Unraveling diagnostic co-morbidity makeup of each HF category as characteristically derived by ECG- and ECHO-findings, a prevalence analysis

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Abstract

Heart Failure (HF) relies mainly on measurements from Echocardiography, in particular Echo-Findings, to estimate Left Ventricle Ejection Fraction (LVEF) and evaluating structural heart disease criteria. As Echocardiography is not available in primary care, the key **structural** (heart chamber enlargements) and **functiona**l abnormality related measurements are not available precluding the ability to diagnose HF other than through mainly symptomatic means. The opportunity for earlier detection of HF is lost.

In this work, we first explore each of the three HF categories, preserved EF, mild-reduced EF, and reduced EF, using various morphological and functional etiology-specific characteristics supported by a literature review and an extensive analysis of a large, dedicated database accumulated over 8 years.

We then explore the typical signs and co-morbidities of HF using prevalence analysis to unravel the diagnostic makeup of each HF category as characteristically derived by ECG- and ECHO-findings. From this, we then conduct a principal component analysis (PCA) of the data to interpret patterns of comorbidities, showing groups of comorbidities frequently associated with each other.

Lastly, we delve into the role of breakthrough methods for the analysis of bio-signals to replicate common ECHO-findings, as alternatives for detecting and diagnosing HF similarly to Echocardiography, thereby providing a simple device for the effective detection of HF for use in Primary Care.

Abbreviations

ECG	Electrocardiography
ECHO	Echocardiography
CHART	Cardio-HART™ from Cardio-Phoenix
HF	Heart Failure
LVSD	Left Ventricular Systolic Dysfunction
ALVSD	Asymptomatic LVSD
DD	Diastolic Dysfunction
DDIM	Impaired Relaxation type DD
LVH	Left Ventricular Hypertrophy
RVH	Right Ventricular Hypertrophy
DCM	Dilated Cardiomyopathy
RVE	Right Ventricular Enlargement
LAE	Left Atrial Enlargement
RAE	Right Atrial Enlargement
WMA	Wall Motion Abnormality
PEEF	Pericardial Effusion
AS	Aortic Stenosis
MS	Mitral Stenosis
MR	Mitral Regurgitation

AR	Aortic Regurgitation
TR	Tricuspid regurgitation
PH	Pulmonary Hypertension
CAD	Coronary Artery Disease
MI	Myocardial Infarction
AF	Atrial Fibrillation
LVEF	Left Ventricular Ejection Fraction [%]
HR	Heart Rate [bpm]
HRV	Heart Rate Variability
PCA	Principal Component Analysis

1 Introduction

The clinical diagnosis of HF relies in part on ECG but primarily on measurements from Echocardiography, to estimate Left Ventricle Ejection Fraction (LVEF) and for evaluating structural heart disease criteria [1][3][4]. As Echocardiography is not available in primary care, the key **structural** and **functiona**l abnormality related measurements are not available. The understanding and prediction of HF is typically limited to symptomatic assessment leading to clinical prognosis at the Primary Care level. Any opportunity for the earlier detection of HF, is lost.

Recently the international consortium of Cardiology professional societies [3], proposed three distinct classes of HF based on LVEF: 1) HFrEF (LVEF ≤40%); 2) HFmrEF (LVEF between 41% to 49%); 3) HFpEF (LVEF of ≥50%).

However, the categorization of heart failure relies on more than just LVEF but also on many other cardiac conditions and pathophysiological characteristics [2], the failure of which to understand can undermine detection and misdirect treatment.

In addition to LVEF, common heart disorders and dysfunctions should be considered for understanding the etiology and source of HF whether preserved, mildly-reduced, or reduced. These include Left Ventricular Systolic and Diastolic Dysfunction (LVSD and DD), Left Ventricular Hypertrophy (LVH), Left Atrial Enlargement (LAE), Dilated Cardiomyopathy (DCM), Wall Motion Abnormality (WMA), Aortic Stenosis (AS) and other valve diseases, e.g., Mitral Regurgitation (MR) [18]. The examined abnormalities and co-morbidities of HF are typically diagnosed by a combination of ECG but especially by ECHO.

Understanding these findings determines more precisely the underlying physiological nature of the abnormal function, not just the HF symptoms.

Health Care should focus on managing HF comorbidity, because patient will be living with HF longer than ever before [43]. In this research, the etiology of each HF category was explored. Using an appropriate database, we extract various relationships or comorbidities between the ECG and ECHO parameters that contribute to HF, and then confirm those relationships via a Principal Component analysis (PCA). Lastly, we conclude with an overview of a bio-signal based system supported by Artificial Intelligence, able to replicate Echo-findings thereby filling

the assessment GAP needed for detecting and diagnosing HF, in its three categories, in Primary Care.

1.1 HFpEF

HFpEF should be suspected in patients with typical HF symptoms and signs (S3 heart sound, displaced apical pulse, and jugular venous distension) of chronic heart failure [7]. Risk factors include older age, female gender, obesity, hypertension, tobacco use, diabetes mellitus, coronary artery disease (CAD), valvular heart disease, and atrial fibrillation (AFib) [7][8][33] and other ECG abnormalities [36].

HFpEF cannot be diagnosed from a single echocardiographic measure such as LVEF, and inclusion of recently validated functional and structural parameters into a diagnostic score may better define this heterogeneous disorder [4].

The term “diastolic HF” is suboptimal for several reasons, because Diastolic HF is not present in all HFpEF patients [5]. Several alternative and complementary pathophysiologic mechanisms exist in HFpEF, including longitudinal LV systolic dysfunction (despite a normal EF), pulmonary hypertension, abnormal ventricular-arterial coupling, abnormal exercise-induced vasodilation, extracardiac volume overload, and chronotropic incompetence [5][21].

HFpEF is associated to other cardiac and non-cardiac comorbidities: LVH and/or LAE are defined by the guideline [1] and HFA-PEFF algorithm [4] as well. LAE associated with abnormal DD [24], since DD contributes to left atrial remodeling [40]. Pulmonary Hypertension (PH) is associated with HFpEF, and it has a substantial adverse impact on symptoms and survival [22][37].

1.2 HFmrEF

HFmrEF is a recently separated HF class, thus fewer research results are available in the literature.

Patients with HFmrEF have a different clinical profile, but more similar to patients with HFpEF [44]; primarily mild LVSD, but with features of DD. The diagnostic criteria for HFmrEF includes any relevant structural heart disease, such as LVH or LAE or DD beside symptoms and the mildly reduced EF (LVEF of 40-49%) [1]. Priority patients who transitioned to HFrEF were more likely to have LAE and had a tendency to have AFib and more comorbidities [32]. However, HFmrEF is associated with different characteristics and a more favorable prognosis than HFrEF [25].

Mild asymptomatic LVSD (ALVSD) might be a predictor of adverse events mainly in subjects with combined DD [26]. Higher LVmass, wall thickness, and internal dimensions are associated with increased HF risk [39].

1.3 HFrEF

HFrEF is a complex clinical condition characterized by structural and/or functional impairment of the left ventricle, resulting in a decrease in heart pump function (LVEF≤40%) [27].

HFrEF is most commonly associated to DCM or CAD [28], LVSD and moderate AS commonly occur together; patients with moderate AS and concomitant LVSD are at high risk for clinical events including all-cause death, hospitalization for HF, and aortic valve replacement [29]. AFib and HF often occur together, and their combination is associated with increased morbidity and mortality compared with each disorder alone [30]. ECG in HF patients is almost always abnormal, and most patients typically have a minimum of three abnormalities, with LVH criteria being the most common abnormality [31]. Severe valve regurgitations such as MR [18], AR [19], TR [27] increase the mortality of HF patients.

1.4 Limitation of LVEF-based categorization

LVEF is limited, because: 1) LVEF alone does not explain the underlying disease characteristic and conditions, for example, LVEF estimates global function but does not indicate LV volume or stroke volume (SV) [15]; 2) is not quite sensitive for subtle LV systolic dysfunction caused by regional WMA (presented in HFpEF), which better detected by mitral annular systolic excursion or systolic velocities or LV global longitudinal strain (GLS) [13][14][15]; 3) lack of the required expertise and equipment. Despite its limitations, the categorization of HF is still based on LVEF, partly for historical reasons [4].

Exercise capacity correlates better with longaxis functional reserve of the LV and with peripheral blood flow than with LVEF [4]. In primary care, the LVEF, GLS or SV could be useful in the early HF detection and correct stratification of patients with HF, particularly when considering suitability of pharmalogical intervention. Currently, these are not available measurement methods available to GPs.

A device suitable for use in Primary Care is sorely lacking, but a promising breakthrough technology appears to address these deficiencies[1] through the use of novel bio-signals that emulate echocardiography findings. The published results help to understand the key abnormalities that are enable the HF classification based on bio-signals.

2 Cardio Phoenix Database Analysis and HF categories

Database consists of medical data from four clinical studies, done at five European clinical centers, between 2011 and 2019. The database contains the bio-signals including ECG and the ECHO images, measurements, and findings for each patient. Echocardiographic assessment was performed after bio-signal recording within 10 days. There are 24000 records with ~30sec length signals. The ground truth of ECG and ECHO findings were validated by a consensus study involving five cardiologists per test.

