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Article

Echocardiographic Prognostication of new onset Heart Failure in a Cohort of Ischemic Heart Disease Patients

Pronóstico Ecocardiográfico de un nuevo evento de Insuficiencia Cardíaca en una Cohorte de Pacientes con Cardiopatía Isquémica

Senbeta Guteta Abdissa

Division of Cardiology, Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University, Ethiopia.

Corresponding author: *Senbeta Guteta Abdissa*
Division of Cardiology, Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University, P.O.Box 28287/1000, Addis Ababa, Ethiopia.
E-mail: drsenbetag@yahoo.com

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ABSTRACT

Background: Echocardiographic predictors for new onset heart failure in patients with ischemic heart disease with reduced left ventricular ejection fraction (HFrEF) or with preserved left ventricular ejection fraction (HFpEF) in Ethiopian and Sub-Saharan African is not well-known.

Methods: Two hundred twenty-eight patients with ischemic heart disease were retrospectively recruited and followed. Analysis on baseline clinical and echocardiographic characteristics of patients, and risk factors for new onset HFpEF and new onset HFrEF were done. The exclusion criteria were known heart failure at baseline and those who did not have echocardiography data.

Results: During the follow up period, heart failure developed in 62.2% (61/98) of ischemic heart disease patients with preserved left ventricular ejection fraction and in 70.1% (92/130) of ischemic heart disease patients with reduced left ventricular ejection fraction. We did not find significant difference between HFrEF and HFpEF in time to new onset heart failure. Systolic blood pressure, diastolic blood pressure, diabetes, left atrium and diastolic left ventricular dimension had significant association with new onset HFrEF on univariate regression analysis. Whereas new onset HFpEF was significantly associated with age, sex, presence of hypertension, Systolic blood pressure and diastolic left ventricular dimension. On cox regression analysis diastolic left ventricular dimension was associated with both new onset HFpEF and HFrEF. Age, diabetes, and dimension of left atrium were also associated with HFrEF.

Conclusion: This cohort study in ischemic heart disease patients suggests a key role for the diastolic left ventricular dimension, left atrium size, diabetes, sex and age as predictors of new

onset HFrEF and HFpEF. Strategies directed to prevention and early treatment of diabetes, dilatation of left ventricle and left atrium may prevent a considerable proportion of HFrEF or HFpEF.

Keywords: echocardiography, ischemic heart disease, new onset heart failure, ventricular ejection fraction

1. Introduction

Heart failure (HF) remains one of the major causes of premature morbidity and mortality (Cheng S & Vasan, 2011, Lam CS *et al.*, 2011). There is a lifetime risk of 20%–46% to develop HF (Huffman *et al.*, 2013) and preventive strategies focused on risk factors and underlying causes are necessary. HF results from any functional or structural impairment of ventricular filling or ejection of blood, with symptoms resulting from impaired left ventricular (LV) structure or function (Yancy CW *et al.*, 2013)

The knowledge of HF risk factors has a crucial role at preventing new onset HF (Jong P *et al.*, 2003, Smith JG *et al.*, 2010). There are many studies that have reported established risk factors for new onset HF. These risk factors include higher age, hypertension, and the presence of ischemic heart disease (IHD) (Kannel WB, 2000, Lee GK *et al.*, 2010). Primarily, studies aimed at identifying risk factors were based on the diagnosis of HF according to signs and symptoms only (Ho KK *et al.*, 1993, McKee PA *et al.*, 1971). Recently, echocardiography is used in the diagnosis and classification of HF based on left ventricular ejection fraction (LVEF). Based on clinical and echocardiographic characteristics, HF is usually categorized as HF with LVEF ≥50% referred to as HF with preserved ejection fraction (HFpEF) and HF with LVEF <50% referred to as HF with reduced ejection fraction (HFrEF) (McMurray JJ *et al.*, 2012).

HFpEF accounts for approximately half of HF in the community (Dunlay SM *et al.*, 2017) and the lack of therapies that improve the prognosis of this condition reflects an incomplete understanding of its pathogenesis. In addition, data on the incidence of new onset HFpEF or HFrEF and their risk factors in Ethiopian and Sub-Saharan setting are scarce. Moreover, only limited information is available regarding the risk factors for incident HFpEF and HFrEF.(Aurigemma GP *et al.*, 2001, Lee DS *et al.*, 2009, Ho JE *et al.*, 2013, Brouwers FP *et al.*, 2013, Ho JE *et al.*, 2016)

The objective of this study was to examine the echocardiographic prognostication of new onset HFpEF, and HFrEF in a cohort of patients with IHD who did not have HF at baseline.

