospital and long-term outcome after the first episode. Int. J. Cardiol. 134, 265–270 (2009).
55. M. Vaduganathan et al. Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: a systematic review. European Journal of Heart Failure (2016) 18, 54–65 doi:10.1002/ejhf.442.
56. Fonarow, G. C. et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J. Am. Coll. Cardiol. 50,768–777 (2007).
57. Roger VL. Epidemiology of heart failure. Circ Res. 2013 Aug 30; 113 (6):646-59. Doi: 10.1161/ CIRCRESAHA. 113. 300268.
58. Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004 Jul 21; 292 (3):344-50.
59. Pardeep S. Jhund and Luigi Tavazzi. Has the ‘epidemic’ of heart failure been replaced by a tsunami of co-morbidities? European Journal of Heart Failure (2016) 18, 500–502 doi:10.1002/ejhf.529.
60. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–2467.
61. Wang J, Khoury DS, Yue Y, et al. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008; 29: 1283-9.

62. Liu YW, Tsai WC, Su CT, et al. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail 2009; 15: 782-9.
63. Phan TT, Shivu GN, Abozguia K, et al. Left ventricular torsion and strain patterns in heart failure with normal ejection fraction are similar to age-related changes. Eur J Echocardiogr 2009;10:793-800.
64. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009; 54: 36-46.
65. Kasner M, Gaub R, Sinning D, et al. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis Eur J Echocardiogr 2010; 11: 743-51.
66. Morris DA, Gailani M, Vaz Pérez A, et al. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. J Am Soc Echocardiogr 2011; 24: 651-62.
67. Yip GW, Zhang Q, Xie JM, et al. insights from speckle-tracking echocardiography. Heart 2011; 97: 287-94.
68. Abe H, Caracciolo G, Kheradvar A, et al. Contrast echocardiography for assessing left ventricular vortex strength in heart failure: a prospective cohort study. Eur Heart J Cardiovasc Imaging 2013; 14: 1049-60.
69. Obokata M, Negishi K, Kurosawa K, et al. Incremental diagnostic value of the strain with leg lifts in heart failure with preserved ejection fraction. JACC Cardiovasc Imaging 2013; 6 749-58.
70. Pellicori P, Kallvikbacka-Bennett A, Khaleva O, et al. Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification? Int J Cardiovasc Imaging 2014; 30:69–79.
71. Kraigher-Krainer E, Shah A, Gupta D et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. JACC 2014 ; 5 : 447-456.
72. Menet A, Graft L, Ennezat PV, et al. Is mechanical dyssynchrony a therapeutic target in heart failure with preserved ejection fraction? Am Heart J 2014; 168: 909-16.
73. Luo XX, Fang F, Lee AP, et al. What can three-dimensional speckle tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? Int J Cardiol 2014;172: 132-7

74. Wang J, Fang F, Wai-Kwok Yip G, et al. Left ventricular long-axis performance during exercise is an important prognosticator in patients with heart failure and preserved ejection fraction. Int J Cardiol 2015; 178: 131–5.
75. Stampehl MR, Mann DL, Nguyen JS, et al. Speckle strain echocardiography predicts outcome in patients with heart failure with both depressed and preserved left ventricular ejection fraction. Echocardiography 2015; 32:71–8.
76. Shah A M, Clagett B, Sweitzer NK et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation. 2015 Aug 4 ; 132(5) :402-14.
77. Kosmala W, Rojek A, Przewlocka-Kosmala M, et al. Contributions of Nondiastolic Factors to Exercise Intolerance in Heart Failure With Preserved Ejection Fraction J Am Coll Cardiol 2016; 67: 659-70.
78. Morris DA, Krisper M, Nakatani S, et al. Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicenter study. Eur Heart J Cardiovasc Imaging 2017; 18: 212-23.
79. Toufan M, Mohammadzadeh Gharebaghi S, Pourafkari L, et al. Systolic longitudinal function of the left ventricle assessed by speckle tracking in heart failure patients with preserved ejection fraction. J Tehran Heart Cent 2015; 10: 194-200.
80. Freed BH, Daruwalla V, Cheng JY, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. Circ Cardiovasc Imag. 2016;9: e003754.
81. Carluccio E, Biagioli P, Zuchi C, et al.Fibrosis assessment by integrated backscatter and its relationship with longitudinal deformation and diastolic function in heart failure with preserved ejection fraction. Int J Cardiovasc Imaging 2016; 32: 1071-80.
82. Iwano H, Kamimura D, Fox ER, et al. Presence and implication of temporal nonuniformity of early diastolic left ventricular wall expansion in patients with heart failure. J Card Fail 2016; 22: 945-53.
83. Hung CL, Yun CH, Lai YH, et al. An observational study of the association among interatrial adiposity by computed tomography measure, insulin resistance, and left atrial electromechanical disturbances in heart failure. Medicine 2016; 95: e3912.
84. Obokata M, Takeuchi M, Negishi K, et al. Relation Between Echocardiogram-Based Cardiac Parameters and Outcome in Heart Failure With Preserved and Reduced Ejection Fraction. Am J Cardiol 2016; 118: 1356–62.

85. DeVore AD, McNulty S, Alenezi F, et al. Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. Eur J Heart Fail 2017;19:893–900.
86. Huang W, Chai SC, Lee SGS, et al. Prognostic Factors after Index Hospitalization for Heart Failure with Preserved Ejection Fraction. Am J Cardiol 2017; 119: 2017– 20.
87. Ci Lo, Lai YH, Chang SN, et al. The associations among co-morbidity, cardiac geometries and mechanics in hospitalized heart failure with or without preserved ejection fraction. Clin Exp Hypertens 2017;1:1-8.
88. Bosch L, Lam CSP, Gong L, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. Eur J Heart Fail 2017.