2.1 Patient Population and HF Risk Factors

The prevalence of the HF associated ECG and ECHO findings can be estimated from the Cardio-Phoenix database, because the collected medical data was specifically from the patient population at risk of HF. Patients are adults with average age of 62.5, of which 51% are females, and having minimum three cardiovascular risks or an existing cardiac condition.

[1] Cardio-HART™, from Cardio-Phoenix Inc., has shown such capabilities. See https://cardiophoenix.com

According to guidance [3] risks for HF (any type) include hypertension, cardiovascular disease, diabetes mellitus, obesity, known exposure to cardiotoxins, and family history of cardiomyopathy (see Stage A at-risk for HF in [3]). All these risks were examined according to the criteria of patient entered into the database.

2.2 ECHO- and ECG-findings

The ground truth of ECHO-findings was established by cardiologist consensus and confirmed with ECHO measurements (listed in Table 4). Table 1 lists the ECHO-findings having cardiologist consensus ground truth, selected based on relevance for referral decision and high prevalence of diseases in the intended population (prevalence >3%).

Table 1 – List of ECHO Findings having cardiologist consensus ground truth

ECHO finding	Baseline Criteria for MILD	Baseline Criteria for MODERATE/SEVERE
LVH	IVSd≥[10/11*]mm and LVMI>[100/115*]g/m^2	IVSd≥[13/14*]mm and LVMI>[115/131*]g/m^2
DCM	LVIDd>[53/59*]mm	LVIDd>[56/63*]mm
RVE	RVOTprox>30mm	RVOTprox>36mm
LAE	LAVI>30ml/m^2	LAVI>40ml/m^2
RAE	RAVI>30ml/m^2	RAVI>40ml/m^2
WMA	Mild Hypokinesis (WMscore≥1)	Hypokinesis, Akinesis, Dyskinesis (WMscore≥2 and LVEF<[54/52*]%)
LVSD	LVEF<[54/52*]%	LVEF<40%
DDIM	E/A<0.85	E/A<0.70
AS	AVpV>2.0m/s	AVpV>3.0m/s
MS	MVA<3.0cm^2 (MVGEm>3.7mmHg)	MVA<1.5cm^2 (MVGEm>5.0mmHg)
AR	ARgrade≥1	ARgrade≥2
MR	MRgrade≥1, MRjet/LAA>20%	MRgrade≥2, MRjet/LAA>30%
TR	TRgrade≥1, TRjet/RAA>20%	TRgrade≥2, TRjet/RAA>30%
PH	RVSP>40mmHg	RVSP>50mmHg

* Different threshold for Female and Male [F/M], according to recommendations for cardiac chamber quantification by echocardiography

The ECG measurement and findings are generated by state-of-the-art ECG algorithms based on 12-lead ECG signal, and confirmed by a minimum one cardiologist (listed in Table 4).

Both the ECG and ECHO interpretations are extended with a summary finding:

- ECG summary classifies the ECG as normal, borderline or abnormal
- ECHO summary classifies the ECHO as Normal, Mild or Abnormal: both moderate or Severe, and where Mild means a minimum one Mild finding, Abnormal means a minimum one Moderate/Severe finding

2.3 Definition of HF categories

Based on consensus recommendation from the Heart Failure Association (HFA) the initial HFpEF diagnosis relies on HF symptoms, standard ECG, standard ECHO and Natriuretic Peptides test [4] (HFA-PEFF algorithm).

The advanced diagnosis of HFpEF should be differentiated from the alternative causes of dyspnea such as HFrEF, valve disease, primary PH, or pericardial effusion [4]. CAD, valve diseases and PH are considered as primary comorbidities of HF [22][28][29][37] [18][19][27], and the etiology of HFpEF relies on these abnormalities in case of non-DD type HF. A PH relationship is confirmed by the H_2FPEF score study, where the pulmonary artery systolic pressure >35mmHg was selected as one of the score elements [36].

HFpEF in a broader sense can be divided into the various types defined in [5]: This wider definition of HFpEF is advantageous in primary care, since early detection of HF is as important as identifying the specific type of HF.

Patients with ALVSD ("Stage B" according to ACC/AHA of HF, NYHA CLASS I) have approximately half the mortality rate (5% annualized) of those with overt symptoms of HF, but their risk of death is 5 to 8 times higher than a normal age-matched population [11][12]. Patients with ALVD are at high risk for developing HF, therefore, they should be considered potential HF patients.

The definition of "Consider HFpEF" category includes CAD, valve disease and PH type HF too, and "Consider HFmrEF/HFrEF" includes ALVSD too, see primary and secondary groups in Table 2.

Table 2 – Definition of HF categories in Cardio Phoenix database

Reference categories of HF - specifically for indication in primary care	Primary group	Secondary group - also included
"Consider HFpEF"	symptomatic HF with LVEF>50%, and DD or LAE or LVH	symptomatic AF symptomatic PH symptomatic AS or MS symptomatic CAD or WMA
"Consider HFmrEF"	symptomatic HF with LVEF<50%, and WMA or LAE or LVH	mild ALVSD with LVEF<50%, but confirmed with risk factors, HF scores and co-morbidities
"Consider HFrEF"	symptomatic HF with LVEF<40%	ALVSD with LVEF<40%, but confirmed with risk factors, HF scores and co-morbidities

The categorization of HF was done according to criteria described in Table 2, using all the available patient data and ground truth. The definition of HFpEF is compatible with the TOPCAT, RELAX, and ARIC studies [35].

The overall database (training + external validation + independent validation) consists of 69.4% absent HF, 13.9% HFpEF, 11.8% HFmrEF, and 4.9% HFrEF. The 69.4% absent category includes normal patients and patients with non-HF CVD – typically with a "mild" CVD condition. The overall HF patient is 30.6% in database, and approximately half of the HF patient has HFpEF type (45.5%).

2.4 Data Limitation and Confirmation

The limitation of the database is the lack of natriuretic peptides level confirmation. However, this was partly substituted with the use of a broader range of ECG and ECHO findings.

Both HF Scoring systems were used to verify the HF categorization in Cardio Phoenix database. Fig. 1 shows the reference three HF categories with the absent HF patients in function of LVEF (vertical axis) and HF Scores (horizontal axis): A) graph - H2FPEF Score, B) graph - HFA-PEFF Score. The two HF Scores have similar results, and the C) graph compares them to each other.

The HFmrEF and HFrEF categories are primarily confirmed by LVEF, but the two HF Scores also show non-normal ranges, similarly for HFpEF categories. Both the HF Scores are calculated using sigmoid probability function instead of strict binary threshold in order to ensure higher resolution and to better resolve borderline cases.