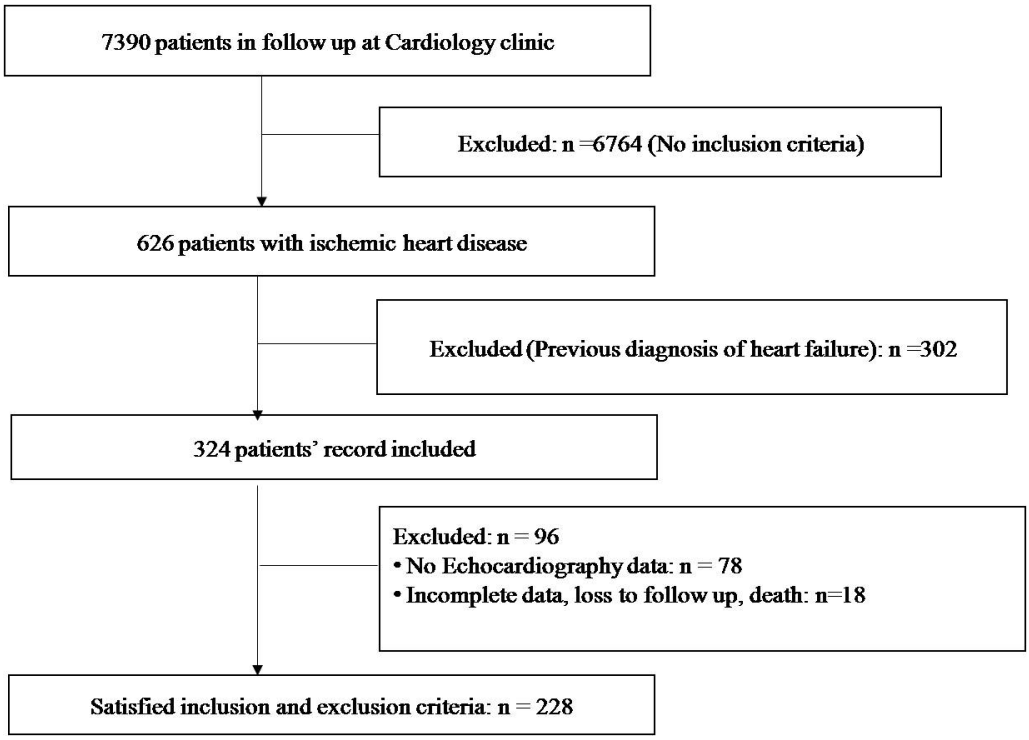
2. Subjects and methods

Study design and clinical setting

This is a retrospective cohort study in Ethiopian patients with IHD that was planned to identify echocardiographic predictors for new onset HF.

The flow chart for participant recruitment and follow-up is shown in figure 1. In summary, there were a total of 7390 patients in follow up at Black Lion Hospital. The inclusion criteria were diagnosis of IHD in follow up until the study exit date, development of HF, or death. While diagnosis of HF before the date of enrolment, incomplete data, absence of echocardiographic data and loss to follow up before the study exit date were the exclusion criteria.

Figure 1.
Flow diagram describing participant recruitment and follow-up in the study.



Patients (age of 18 years and above) with IHD fulfilling the recruitment criteria were enrolled in the study starting from November 30, 2015. A total of 228 IHD patients who had echocardiography at baseline were included in the cohort. We followed each study participant up for 24 months or until the diagnosis of HF was made. Patients with IHD or HF were identified based on the treating Physician's final diagnosis that was made based on symptoms and echocardiography findings. The study was approved by the institutional review board of the College and permission to use de-identified personal healthcare information for all included subjects was obtained.

Definition of Variables

Preceding IHD diagnosis was made in patients who had a clinical diagnosis of MI, and/or a history of angina or angina-driven coronary revascularization. The diagnosis of IHD was made based on information from patient records where the attending physician (Cardiologist) made the diagnosis. Previous HF was identified if patients had physician documented diagnosis of HF or if they had typical signs and symptoms consistent with a HF syndrome and/or used furosemide as part of their treatment. If a patient was diagnosed with HF or used furosemide during the 24 months follow-up, then they were categorized in a group with new onset HF. If no HF diagnosis was made during the follow-up period, they were categorized into the group with no new onset HF. Based on echocardiographic LVEF data patients were categorized into either HFpEF (LVEF ≥50%) or HFrEF (LVEF <50%) groups depending on the diagnosis of HF and LVEF data.

Outcome measures

The primary outcome of interest was new onset HF.

Data Collection

Data on baseline characteristics, diagnosis, and date of diagnosis of HF and IHD, functional classification of HF based on New York Heart Association (NYHA), risk factors, comorbidities, and complementary laboratory tests were collected from the medical records by trained medical staff. Transthoracic echocardiography findings, medications and hospital admission records were collected from the medical records of the patients.

Statistical analysis

Baseline characteristics were presented as frequency and percentages for categorical variables. Continuous parametric variables were expressed as means (± standard deviation) or medians (interquartile range) depending on their distribution. Comparisons between categorical data were performed with the use of Pearson's Chi-square test while comparisons of continuous data were done with the use of Student t-test.

Factors predicting the risk of new onset HF were explored in a univariate and multivariate logistic and Cox-regression model with new onset HF as the outcome (dependent) variable and the covariates as predictor (independent) variables. In the multivariate model, all variables associated with the evaluated endpoint at the 0.10 level in the univariate analysis were entered in the model for determination of predictors of new-onset HF. For each covariate, HR, 95% CI and p-value are reported. Covariates included in the multivariable analysis were age, gender, comorbidities including diabetes mellitus (DM), hypertension (HTN), LVEF, diastolic left ventricular dimension (LVD) and left atrial (LA) dimension.

The cumulative probability of new onset HF and time to new onset HF was illustrated with Kaplan-Meier time to event curve estimates. Cox regression analysis was used to calculate the hazard ratios for predictors of HF. A two-sided p value of <0.05 was considered to indicate statistical significance. Data were analyzed with SPSS software V.23.

3. Results

Baseline clinical variables and HF diagnosis

Table 1 shows the baseline data of patients who developed and who did not develop HF during follow-up. The follow-up duration of the 228 study participants was 24 months. All study participants had echocardiography at baseline. LVEF determination at baseline was performed by echocardiography.

Table 1.

Baseline characteristics of patients who developed new-onset heart failure and of patients without heart failure during follow-up.

	All patients (n=228)	New onset heart failure		P-value
Variables		Yes (n=153, 67.1%)	No (n=75, 32.9%)	
Age at enrolment (years)				
45 and less (n, %)	52 (22.8)	26 (17.0)	26 (34.7)	1.00
46-55 (n, %)	72 (31.6)	49 (32.0)	23 (30.7)	0.044
56-65	63 (27.6)	47 (30.7)	16 (21.3)	0.007

	All patients (n=228)	New onset heart failure		P-value
Variables		Yes (n=153, 67.1%)	No (n=75, 32.9%)	
66 and above	41 (18.0)	31 (20.3)	10 (13.3)	0.013
Mean (±SD) age	56.8 (11.6)	57.1 (10.9)	52.4 (12.3)	0.003
Sex				
Male (%)	156 (68.4)	99 (63.5)	57 (36.5)	0.085
Female (%)	72 (31.6)	54 (75.0)	18 (25.0)	1.00
Smoking status				
Never smoked (%)	193 (84.6)	131 (85.6)	62 (82.7)	1.00
Ever/Current smoker (%)	35 (15.4)	22 (14.4)	13 (17.3)	0.56
SBP (mmHg)-baseline	128.71 +/-20.24	128.38 +/-19.37	129.37+/-22.07	0.74
DBP (mmHg)-baseline	79.83 +/-10.04	79.27 +/-10.17	80.99 +/-9.73	0.24
Laboratory Data				
LVEF (Mean, %)	46.3 +/-13.4	45.6 +/-13.6	47.6 +/-13.0	0.29
LVDd (Mean, mm)	51.2 +/-10.3	51.9 +/-11.0	50.0 +/-9.0	0.23
LAD (Mean, mm)	36.5 +/-6.8	37.4 +/-6.8	34.6 +/-6.4	0.005
Hemoglobin (Mean, g/dl)	14.5 +/-2.0	14.4 +/-1.9	14.9 +/-2.0	0.08
WBC count (Mean, mm3)	7978.6 +/-2795.1	8318.7 +/-2561	7772.1 +/-2962.6	0.31
	All patients (n=228)	New onset heart failure		P-value
Variables		Yes (n=153, 67.1%)	No (n=75, 32.9%)	
Pulse rate-baseline	80.0+/-15.3	81.0+/-15.1	77.6+/-15.5	0.26
Hypertension	110 (48.2)	79 (71.8)	31 (28.2)	0.14
Diabetes	75 (32.9)	57 (37.3)	18 (24.0)	0.045
Dyslipidemia at baseline	38 (16.7)	26 (17.0)	12 (16.0)	0.85
Medications (%)				
Aspirin	207 (90.8)	140 (91.5)	67 (89.3)	0.59
Statins	198 (86.8)	132 (86.3)	66 (88.0)	0.72
B-blockers	190 (83.3)	133 (86.9)	57 (76.0)	0.04
RAS inhibitors	193 (84.6)	135 (88.2)	58 (77.3)	0.03
Loop diuretics	97 (42.5)	94 (61.4)	3 (4.0)	< 0.0001
Aldosterone antagonists	67 (29.4)	61 (39.9)	6 (8.0)	< 0.0001
Clopidogrel	25 (11.0)	13 (8.5)	12 (16.0)	0.09
Digoxin	24 (10.5)	24 (15.7)	-	< 0.0001
Hydrochlorthiazide	29 (12.7)	18 (11.8)	11 (14.7)	0.54
Calcium channel blocker	23 (10.1)	14 (9.2)	9 (12.0)	0.50
Use of antidiabetic medication	75 (32.9)	57 (37.3)	18 (24.0)	0.045
Insulin	21 (9.2)	18 (11.8)	3 (4.0)	0.057
Metformin	64 (28.1)	47 (30.7)	17 (22.7)	0.20
Sulfonilureas	8 (3.5)	8 (5.2)	-	0.04

CCB, calcium channel blocker; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular dimension; LAD, left atrial dimension; RAS, renin angiotensin system; SBP, systolic blood pressure; WBC, white blood cell count.