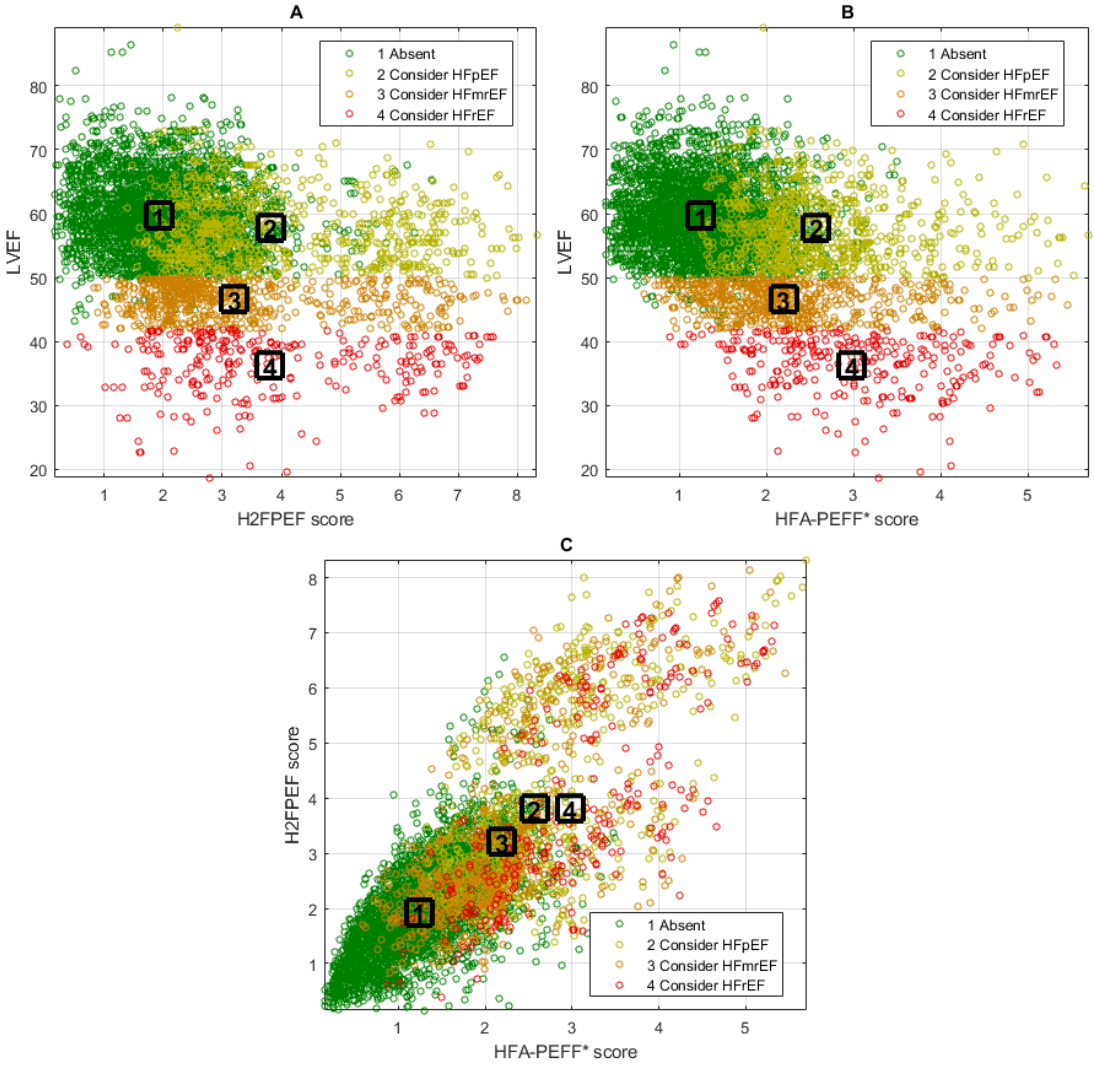

Figure 1 – Scatter plot of HF categories in function of LVEF (vertical) and HF scores (horizontal)

The confirmation performance is acceptable taking into account the general uncertainties of echo measurements, and the primary care opportunities and requirements for considering HF categories based on risk factors, symptoms/signs, and a novel bio-signal-based interpretation AI system.

3 Prevalence statistics along four HF categories

3.1 Method

Five separate prevalence statistics are calculated on patient groupings into a) All – all the patient records, b) Absent HF records, c) HFpEF records, d) HFmrEF records and e) HFrEF records.

3.2 Results

Table 3, 4 and 5 lists all the relevant information measurements and findings in the examined patient population. In each row, the worst or most abnormal (typically the maximum, but in some cases the minimum) values are highlighted with bold text. Similarly, the highest standard deviation is also highlighted, which denotes the highest variability.

Table 3 – Distribution statistics of ECHO and ECG interpretation in Cardio Phoenix Database along the four HF category (Abbreviations: "M" – Mean value, "STD" - standard deviation) – 1st part

	HF category		All		Absent HF		Cons. HFpEF		Cons. HFmrEF		Cons. HFrEF	
Group	**Field**	**Unit**	**M**	**STD**	**M**	**STD**	**M**	**STD**	**M**	**STD**	**M**	**STD**
General and Body Size	Age	year	62.5	13.8	59.4	**13.9**	**71.8**	9.2	68.3	10.6	67.8	11.9
	Female		51%	-	54%	-	50%	-	41%	-	**27%**	-
	BMI	kg/m^2	27.9	5.2	27.5	5.1	28.7	5.4	28.7	5.2	**29.1**	**5.9**
	BSA	m^2	1.9	0.2	1.9	0.2	1.9	0.2	1.9	0.2	2.0	0.3
	Height	cm	167.5	9.1	167.7	9.2	165.9	8.6	167.6	9.1	168.6	9.1
	Weight	kg	78.3	16.7	77.4	16.4	79.1	16.9	80.8	16.4	83.0	19.0
	Systolic BP	mmHg	127.8	13.3	127.3	13.1	**130.0**	14.0	128.8	13.3	126.2	**13.5**
	Diastolic BP	mmHg	78.6	9.9	78.7	9.7	77.9	9.9	**79.1**	9.7	77.7	**13.2**
ECG measurements	HR	bpm	70.0	13.6	68.5	11.9	72.5	15.8	72.8	16.3	**78.3**	16.9
	RRstd	ms	59.2	61.8	46.7	45.6	87.9	81.6	82.1	78.2	**100.5**	85.8
	LF/HF (0.15Hz)	ms	1.6	0.9	1.8	0.9	1.4	0.9	1.3	0.9	**1.1**	0.7
	QRSaxis	deg	25.1	39.8	29.6	36.1	16.9	45.0	15.3	42.1	**8.0**	52.6
	PQ interval	ms	181.8	37.7	175.2	29.3	**199.9**	48.4	192.1	47.7	199.7	**51.8**
	P interval	ms	117.5	18.4	118.0	14.2	115.4	25.6	117.6	24.2	114.9	28.5
	P terminal force	mVms	3.0	2.7	3.1	2.5	2.5	2.7	2.8	3.0	**3.3**	**3.8**
	QT interval	ms	408.6	37.5	407.1	34.2	**413.6**	42.9	411.8	43.9	407.4	**45.5**
	QTc (Framingham)	ms+	425.1	26.0	421.5	23.1	433.3	29.2	431.4	29.1	**436.7**	**33.8**
	QRS interval	ms	92.3	21.1	88.8	17.5	97.8	24.5	99.3	23.8	**110.7**	**30.2**
	VAT (Rwave peak time)	ms	43.1	11.4	41.1	9.3	46.1	13.8	47.0	12.8	**52.8**	**16.2**
	Taxis	deg	33.2	49.5	36.3	38.6	26.0	63.1	28.4	66.4	**22.0**	**80.9**
	Rsum (V1:V6)	uV	4282	2138	4397	2098	4186	2224	4052	2148	**3487**	2207
	LVH Score	score	166	201	124	153	248	240	253	260	**351**	**272**

Table 4 – Distribution statistics of ECHO and ECG interpretation in Cardio Phoenix Database along the four HF category – 2nd part

	HF category		All		Absent HF		Cons. HFpEF		Cons. HFmrEF		Cons. HFrEF	
Group	**Field**	**Unit**	**M**	**STD**	**M**	**STD**	**M**	**STD**	**M**	**STD**	**M**	**STD**
ECHO measurements	IVSd	mm	10.2	1.8	9.9	1.6	**11.4**	2.0	10.5	1.8	10.1	2.0
	LVIDd	mm	51.6	6.8	49.8	5.2	53.1	6.5	55.5	7.3	**62.7**	9.7
	LVIDs	mm	33.8	6.8	31.4	4.3	34.2	5.3	40.3	5.5	**49.8**	8.5
	LVEF	%	57.7	8.2	60.6	5.7	58.8	5.4	47.6	2.3	**37.3**	4.6
	RWT	%	34.4	6.7	34.8	6.2	**36.0**	7.3	32.8	6.7	28.5	8.1
	LVmass	g	187.8	62.0	170.5	48.0	222.0	67.3	219.2	66.7	**258.8**	85.8
	LVMI (LVmass/BSA)	g/m^2	98.8	30.8	90.1	22.7	117.1	33.8	114.4	35.9	**132.7**	43.6
	LAV	mL	36.6	20.8	29.6	11.0	50.4	24.4	48.3	26.8	**69.0**	32.8
	LAVI (LAV / BSA)	mL/m^2	19.3	11.1	15.7	5.6	26.6	12.6	25.4	15.1	**35.8**	18.8
	RAV	mL	40.1	25.0	33.7	14.1	52.4	32.4	51.0	36.5	**70.6**	38.8
	RAVI (RAV / BSA)	mL/m^2	21.1	13.1	17.8	7.1	27.7	16.7	26.7	19.9	**36.5**	20.7
	AVpV	m/s	1.4	0.5	1.3	0.4	**1.7**	0.8	1.5	0.7	1.4	0.7
	AVpGrad	mmHg	8.9	9.4	7.3	5.4	**14.9**	16.0	10.2	11.9	10.5	13.1
	ARgrade	grade	0.4	0.8	0.2	0.6	**0.8**	1.0	0.5	0.9	0.7	1.0
	ARjet Area	cm^2	0.6	1.8	0.4	1.3	**1.4**	2.8	0.9	2.0	1.1	2.3
	MVGE mean	mmHg	2.0	1.4	1.8	1.1	2.4	2.0	2.3	1.6	**2.7**	1.8
	MV E Vmax	m/s	0.80	0.26	0.77	0.22	0.86	0.34	0.85	0.29	**0.93**	0.31
	MV A Vmax	m/s	0.78	0.29	0.78	0.23	0.83	0.40	0.76	0.36	**0.64**	0.42
	MV E/A		1.1	0.4	1.0	0.4	1.0	0.6	1.1	0.5	**1.4**	0.7
	MRgrade	grade	1.4	1.1	1.1	0.9	2.0	1.0	1.8	1.1	**2.5**	1.1
	MRjet/LAA	%	13.5	15.1	10.4	12.5	19.2	15.5	18.5	18.0	**29.1**	21.7
	TRgrade	grade	1.2	1.0	0.9	0.9	1.8	1.1	1.4	1.1	**2.0**	1.2
	TRjet/RAA	%	12.5	16.1	9.4	13.9	21.3	19.5	15.4	16.2	**23.3**	18.2
	RVSP (mPAP)	mmHg	18.9	11.8	16.3	8.3	26.6	16.0	21.5	13.6	**28.8**	18.1
	PEEF (maximum)	mm	0.3	1.7	0.2	1.4	0.5	2.2	0.4	1.9	**0.6**	2.0
	RVOTend-distal	mm	30.4	16.2	28.1	13.2	34.9	19.5	33.2	19.4	**43.4**	24.8
	RVOTprox	mm	26.8	5.8	25.8	5.5	28.9	5.5	28.3	5.7	**30.4**	6.7
	RVDd M-mode	mm	29.2	5.1	28.3	4.6	31.1	5.4	30.9	5.4	**33.1**	6.4
	RVDs M-mode	mm	14.3	4.9	13.4	4.1	16.2	5.4	15.8	5.7	**18.0**	7.4
	RAD (A4C)	mm	38.4	7.5	36.5	6.1	42.2	8.2	41.5	8.7	**46.5**	9.5
	RADI (RAD / BSA)	mm/m^2	20.4	4.2	19.5	3.4	22.4	4.9	21.7	5.1	**24.0**	5.7
	WMscore	score	0.3	0.7	0.2	0.5	0.5	1.1	0.5	0.9	**0.9**	1.3
HF Score	H_2FPEF Score	score	2.43	1.39	1.93	0.86	**3.82**	1.59	3.21	1.59	3.81	1.73
	HFA-PEFF score	score	1.62	0.89	1.24	0.54	2.57	0.83	2.20	0.89	**2.98**	0.98