During the follow up period, new onset HF was diagnosed in 67.1% (153/228). There were significant differences in HF incidence rate between the age groups, but no difference in new onset HF was found between men and women. In comparison to participants who did not develop HF during follow-up, participants who developed HF were older, with a higher prevalence of diabetes, and larger left atrium size. Participants who developed HF also were more likely to be taking beta-blocker, Renin Angiotensin System (RAS) inhibitor, loop diuretic, aldosterone antagonist, digoxin, and antidiabetic medications.

As shown in table 2, 57.0% (130/228) of the patients had reduced LVEF at baseline. During the follow up period, new onset HF developed in 70.1% (92/130) of patients with reduced LVEF and in 62.2% (61/98) of patients with preserved LVEF. There were differences in baseline variables between participants with preserved LVEF, and reduced LVEF. In comparison with participants with reduced LVEF, participants with preserved LVEF were more likely to have higher systolic blood pressure (SBP), higher diastolic blood pressure (DBP), and higher prevalence of hypertension and less likely to develop advanced HF symptoms. Patients with preserved LVEF at baseline also had smaller left ventricular size and smaller LA size. They were less likely to have dilated LA and less likely to be taking aldosterone antagonists.

Table 2.

Characteristics of patients with preserved EF (>=50%), or reduced EF (<50%)

Variables	rEF n=130 (57.0%)	pEF n=98 (43.0%)	P-value
Age at enrolment (years)			
45 and less (n, %)	29 (55.8)	23 (44.2)	1.00
46-55 (n, %)	48 (66.7)	24 (33.3)	0.22
56-65 (n, %)	37 (58.7)	26 (41.3)	0.75
66 and above (n, %)	16 (39.0)	25 (61.0)	0.11
Mean (±SD) age	54.68 (10.57)	56.65 (12.67)	0.20
Sex			
Male (%)	95 (60.9)	61 (39.1)	1.00
Female (%)	35 (48.6)	37 (51.4)	0.08
Smoking status			
Never smoked (%)	108 (56.0)	85 (44.0)	1.00
Ever/Current smoker (%)	22 (62.9)	13 (37.1)	0.45
SBP (mmHg)-baseline	124.57 (19.27)	134.01(20.32)	0.001
DBP (mmHg)-baseline	78.55 (9.14)	81.47 (10.91)	0.03
Hypertension	53 (48.2)	57 (51.8)	0.009
Diabetes	45 (60.0)	30 (40.0)	0.52
Dyslipidemia at baseline	20 (52.6)	18 (47.4)	0.55
New onset Heart Failure	92 (60.1)	61 (39.9)	0.18
NYHA Fc 3 or 4	43 (68.3)	20 (31.7)	0.03
Laboratory Data at baseline			
LVDd (Mean, mm)	56.04(9.62)	45.53(7.99)	< 0.0001

Variables	rEF n=130 (57.0%)	pEF n=98 (43.0%)	P-value
LAD (Mean, mm)	38.08(6.68)	34.51(6.36)	< 0.0001
Variables	rEF n=130 (57.0%)	pEF n=98 (43.0%)	P-value
LA dilatation	38 (69.1)	17 (30.9)	0.01
Hemoglobin (Mean, g/dl)	14.29 (2.02)	14.85 (1.84)	0.06
WBC count (Mean, mm3)	8247.98(2787.71)	7651.11(2786.54)	0.16
Medications (%)			
Aspirin	121 (58.5)	86 (41.5)	0.17
Statins	112 (56.6)	86 (43.4)	0.72
B-blockers	109 (57.4)	81 (42.6)	0.81
RAS inhibitors	115 (59.6)	78 (40.4)	0.07
Loop diuretics	62 (63.9)	35 (36.1)	0.07
Aldosterone antagonists	56 (83.6)	11 (16.4)	< 0.0001
Clopidogrel	16 (64.0)	9 (36.0)	0.46
Digoxin	19 (79.2)	5 (20.8)	0.02
Hydrochlorthiazide	13 (44.8)	16 (55.2)	0.16
Calcium channel blocker	9 (39.1)	14 (60.9)	0.07
Antidiabetic medication	45 (60.0)	30 (40.0)	0.52
Insulin	14 (66.7)	7 (33.3)	0.35
Metformin	39 (60.9)	25 (39.1)	0.46
Sulfonilureas	5 (62.5)	3 (37.5)	0.75

CCB, calcium channel blocker; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular dimension; LAD, left atrial dimension; RAS, renin angiotensin system; SBP, systolic blood pressure; WBC, white blood cell count; pEF, preserved; rEF, reduced EF.

Risk factors for incident HF, HFrEF, HFpEF

Baseline variables with incident total HF, HFrEF, and HFpEF on univariate logistic regression analysis are shown in Tables 3-5. Predictors for new onset total HF on univariate analysis, as shown in Table 3 were age (COR 1.04 (95% CI 1.01-1.07), p = 0.003), diabetes (COR 1.88 (95% CI 1.01-3.51), p = 0.045) and left atrium size (COR 1.07 (95% CI1.02-1.12), p = 0.006).

Table 3. Factors associated with new-onset HF among IHD patients in univariate analysis.

	IHD patients with HF		COR (95% CI)*	P-value
Variables	Yes (n=153, 67.1%)	No (n=75, 32.9%)		
Baseline age (years)				
45 and less (n, %)	26 (17.0)	26 (34.7)	1.00	
46-55 (n, %)	49 (32.0)	23 (30.7)	2.13 (1.02-4.45)	0.044
56-65	47 (30.7)	16 (21.3)	2.94 (1.34-6.45)	0.007
66 and above	31 (20.3)	10 (13.3)	3.10 (1.27-7.60)	0.013
Mean (±SD) age	57.1 (10.9)	52.4 (12.3)	1.04 (1.01-1.07)	0.003
Sex				

	IHD patients with HF		COR (95% CI)*	P-value
Variables	Yes (n=153, 67.1%)	No (n=75, 32.9%)		
Male (%)	99 (63.5)	57 (36.5)	1.00	
Female (%)	54 (75.0)	18 (25.0)	1.73 (0.92-3.23)	0.085
Smoking status				
Never smoked (%)	131 (85.6)	62 (82.7)	1.00	
Ever/Current smoker (%)	22 (14.4)	13 (17.3)	1.08 (0.82-1.42)	0.56
DM				
Yes (%)	57 (76.0)	18 (24.0)	1.88 (1.01-3.51)	0.045
No (%)	96 (62.7)	57 (37.3)	1.00	
HTN				
Yes (%)	79 (71.8)	31 (28.2)	1.52 (0.87-2.65)	0.144
No (%)	74 (62.7)	44 (37.3)	1.00	
SBP	128.38(19.36)	129.37(22.07)	0.99 (0.98-1.01)	0.74
DBP	79.27(10.17)	80.99(9.73)	0.98 (0.96-1.01)	0.24
		IHD patients with HF	COR (95% CI)*	P-value
LVEF < 40%				
Yes (%)	57 (76.0)	18 (24.0)	1.88 (1.01-3.51)	0.047
No (%)	96 (62.7)	57 (37.3)	1.00	
LVEF < 50%				
Yes (%)	92 (60.1)	61 (39.9)	0.68 (0.39-1.19)	0.18
No (%)	38 (50.7)	37(49.3)	1.00	
LAD mean (±SD)	37.43 (6.76)	34.64 (6.43)	1.07 (1.02-1.12)	0.006
LVDd	51.87 (10.96)	50.03 (8.95)	1.02 (0.99-1.05)	0.23
Nephropathy				
Yes (%)	43 (64.2)	24 (35.8)	1.07 (0.87-1.31)	0.54
No (%)	110 (68.3)	51 (31.7)	1.00	
Dyslipidemia				
Yes (%)	26 (68.4)	12 (31.6)	1.08 (0.51-2.27)	0.85
No (%)	127 (66.8)	63 (33.2)	1.00	

COR, Crude Odds Ratio; CI, Confidence Interval; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular dimension; LAD, left atrial dimension; SBP, systolic blood pressure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction.

As shown in table 4, predictors identified for HFrEF were diabetes (COR 1.89(95% CI 1.02-3.51), p = 0.04), SBP (COR 0.97(95% CI 0.95-0.99), p = 0.001), DBP (COR 0.95(95% CI 0.91-0.98), p = 0.002), LA size (COR 1.08(95% CI 1.03-1.14), p = 0.002) and increasing diastolic LVD (COR 1.13(95% CI 1.09-1.18), p < 0.0001).

Table 4.
Factors associated with new-onset HFrEF among IHD patients in univariate analysis.

	IHD patients with HFrEF		COR (95% CI) *	P-value
Variables	Yes (57, 25.0%)	No (171, 75.0%)		
Baseline age (years)				
45 and less (n, %)	10 (17.5)	42 (24.6)	1.00	
46-55 (n, %)	19 (33.3)	53 (31.0)	1.51 (0.63-3.58)	0.35
56-65	22 (38.6)	41 (24.0)	2.25 (0.95-5.34)	0.07
66 and above	6 (10.5)	35 (20.5)	0.72 (0.24-2.18)	0.56
Mean (±SD) age	55.81 (10.09)	55.43 (12.01)	1.003 (0.98-1.03)	0.83
Sex				
Male (%)	41 (26.3)	115 (73.7)	1.00	
Female (%)	16 (22.2)	56 (77.8)	0.80 (0.41-1.55)	0.51
Smoking status				
Never smoked (%)	48 (24.9)	145 (75.1)	1.00	
Ever/Current smoker (%)	9 (25.7)	26 (74.3)	1.05 (0.46-2.39)	0.92
DM				
Yes (%)	25 (33.3)	50 (66.7)	1.89 (1.02-3.51)	0.04
No (%)	32 (20.9)	121 (79.1)	1.00	
HTN				
Yes (%)	22 (20.0)	88 (80.0)	0.59 (0.32-1.09)	0.09
No (%)	35 (29.7)	83 (70.3)	1.00	
SBP	120.25 (17.78)	131.44(20.28)	0.97 (0.95-0.99)	0.001
DBP	76.00 (9.09)	81.07(10.04)	0.95 (0.91-0.98)	0.002
LAD mean (±SD)	39.08 (6.70)	35.58 (6.57)	1.08 (1.03-1.14)	0.002
	IHD patients with HFrEF		COR (95% CI) *	P-value
LVDd mean (±SD)	59.41 (9.63)	48.56 (9.09)	1.13 (1.09-1.18)	< 0.0001
Nephropathy				
Yes (%)	19 (28.4)	48 (71.6)	1.49 (0.70-3.18)	0.31
No (%)	38 (23.6)	123 (76.4)	1.00	
Dyslipidemia				
Yes (%)	12 (31.6)	26 (68.)	1.28 (0.67-2.44)	0.45
No (%)	45 (23.7)	145 (76.3)	1.00	