Table 5 – Distribution statistics of ECHO and ECG interpretation in Cardio Phoenix Database along the four HF category – 3rd part

	HF category		All		Absent HF		Cons. HFpEF		Cons. HFmrEF		Cons. HFrEF	
Group	Field	Unit	M	STD	M	STD	M	STD	M	STD	M	STD
ECHO-Finding	LVH		14.0%		7.1%		**37.1%**		20.8%		30.3%	
	DCM		9.9%		3.0%		13.2%		24.3%		**64.2%**	
	RVE		4.6%		2.0%		9.3%		7.3%		**20.1%**	
	LAE		8.8%		0.4%		27.0%		20.3%		**48.0%**	
	RAE		6.5%		1.2%		16.1%		13.6%		**38.0%**	
	WMA		8.0%		1.6%		5.5%		34.4%		**42.8%**	
	LVSD		4.9%		0.0%		0.0%		0.0%		**100.0%**	
	DD Impaired Relaxation		22.7%		19.8%		**39.5%**		23.2%		14.5%	
	DD Pseudonormal		3.5%		1.7%		5.9%		8.0%		**10.7%**	
	DD Restrictive Filling		2.9%		1.1%		6.1%		5.4%		**13.6%**	
	AS		5.7%		1.7%		**22.0%**		8.3%		11.1%	
	MS		2.8%		1.0%		**8.4%**		5.5%		6.6%	
	AR		7.0%		3.9%		15.5%		11.0%		**17.4%**	
	MR		12.7%		6.1%		27.1%		20.4%		**47.5%**	
	TR		9.9%		4.4%		24.3%		15.5%		**32.4%**	
	PH		3.7%		0.3%		12.5%		7.0%		**19.4%**	
	Abnormal ECHO		37.9%		16.2%		81.2%		88.5%		**100.0%**	
ECG-Finding	S. Bradycardia		3.2%		3.3%		2.6%		**4.0%**		1.5%	
	S. Tachycardia		1.3%		1.2%		1.1%		1.2%		**3.2%**	
	AFib		8.2%		0.6%		**28.7%**		20.1%		28.6%	
	PVC		15.3%		9.9%		23.8%		26.8%		**39.7%**	
	PAC		14.8%		12.7%		20.1%		17.6%		**22.3%**	
	Prolonged PR		7.3%		6.8%		8.7%		7.9%		**10.2%**	
	Prolonged QT		3.6%		2.6%		**7.1%**		4.8%		6.1%	
	BBB		7.7%		5.3%		12.0%		12.1%		**18.6%**	
	ST-T deviation		17.9%		9.8%		32.3%		34.8%		**50.3%**	
	Ischemic ST-T		14.3%		11.3%		19.1%		21.0%		**25.7%**	
	MI		15.7%		11.1%		22.5%		27.4%		**33.9%**	
	Possible LVH		10.9%		5.6%		20.8%		20.7%		**34.2%**	
	Possible RVH		1.3%		0.9%		2.4%		1.2%		**4.3%**	
	Leftward Axis		9.6%		6.4%		15.5%		15.4%		**24.5%**	
	Rightward Axis		1.7%		1.5%		2.3%		1.6%		**2.7%**	
	Abnormal ECG		40.9%		27.6%		67.5%		68.7%		**87.1%**	
	Borderline ECG		25.0%		**28.6%**		18.3%		17.8%		10.6%	

Most of the measurements and findings show most of the abnormal mean values for the HFrEF category. Interestingly, the exceptions help us to understanding the HFpEF and HFmrEF categories:

- HFpEF shows highest value of Systolic BP (not significant), IVSd, RWT%, AoV Vmax, AR Grade and Jet Area, PQ and QT interval, in addition LVH, DDIM, AS/MS, AFib and Prolonged QT from findings.
- HFmrEF shows highest value of Diastolic BP (not significant), highest prevalence of Sinus Bradycardia. The prevalence of WMA and MI are significantly higher than in HFpEF and closer to HFrEF values.
- In case of other parameters and findings, the HFrEF has the worst mean values and highest deviation.

The distribution of several parameters confirms published results in [32].

The limitation of ECG interpretation for HF can be observed in the Abnormal ECG Summary finding, shown in Table 4: Abnormal ECG Summary covers 67.5% of HFpEF, 68.7% of HFmrEF and 87.1% of HFrEF. Abnormal ECHO Summary have higher percentages, abnormal 81.2% for HFpEF", 88.5% for HFmrEF and 100.0% for HFrEF".

3.3 Discussion

3.3.1 Typical characteristics of HF categories

HFpEF represents approximately 50% of HF cases and increasingly recognized as a leading cause of morbidity and mortality, confirmed by the research [6][35]. The prevalence distribution in the Cardio-Phoenix database between the three categories of HF confirms this 50%, moreover it shows that HFmrEF has double the prevalence compared to HFrEF patients.

HFpEF from HFmrEF does not so much differ in prevalence and disease severity as by disease type. HFpEF mostly includes DD, LVH and mild/moderate valve disease patients, whereas HFmrEF includes patients with ischemic problems: WMA, MI, and ST-T deviation.

HFpEF group of patients are typically older, having hypertension, obesity, where the typical structural abnormalities are the LVH, the typical function abnormality is the DD, the typical hemodynamical problem is any aortic/mitral valve disease or PH, and the typical electrophysiological problem is AFib.

The abnormalities that typically occur in HFmrEF compared to HFpEF and HFrEF have not been as comprehensively investigated. Our analysis provides some relationships as presented in these statistics:

- LVH is already representative within HFpEF and cannot be defined as a typical indicator of HFmrEF, but the DCM prevalence significantly increased in cases of HFmrEF compared to HFpEF (see Table 3)
- WMA is an important source of mildly reduce systolic function, with 10 times higher prevalence compared to patients with HFpEF.
- MI has an increased trend from HFpEF whereas patients with HFmrEF have MI with almost the same prevalence as in HFrEF, confirming previous study [32].
- Sinus bradycardia has the highest prevalence in HFmrEF compared to the other HF categories.

HFmrEF group of patients have similar comorbidities as HFpEF, but different type of problems: their typical structural abnormality is mild DCM, the typical functional abnormality is WMA with either MI or ST-T deviation, and the typical electrophysiological problem is AFib, PVC and sinus bradycardia (valve diseases are less typical compared to HFpEF).

HFrEF group of patients have the highest levels of comorbidity and severity: the typical structural abnormalities are the DCM, left and right atrial and ventricular enlargement, the typical functional abnormality is LVSD, the typical hemodynamical problem is mitral/tricuspid regurgitation and PH, and all the common ECG abnormalities shows higher prevalence including the ECG LVH and ECG RVH criteria.

Furthermore, right-side heart abnormalities (RAE, RVE, RVH) show significant increase in HFrEF categories, a less known and less researched area in HF studies. The overall comorbidity ratio shows an increasing trend with the decreasing of systolic function and exacerbation of HF. However, recent COVID-19 related literature is increasingly referring to right side heart abnormalities with HFpEF, associated with COVID-19 [16][17].

3.3.2 Heart failure and co-morbidities

Table 6 shows the HF categories and the most important associated co-morbidities as the summary of prevalence analysis. The list of typical abnormalities or co-morbidities are listed using both the literature and statistical analysis based on the presented data.