COR, Crude Odds Ratio; CI, Confidence Interval; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular dimension; LAD, left atrial dimension; SBP, systolic blood pressure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction

And risk factors for HFpEF were age (COR 1.03(95% CI 1.003-1.06), p = 0.03), sex (COR 2.37(95% CI 1.29-4.37), p = 0.006), hypertension (COR 2.40(95% CI 1.31-4.39), p = 0.005), SBP (COR 1.02(95% CI 1.01-1.04), p = 0.006) and increasing diastolic LVD (COR 0.89(95% CI 0.86-0.93), p < 0.0001) (table 5).

Table 5.
Factors associated with new-onset HFpEF among IHD patients in univariate analysis.

	IHD patients with HFpEF		COR (95% CI)*	P-value
Variables	Yes (n=%)	No (n=%)		
Baseline age (years)				
45 and less (n, %)	11 (18.0)	41 (24.6)	1.00	
46-55 (n, %)	15 (24.6)	57 (34.1)	0.98 (0.41-2.35)	0.97
56-65	17 (27.9)	46 (27.5)	1.38(0.58-3.28)	0.47
66 and above	18 (29.5)	23 (13.8)	2.92(1.18-7.23)	0.02
Mean (±SD) age	58.33 (12.16)	54.50 (11.17)	1.03 (1.003-1.06)	0.03
Sex				
Male (%)	33 (21.2)	123 (78.8)	1.00	
Female (%)	28 (38.9)	44 (61.1)	2.37 (1.29-4.37)	0.006
Smoking status				
Never smoked (%)	54 (28.0)	139(72.0)	1.00	
Ever/Current smoker(%)	7(20.0)	28(80.0)	0.64 (0.27-1.56)	0.33
DM				
Yes (%)	21(28.0)	54 (72.0)	1.10 (0.59-2.04)	0.77
No (%)	40(26.1)	113(73.9)	1.00	
HTN				
Yes (%)	39 (35.5)	71(64.5)	2.40 (1.31-4.39)	0.005
No (%)	22(18.6)	96(81.4)	1.00	
SBP	135.02(17.91)	126.35(20.60)	1.02 (1.01-1.04)	0.006
DBP	81.69(10.85)	79.13(9.66)	1.03 (0.99-1.06)	0.09
LA	35.27 (6.57)	36.91 (6.80)	0.96 (0.92-1.01)	0.13
	IHD patients with HFpEF		COR (95% CI)*	P-value
LVDd	44.43 (8.04)	53.90 (9.91)	0.89 (0.86-0.93)	< 0.0001
Nephropathy				
Yes (%)	19 (28.4)	48 (71.6)	1.12 (0.59-2.12)	0.72
No (%)	42 (26.1)	119 (73.9)	1.00	
Dyslipidemia				
Yes (%)	9 (23.7)	29 (76.3)	0.82 (0.37-1.86)	0.64
No (%)	52 (27.4)	138 (72.6)	1.00	

COR, Crude Odds Ratio; CI, Confidence Interval; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular dimension; LAD, left atrial dimension; SBP, systolic blood pressure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction.

Table 6 shows cox regression with multivariable sub-distribution of hazard ratios. From the 153 patients with new onset HF, 60.1% (92/153) where those with HFrEF while 39.9% (61/153) where those with HFpEF. Diabetes (HR 2.07 (95% CI 1.33-3.22), p = 0.001) and left atrium dimension

(HR 1.03 (95% CI 1.001-1.065), p = 0.04) were associated with total HF. Age 46-55 (HR 0.4 (95% CI 0.17-0.94), p = 0.036), Age 66 and above (HR 0.36 (95% CI 0.13-0.98), p = 0.047), diabetes (HR 2.80 (95% CI 1.55-5.07), p = 0.001); left atrium dimension (HR 1.07 (95% CI 1.13-1.12), p = 0.002) and increasing diastolic LVD (HR 1.06 (95% CI 1.03-1.09), p < 0.0001) were associated with HFrEF. Diastolic LVD was also associated with HFpEF (HR 0.93 (95% CI 0.90-0.97), p < 0.0001).