Table 6 – HF category and related ECHO and ECG-based co-morbidities and abnormalities

Heart Failure category	Symptoms ± Signs criteria	LVEF criteria	Structural heart diseases criteria	Typical co-morbidities ("+" denotes the disease plus the previous ones)
Absent	No	>50%		Non-significant or mild abnormalities
HFpEF	Yes		DD or LVH and/or LAE	Arrhythmia (AFib) Regional LVSD Regional WMA Valve diseases (AS, AR) PH Leftward Axis
HFmrEF	Yes	40-49%		+ Global LVSD + Global WMA + More severe ischemia/CAD + Mild Dilated LV
HFrEF	Yes	<40%		+ Dilated LV (DCM) + More severe valve diseases + Right Heart Enlargement

Color Legend:
Primarily ECHO finding
Primarily ECG finding

4 Prevalence comorbidity statistics

4.1 Method

Comorbidity for the diagnosis and prognostication of HFpEF is still widely debated, and research introduces various criteria and scoring systems [35].

In the presented analysis LVEF was used as an independent variable to estimates the prevalence of ECG and ECHO abnormalities. LVEF as a continual measurement is split into 9 categories

with center values seen in Fig. 2. Patient were grouped along these categories and the prevalence of ECHO and ECG findings calculated.

Heart disease progresses with age, and cardiac comorbidity statistics confirm both the disease progression and the increased comorbidity factor with increasing age.

4.2 Results

The results are plotted in Fig. 2 together with the average value of some principal ECHO measurements.

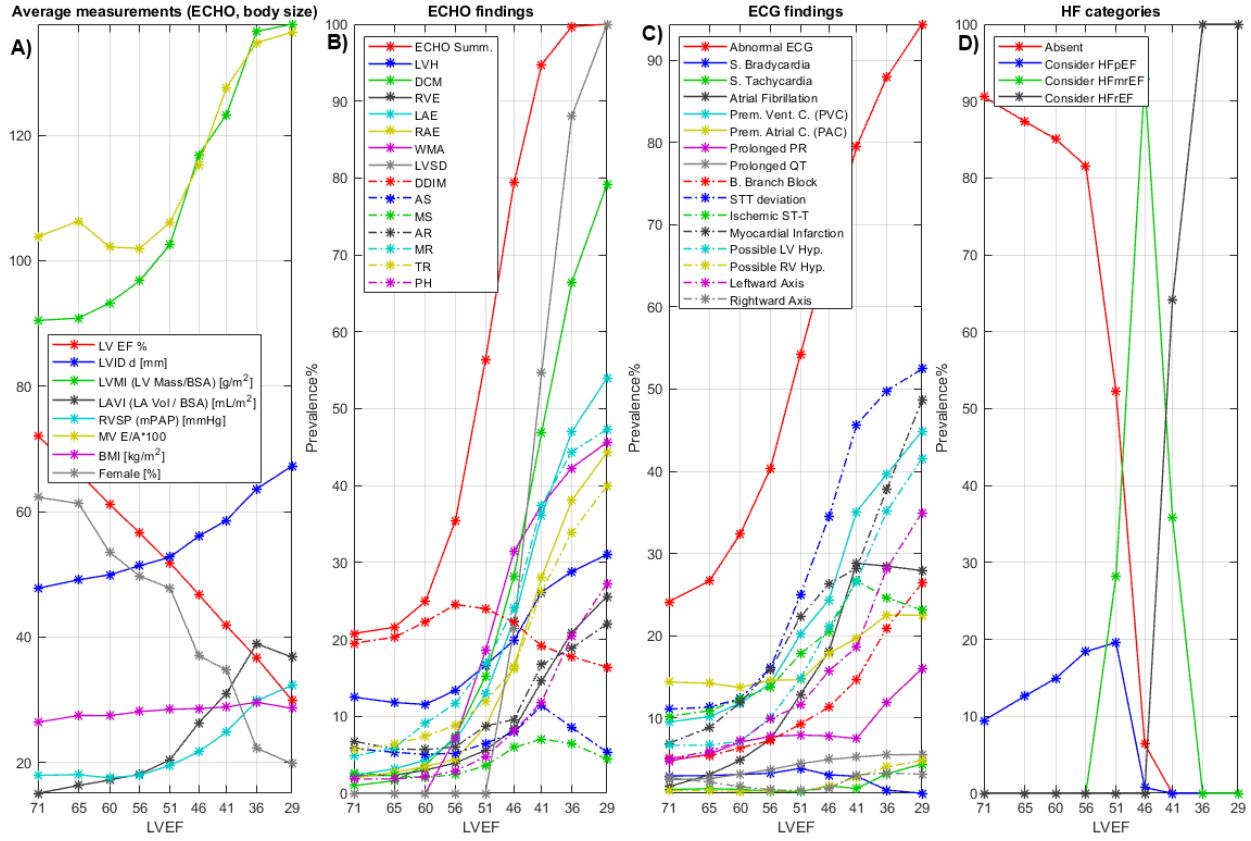

Figure 2 – Comorbidity analysis in function of LVEF categories (in descending order): A) Average ECHO measurements plus BMI and Female, B) ECHO-finding prevalence, C) ECG-finding prevalence, D) HF categories prevalence

The 1st graph of Fig. 2 shows a deteriorating trend of all the key ECHO-measurements as a function of LVEF. Obesity is measured by average BMI shows a slight increasing trend, and the percentage of Female patients drastically decrease with the decreasing LVEF. This confirms that the HFpEF patient is biased to females, and the HFrEF patient biased to males.

The 2nd graph of Fig. 2 shows constant increasing prevalence of almost all ECHO-findings, except: DDIM having maximum around LVEF=56%; AS and MS having maximum around LVEF=41%. DDIM and aortic-mitral stenosis patients belong mostly to the HFpEF and HFmrEF categories.

The 3nd graph of Fig. 2 shows constant increasing prevalence of almost all ECG-findings, except: S. Bradycardia having maximum around LVEF=51%; Ischemic ST-T having maximum around LVEF=41%; Rightward Axis having maximum around LVEF=71% and LVEF=36%. Typically, the HF patient has LVH with leftward axis, the Rightward Axis decreasing, but the typical right-side disease patients belong to HFrEF, that is why it is increasing again at the LVEF<40% groups.

The 4th graph of Fig. 2 shows the prevalence of the discussed HF categories, primarily separated based on LVEF. The maximum prevalence of HFpEF is around LVEF=51%, hence below 50% the HFmrEF replacing the HFpEF classification and below 40% HFrEF replacing HFmrEF classification.

5 PCA comorbidity statistics

5.1 Method

A Principal Component Analysis (PCA) was completed to interpret patterns of comorbidities, i.e. group of comorbidities associated with each other [10]. PCA is a data reduction method that transforms the original set of variables into a smaller set of Principal Components (PCs), which are linear combinations of the original variables. PCs retain as much of the variability in the data set as possible, with the first component retaining the greatest amount of the variation present and the other components progressively retaining a decreasing amount of variation [9].

In this PCA the largest variance is discovered in the data of the most important ECG, ECHO and patient body size measurements, which help to understand the interactions or co-morbidities of common cardiovascular diseases.

5.2 Results

Table 7 lists the parameters included in PCA and the associated CVD. ECG, ECHO and body size data was extended with two different HFpEF scores, previously used in section 2.4: the HFA-PEFF score [4] and the H2FPEF score [36].

Table 7 – List of PCA included measurements

Category	Abbr.	Unit	Parameter Description
ECHO parameters	LVEF	%	LV Ejection Fraction (Quinones Equation)
	LVMI	g/m^2	Left Ventricular Mass Index
	LVIDd	mm	End-diastolic Left Ventricular Diameter (internal)
	RVOTprox	mm	Right Ventricular Outflow Tract Proximal
	LAVI	mL/m^2	Left Atrial Volume Index
	RAVI	mL/m^2	Right Atrial Volume Index
	WMscore	score	Wall Motion Score (1-Mild Hypokinesis, 2-Diffuse Hypokinesis, 3-Akinesis, 4-Dyskinesis, 5-Aneurism)
	E/A		E/A Wave Velocity
	AVpV	m/s	Aortic Valve Peak Velocity (Vmax)
	MVGEm	mmHg	Mitral Valve Mean Gradient E wave
	ARgrade	grade	Rate of Aortic Regurgitation
	MRjet/LAA	%	Mitral Regurgitation Jet Ratio in Left Atrium Area
	TRjet/RAA	%	Tricuspid Regurgitation Jet Ratio in Right Atrium Area
	RVSP	mmHg	Right Ventricular Systolic Pressure
ECG parameters	HR-Mean	bpm	Heart Rate Mean Value
	RRmedian	s	median RR interval
	RR std	ms	Standard Dev. of RR intervals - SDNN
	PNN50%	%	Rate of |dRR intervals| > 50ms - PNN50
	LF/HF	ms/ms	Low (0.04Hz-0.15Hz) per high (0.15Hz-0.4Hz) frequency parts of RR interval spectrum
	QRSaxis	deg/100	QRS axis in frontal plane
	PQint	ms	PQ Interval
	PRa	ms	corrected PR interval (PRa=PR+a*(60/RR-70); Age<60:a=0.26, Age>60:a=0.42)
	Pint	ms	P Wave Interval
	Paxis	deg	P wave axis
	P-area	mVms	P negative area in V1 lead (P terminal force)
	QTint	ms	QT Interval
	QTc-Fram	ms+	Corrected QT int. Framingham's: QTc=QT+0.154(1-RR)
	QTc-CHART	ms+	Corrected QT interval, where the correction was made by age and body size
	QRSint	ms	QRS Interval
	VAT	ms	Global Rwave peak time (intrinsicoid deflection)
	STint	ms	ST interval
	Taxis	deg	T wave axis
	LVHsc	score	LVH modified Romhilt-Estes score
HF Scores	HFA-PEFFsc	score	HFA-PEFF diagnostic algorithm and scoring system for HFpEF (0-6)
	H2FPEFsc	score	H2FPEF score by Yogesh N.V. Reddy, developed to HFpEF (0-9)
Body Size	Age	year	Age
	Gender		Gender (1 - Male, 2 – Female)
	BMI	kg/m^2	Body Mass Index (weight[kg]/height[m]^2)
	BSA	m^2	Body Surface Area (sqrt(Height[cm]*Weight[kg])/60)
	Height	cm	Height
	Weight	kg	Weight
	CBSI	m+ 1/5kg$^{0.27}$	CHART Body Size Index (CBSI=Height[m]+0.2Weight[kg]$^{0.27}$) Note: CBSI is more appropriate body size index compared to BSI