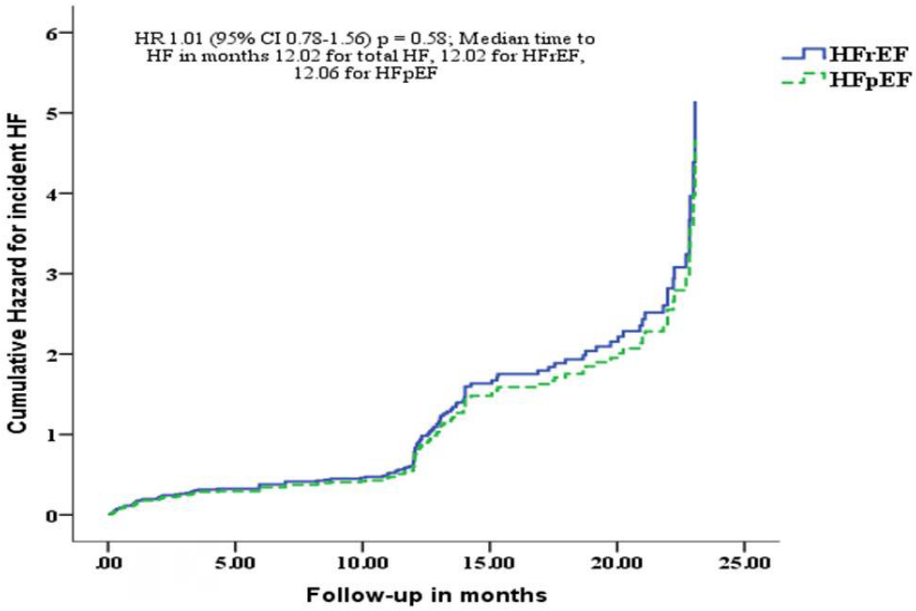
Table 6.
Cox regression: multivariable sub-distribution of HRs

Variables	Total HF HR (95% CI)	P-value	HFrEF HR (95% CI)	P-value	HFpEF HR (95% CI)	P-value
Baseline age (years)						
45 and less	1.00		1.00		1.00	
46-55	0.67 (0.34-1.35)	0.26	0.40(0.17-0.94)	0.036	1.47(0.41-5.21)	0.55
56-65	0.92(0.47-1.78)	0.80	0.77(0.34-1.75)	0.54	1.67(0.50-5.56)	0.40
66 and above	0.80(0.39-1.68)	0.56	0.36(0.13-0.98)	0.047	2.64(0.75-9.26)	0.13
Sex						
Male	1.00		1.00		1.00	
Female	0.75 (0.48-1.18)	0.22	0.59(0.30-1.17)	0.13	1.11(0.60-2.06)	0.74
SBP (mmHg)-baseline	0.992(0.979-1.006)	0.26	0.99(0.97-1.004)	0.14	1.01 (0.98-1.03)	0.59
DBP (mmHg)-baseline	1.022(0.997-1.048)	0.09	1.02(0.98-1.05)	0.41	1.04(0.99-1.08)	0.09
Diabetes	2.07(1.33-3.22)	0.001	2.80(1.55-5.07)	0.001	1.72(0.85-3.48)	0.14
Hypertension	1.16(0.70-1.92)	0.57	1.68(0.87-3.25)	0.12	0.81 (0.33-2.00)	0.81
LAD	1.03(1.001-1.065)	0.04	1.07(1.03-1.12)	0.002	0.98 (0.94-1.03)	0.52
LVDd	1.01(0.99-1.03)	0.55	1.06(1.03-1.09)	<0.0001	0.93 (0.90-0.97)	<0.0001

*HR=Hazard Ratio, CI=Confidence Interval, DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; LVDd, diastolic left ventricular dimension; LAD, left atrial dimension; SBP, systolic blood pressure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction

As shown in Figure 2, there was no significant difference between HFrEF and HFpEF in the time to incident HF (HR 1.01 (95% CI 0.78-1.56), p = 0.58). The median time to HF diagnosis after enrollment was 12.02 (IQR 3.39–14.00) months for all 153 patients with HF, 12.02 (3.42–13.31) months for participants who developed HFrEF, and 12.06 (2.66–15.28) months for those who developed HFpEF.

Figure 2.
Cumulative hazard for incident HF with reduced EF (HFrEF) and incident HF with preserved EF (HFpEF).



4. Discussion

This cohort study has shown a range of risk factors for new onset HFpEF and HFrEF in patients with IHD. The median time to HF after enrollment was about 12 months. There was no significant difference between HFrEF and HFpEF in the time to new onset HF. Risk factors for new onset HF in the overall groups of IHD patients were age, sex, diabetes, LA dimension and diastolic LVD. Increasing diastolic LVD was found to be a risk factor for both new onset HFpEF and new onset HFrEF. Age, diabetes; and LA dimension were also found to be risk factors for new onset HFrEF.