Fig. 3 shows the scatter plot of HF categories in function of PCA1 and PCA2: the left graph (A.) shows the four HF categories, where the centers are marked with black squares and numbers; the right graph (B) shows the body size categories according to CHART Body Size Index (CBSI),

where the CBSI<2.2 represent the smaller body size, 2.2<CBSI<2.4 represent the middle body size, and CBSI>2.4 represent the bigger body size (more details about why CBSI is used instead of BSI see in supplementary material 8.1). PCA1 parameter is a good indication for HF with significant difference between Absent and HFpEF, and between HFpEF and HFrEF. There is no significant difference between the two mild HF categories, HFpEF and HFmrEF.

The second component PCA2 represents the body size, which is not a pathological direction as is PCA1. PCA2 is an independent perpendicular direction to PCA1, which carries the second biggest variance of data.

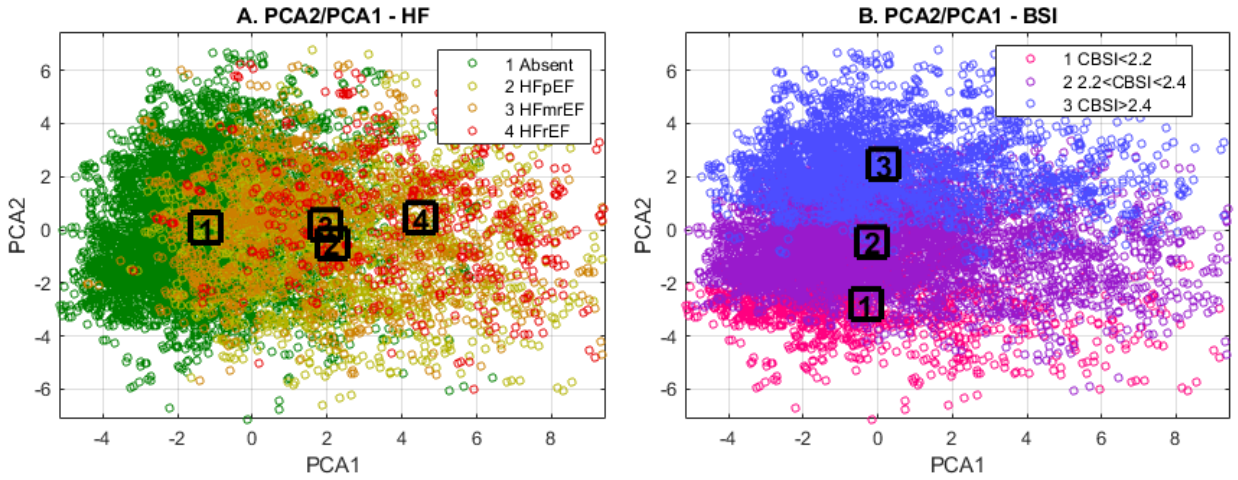

Figure 3 – 2D scatter plot of HF categories (A) and body size categories (B) in function of PCA1 and PCA2

Fig. 4 shows the scatter plot of the three HR categories - separated by average HR parameters - in function PCA1 and PCA3 (C.) and the Heart Rate Variability (HRV) categories – separated by standard deviation of RR intervals (RRstd) parameters in function of PCA1 and PCA4 (D.). The PCA1 seems independent from HR but dependent from HRV. PCA3 represents the HR value, and PCA4 the HRV values.

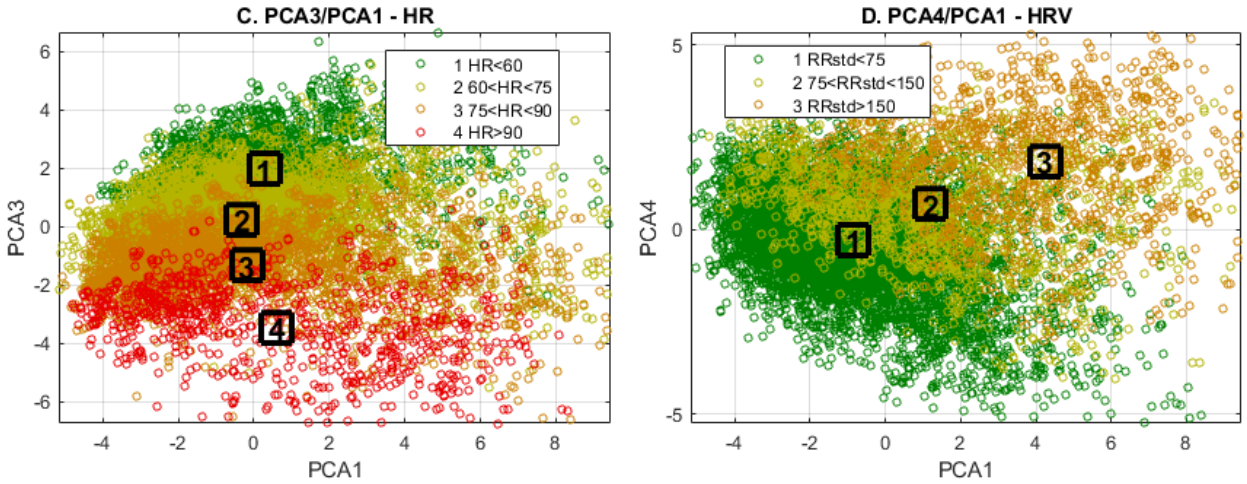

Figure 4 – 2D scatter plot of (C) HR categories in function of PCA3 and PCA1, (D) HRV categories in function of PCA4 and PCA1

Fig. 5 show the scatter plot of four HF categories in function PCA1 and PCA5 (E.) and in function of PCA4 and PCA5 (F.). PCA5 shows a DD related pathological direction, therefore has slightly higher separator between HFpEF and HFmrEF.

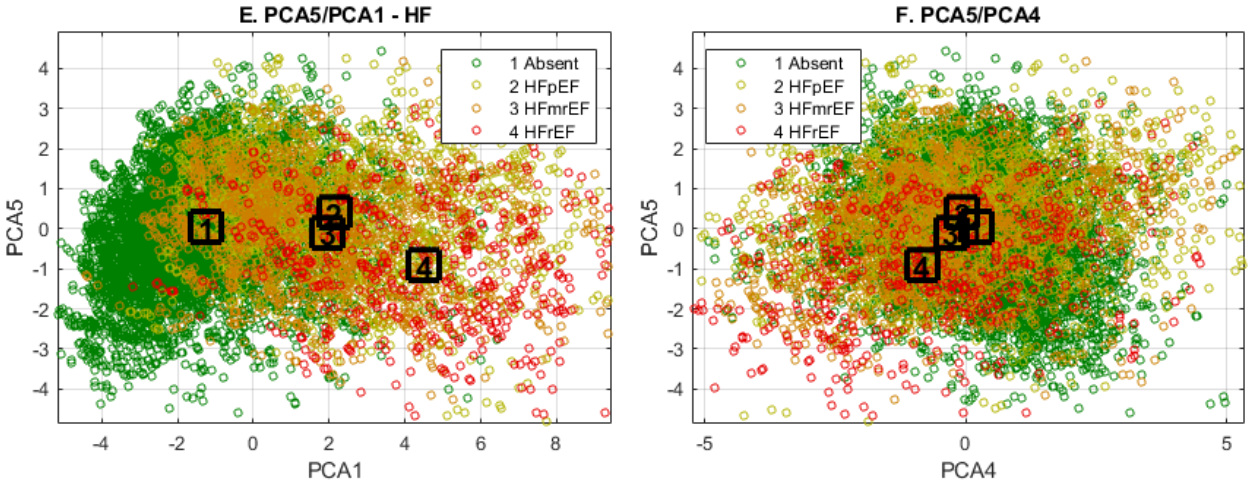

Figure 5 – 2D scatter plot of HF categories in function of (E) PCA5 and PCA1 and (F) PCA5 and PCA4

Fig. 6 shows the PCA coefficients of the first five components, where the input parameters are sorted by the absolute values of PCA1's coefficients.

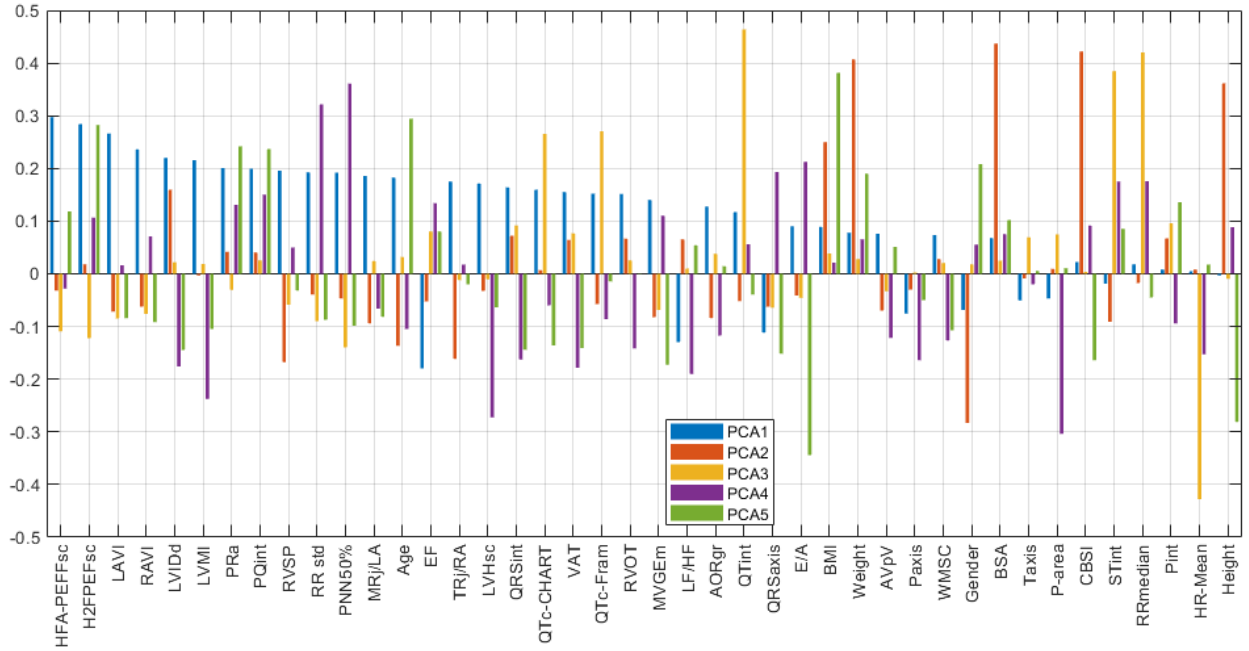

Figure 6 – Linear Coefficients of PCA1, PCA2, PCA3, PCA4 and PCA5, calculated on the relevant ECHO, ECG, HFpEF scores and body size parameters

5.3 Analysis

Each of the PCs point in a specific direction, which can be determined or represented by some input parameters identified by Fig. 7. The presented first five PCA are considered the most

important dimensions in the 42-dimension space. These first five PCA's cover 53% of all the variance provided by the 42 dimensions: 18.3%, 11%, 9%, 5.6% and 4.8% (summary 53%).

5.3.1 PCA1

The analysis shows that most of the common heart diseases have strong comorbidity, since all take part in the PCA1: heart failure and systolic dysfunction, atrial and ventricular enlargements, PH, mitral and tricuspid regurgitation, LVH.

The different natures of HFpEF and HFmrEF were not involved by the presented principal components. However, the LVEF can separate these two categories, see in Fig. 7, which show the four types of HF in 2D space of PCA1 and LVEF parameter. The big role of PCA1 can be observed in Fig. 7, where PCA1 distinguishes HFpEF from HF absent patients, which is not distinguishable by LVEF. LVEF can only distinguish HFmrEF and HFrEF from patients with LVEF>50%.

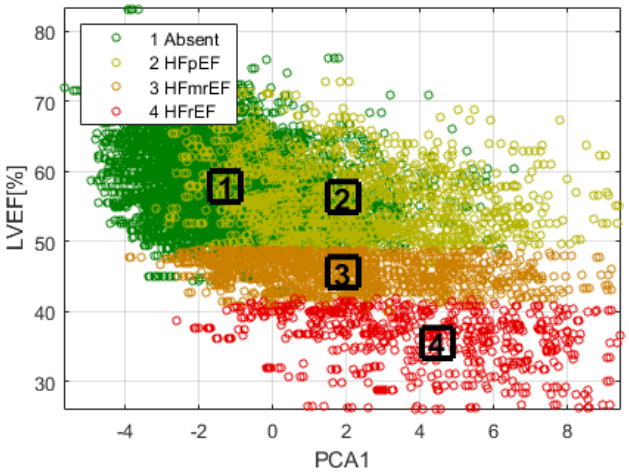

Figure 7 – Four group of HF patients in space of PCA1 and LVEF. LVEF can separate HFmrEF and HFrEF, but PCA1 can separate the HFpEF from absent patient contrary to LVEF.

5.3.2 Other PCs

The PCA2, 3 and 4 can be considered as independent components from PCA1 and from each-other. These fulfill the supplementary directions: PCA2 - body size, PCA3 - HR and PCA4 - arrhythmias.

PCA2 result confirms the important need of data normalization (for ECHO and ECG measurements) by body size or at the very least by gender. However, body size is preferred represented by BSA or CBSI because it relates more to the individual compared to the binary gender.

The PCA5 is a supplementary diagnostic component for HF that helps to distinguish categories of DD and categories of HF. PCA5 shows higher distance between HFpEF and HFmrEF compared to PCA1.

6 Discussion

The covariance pattern of ECG- and ECHO-measurements representing cardiac function was investigated by the PCA. The first principal component (PCA1) is interpreted as the overall comorbidity degree. The PCA established that the PCA1 is representative of **structural abnormalities:** the atrial and ventricular enlargements. The direction of this component is mostly suitable to the HF severity categories and confirmed by the HFpEF diagnostic scores. These scores are the most important participants in PCA1, not surprising as they rely mainly on key ECHO-measurements: E/e', LVMI, LAVI and RVSP.

Besides HFpEF scores, the LAE defined by LAVI is the most representative ECHO-finding in the overall comorbidity rate, which coincides with the probability direction of HF.

However, no single ECHO-measurement is suitable to identify all HF patients, hence the reason for the HF score approaches, where a set of relevant ECHO-findings are aggregated in order to account for the varying nature of HF.

For example, ECG algorithms predicting LVEF<35%, like [41][42], target only HFrEF category and are inherently unsensitive for the larger group of HF patients found in primary care (HFmrEF and HFpEF).

In PCA1, the second group of coefficients are related to the **functional abnormalities**. Astonishingly, LVEF is the 14th input parameter according to the coefficient's values, having similar impact as age, arrhythmia, prolonged PR, RVSP and Mitral/Tricuspid regurgitation. This means LVEF, age, arrhythmia, PR and valve diseases are less representative of the overall comorbidity compared to HFpEF scores and chamber enlargements.

The analysis of the prevalence of the HF categories showed that the abnormal ECHO has higher sensitivity in diagnosing all three HF categories compared to abnormal ECG.

The low performance by ECG is primarily due to its poor sensitivity for heart **structural abnormalities**, and poor specificity for heart **functional abnormalities** (well-known from the literature). ECG's inherent limitations and typical rule-based approach suffers from low sensitivity for atrial and ventricular enlargements that make it unsuitable for detection of HF in a primary care situation.

6.1 Bio-signal ECHO-findings for primary care

A promising solution is the Cardio-HART or CHART[2] system which, using novel bio-signals analyzed by Artificial Intelligence, can predict 14 ECHO-findings, also called HART-findings[3], including: LV systolic and Diastolic dysfunction, Left and Right Atrial enlargement, Left and Right ventricular enlargement, Aortic and Mitral Stenosis, Aortic, Mitral and Tricuspid regurgitation, and PH.

As such, bio-signal derived ECHO-findings processed through the CHART AI system, can predict the structural and functional abnormalities and measurements essential to the detection

[2] Cardio-HART™ from Cardio-Phoenix

[3] FDA require that Cardio-Phoenix not use the term Echo-findings as they are derived from images, whereas HART-findings™ are bio-signal derived. Echo-findings are disease equivalent to HART-findings™

accuracy for HF. This means that on initial patient presentation to Primary Care, practitioners will be able to recognize HF, including classifying its severity and category, precluding purely symptomatic based detection of HF through repeated and costly clinical visits and testing, that delays access to treatment especially when symptoms remain inconclusive.

6.2 Study Limitation

The right side of the heart is less represented by the included ECHO-parameters and ECG even less, as such their place in the statistical results is limited.

Nonetheless, right-side heart failure and its structural, functional abnormalities and related pulmonary disease co-morbidities (COPD, Covid-19) have attracted growing attention in the last few years. Right-heart side study through a bio-signal approach shows strong potential.

Further research is warranted to investigate in more detail the relationship between HF categories and right-side HF through the window of bio-signals, risk factors, detectable abnormalities, COPD and other co-morbidities and symptoms.

7 Conclusion

The prevalence-based comorbidity analysis shows that the above-mentioned ECHO findings are strong indicators for HF and its category. More precisely, Echo shows the **enlarged heart** with decreased myocardial contractility and general **abnormal heart functioning**.

As Echocardiography is not available in primary care, the key **structural** (heart chamber enlargements) and **functiona**l abnormalities related measurements are not available precluding the ability to diagnose HF other than through mainly symptomatic means.

The current results suggest that a key set of ECHO-findings are sufficiently representative of HF when taken together as opposed to a single measurement, like LVEF. The two HF score techniques discussed in this study, the HFA-PEFF score [4] and the H2FPEF score [36], validate this approach, as they rely on Echo-finding indicators for the critical components of their score, precisely to avoid reliance on LVEF. The use of LVEF only would lead to a limited HF prediction capability focusing only on the HFrEF category, ignoring HFpEF altogether and much of HFmrEF, resulting in a high incidence of FN.

As such, the bio-signal based approach classifying a set of ECHO-findings is recommended, in contrast, single LVEF would inherit its limitation.

The use of novel bio-signals of a physiological nature such as those found in Cardio-HART™ can provide to primary care, and users of the various Scoring techniques, the missing echocardiography elements to understanding the structural and functional abnormalities and thereby increase HF detection accuracy for all 3 types of HF, even in asymptomatic patients.

8 References

[1] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J 2016;18:891-975.

[2] Andronic, Anca Andreea, Sorina Mihaila, and Mircea Cinteza. "Heart failure with mid-range ejection fraction–a new category of heart failure or still a gray zone." Maedica 11.4 (2016): 320.
[3] Bozkurt, Biykem, et al. "Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure." Journal of cardiac failure (2021).
[4] Pieske, Burkert, et al. "How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)." European heart journal 40.40 (2019): 3297-3317.
[5] Afsin Oktay, A., and Sanjiv J Shah. "Diagnosis and management of heart failure with preserved ejection fraction: 10 key lessons." Current cardiology reviews 11.1 (2015): 42-52.
[6] Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011; 13: 18-28.
[7] Gazewood, John D., and Patrick L. Turner. "Heart failure with preserved ejection fraction: diagnosis and management." American family physician 96.9 (2017): 582-588.
[8] Simmonds, Steven J., et al. "Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding." Cells 9.1 (2020): 242.
[9] Jolliffe I. Principal Component Analysis. New York: Wiley Online Library; 2002.
[10] De Francesco, Davide, et al. "Patterns of co-occurring comorbidities in people living with HIV." Open forum infectious diseases. Vol. 5. No. 11. US: Oxford University Press, 2018.
[11] Heart Failure Society of America. "Section 5: Management of Asymptomatic Patients With Reduced Left Ventricular Ejection Fraction." Journal of cardiac failure 12.1 (2006): e26-e28.
[12] Wang, Thomas J., et al. "Natural history of asymptomatic left ventricular systolic dysfunction in the community." Circulation 108.8 (2003): 977-982.
[13] Bshiebish, Hasanain Ali Hameed, Ali Hussein Al-Musawi, and Safaa Ali Khudeir. "Role of global longitudinal strain in assessment of left ventricular systolic function in patients with heart failure with preserved ejection fraction." Journal of the Saudi Heart Association 31.2 (2019): 100-105.
[14] Sahlen, Anders, and Reidar Winter. "How should we measure global and regional left ventricular systolic function?." Journal of echocardiography 9.2 (2011): 41-50.
[15] Kraigher-Krainer, Elisabeth, et al. "Impaired systolic function by strain imaging in heart failure with preserved ejection fraction." Journal of the American College of Cardiology 63.5 (2014): 447-456.
[16] Lan, Yonghao, Wei Liu, and Yujie Zhou. "Right Ventricular Damage in COVID-19: Association Between Myocardial Injury and COVID-19." Frontiers in Cardiovascular Medicine 8 (2021): 82.
[17] Mehra, Mandeep R., and Frank Ruschitzka. "COVID-19 illness and heart failure: a missing link?." (2020): 512-514.
[18] Lüscher, Thomas F. "Heart failure subgroups: HFrEF, HFmrEF, and HFpEF with or without mitral regurgitation." (2018): 1-4.
[19] Chaliki, Hari P., et al. "Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function." Circulation 106.21 (2002): 2687-2693.
[20] Quiñones, Miguel A., et al. "A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography." Circulation 64.4 (1981): 744-753.
[21] Prasad A, Hastings JL, Shibata S, et al. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. Circ Heart Fail 2010; 3: 617-26.
[22] Hussain, Nehal, et al. "Pulmonary hypertension in patients with heart failure and preserved ejection fraction: differential diagnosis and management." Pulmonary circulation 6.1 (2016): 3-14.
[23] Piskorz, Daniel, et al. "Association of systolic dysfunction with left ventricular hypertrophy and diastolic dysfunction in hypertensive patients." Revista de la Facultad de Ciencias Medicas (Cordoba, Argentina) 71.4 (2014): 158-164.
[24] Movahed, Mohammad Reza, and Yuji Saito. "Obesity is associated with left atrial enlargement, E/A reversal and left ventricular hypertrophy." Experimental & Clinical Cardiology 13.2 (2008): 89.
[25] Carson, Peter, et al. "Mild systolic dysfunction in heart failure (left ventricular ejection fraction> 35%): baseline characteristics, prognosis and response to therapy in the Vasodilator in Heart Failure Trials (V-HeFT)." Journal of the American College of Cardiology 27.3 (1996): 642-649.
[26] Gori, Mauro, et al. "Is mild asymptomatic left ventricular systolic dysfunction always predictive of adverse events in high-risk populations? Insights from the DAVID-Berg study." European journal of heart failure 20.11 (2018): 1540-1548.

[27] Mutlak, Diab, et al. "Tricuspid regurgitation in acute heart failure: is there any incremental risk?." European Heart Journal-Cardiovascular Imaging 19.9 (2018): 993-1001.
[28] McCrohon, J. A., et al. "Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance." Circulation 108.1 (2003): 54-59.
[29] van Gils, Lennart, et al. "Prognostic implications of moderate aortic stenosis in patients with left ventricular systolic dysfunction." Journal of the American College of Cardiology 69.19 (2017): 2383-2392.
[30] Anter, Elad, Mariell Jessup, and David J. Callans. "Atrial fibrillation and heart failure: treatment considerations for a dual epidemic." Circulation 119.18 (2009): 2516-2525.
[31] Karaye, Kamilu M., and Mahmoud U. Sani. "Electrocardiographic abnormalities in patients with heart failure." Cardiovascular journal of Africa 19.1 (2008): 22.
[32] Webb, Jessica, et al. "Is heart failure with mid range ejection fraction (HFmrEF) a distinct clinical entity or an overlap group?." IJC heart & vasculature 21 (2018): 1-6.
[33] Lee, D.S.; Gona, P.; Vasan, R.S.; Larson, M.G.; Benjamin, E.J.; Wang, T.J.; Tu, J.V.; Levy, D. 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 2009, 119, 3070–3077.
[34] Lang, Roberto M., 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." European Heart Journal-Cardiovascular Imaging 16.3 (2015): 233-271.
[35] Parcha, Vibhu, et al. "Diagnostic And Prognostic Implications of Heart Failure With Preserved Ejection Fraction Scoring Systems." Journal of Cardiac Failure 26.10 (2020): S38.
[36] Reddy, Yogesh NV, et al. "A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction." Circulation 138.9 (2018): 861-870.
[37] Kjaergaard, Jesper, et al. "Prognostic importance of pulmonary hypertension in patients with heart failure." The American journal of cardiology 99.8 (2007): 1146-1150.
[38] Gradman, Alan H., and Fadi Alfayoumi. "From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease." Progress in cardiovascular diseases 48.5 (2006): 326-341.
[39] Velagaleti, Raghava S., et al. "Left ventricular hypertrophy patterns and incidence of heart failure with preserved versus reduced ejection fraction." The American journal of cardiology 113.1 (2014): 117-122.
[40] El Aouar, Lilia Maria Mameri, et al. "Relationship between left atrial volume and diastolic dysfunction in 500 Brazilian patients." Arquivos brasileiros de cardiologia 101.1 (2013): 52.
[41] Attia, Zachi I., et al. "Screening for cardiac contractile dysfunction using an artificial intelligence–enabled electrocardiogram." Nature medicine 25.1 (2019): 70-74.
[42] Alhamaydeh, Mohammad, et al. "Identifying the most important ECG predictors of reduced ejection fraction in patients with suspected acute coronary syndrome." Journal of electrocardiology 61 (2020): 81-85.
[43] Groenewegen, Amy, et al. "Epidemiology of heart failure." European journal of heart failure 22.8 (2020): 1342-1356.
[44] Delepaul, Benoit, et al. "Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines?." ESC heart failure 4.2 (2017): 99-104.