Older age and diabetes as risk factors for incident total HF in this study are consistent with previous studies findings that reported established risk factors for incident HF. However, female sex as risk factor in this study is not consistent with study by Yang et al that reported male gender as an established risk factor. In addition, we found that LA dimension is one of the predictors of new onset HF (Yang H *et al.*, 2015, Chae CU *et al.*, 1999)

This study also showed that prognostic factors for HFrEF were diabetes, SBP, DBP, bigger LA and bigger diastolic LVD. Prognostic factors identified for HFpEF were age, female sex, hypertension, SBP and diastolic LVD. On cox regression analysis diabetes and LA dimension remained to be associated with total HF. Moreover age, diabetes, bigger LA dimension and bigger diastolic LVD remained to be significantly associated with HFrEF while diastolic LVD was associated with HFpEF. When compared to patients with reduced LVEF, those with preserved LVEF were more likely to have higher SBP, higher DBP, higher prevalence of hypertension, smaller LVD, smaller LA size and were less likely to develop advanced HF symptoms.

Few studies have examined the risk factors for new onset HFpEF and HFrEF separately. (Aurigemma GP *et al.*, 2001, Lee DS *et al.*, 2009, Ho JE *et al.*, 2013, Brouwers FP *et al.*, 2013, Ho JE *et al.*, 2016) The

fining of age, hypertension, and SBP as risk factors for HFpEF in a pooled analysis of HFpEF (LVEF >45%) and HFrEF(LVEF ≤45%) cohorts is similar to the present study. Age, diabetes, SBP, DBP as predictors of HFrEF in the pooled analysis is also similar to the finding in the present study (Ho JE *et al.*, 2016). In contrast to previous studies of predictors of new onset HFpEF and HFrEF, this study provides information about LA and LVD (Aurigemma GP *et al.*, 2001, Brouwers FP *et al.*, 2013) as risk factors for HFpEF and HFrEF. The association of age and diabetes with new onset HFrEF in this cohort agreed with the previous studies (Ho JE *et al.*, 2013, Brouwers FP *et al.*, 2013, Ho JE *et al.*, 2016). Risk factor that was common to both HFrEF and HFpEF in this study was age. The finding of age 56-65, diabetes, bigger LA and bigger diastolic LVD as prognostic factor for HFrEF was maintained in multivariable analysis after adjusting for gender.

Key findings of this study suggested diabetes, size of LA and size of diastolic LVD play major role as predictors of total HF, HFpEF and HFrEF. The finding of LA diameter as an independent predictor for HF was also shown in previous studies (Kizer *et al.*, 2006, Gardin *et al.*, 2001). Atrial stretch leads to neurohormonal activation and secretion of atrial natriuretic peptide, which may have a role in the development of atrial dysrhythmias and HF (Kizer *et al.*, 2006, Yamada *et al.*, 2000).

The finding of increased LV internal dimensions as positively associated with incident HF is also similar to previous studies from Framingham investigators and the Cardiovascular Health Study cohort. (Gardin *et al.*, 2001, Vasan *et al.*, 1997, Lauer *et al.*, 1992) Increased LV size is an indicator of LV remodeling that eventually leads to HF. Data from the echocardiographic studies of the SAVE (Studies of Ventricular Enlargement) trial and Val-HeFT (Valsartan Heart Failure Trial) demonstrated that baseline end-diastolic LVD and changes over time were independent predictors of HF and other outcomes (Wong M *et al.*, 2004, St. John Sutton M *et al.*, 1994).

One of the strengths of this study is baseline echocardiographic parameters that provided risk factor information for HFpEF and HFrEF. The diagnosis of HF in an outpatient setting, with optimal duration of follow-up is also the other strength of the study. This enabled the collection of information on risk factor before the diagnosis of HF was made, and the identification of many risk factors for new onset HFpEF and HFrEF.

The limitations of this study included its retrospective cohort design and its intrinsic biases. This study cohort was from Ethiopian population, and the generalizability of the findings to other geographic regions could not be determined. Additionally, the study population was referral-based, and thus, whether the findings can be generalized to non-referral-based populations is unknown. Despite attempts to capture all new onset cases of HF, some cases of early HF may have been missed, and cases may also have been missed because of the reliance on retrospective review to pick up HF. Furthermore, outcome ascertainment based on chart review may have underestimated the number of events. However, given the referral of majority of IHD patients to Black Lion Hospital it is relatively unlikely that such underestimation would be significant.

5. Conclusion

Echocardiographic and clinical predictors for new onset HFpEF and HFrEF were identified. In particular, the data suggest a major role for LA size, diastolic LVD, diabetes, sex and age as predictors in HFrEF and HFpEF. Regular determination of LA and LVD at baseline is recommended for directing appropriate treatment. Strategies directed to prevention and early treatment of diabetes, dilatation of left ventricle and left atrium may prevent a considerable proportion of HFrEF or HFpEF in patients with IHD.

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8. Conflict of interest

The author declares that there is no conflict of interest

9. Ethical approval

The study was approved by the institutional review board of the College of Health Sciences, and permission to use de-identified personal healthcare information for all included subjects was obtained.

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RESUMEN

Antecedentes: Los predictores ecocardiográficos de nuevos eventos de insuficiencia cardiaca en pacientes con cardiopatía isquémica con fracción de eyección ventricular preservada (HFpEF) o con fracción de eyección ventricular reducida (HFrEF) no son bien conocidos en la Africa etíope y subsahariana.

Métodos: Doscientos veintiocho pacientes con cardiopatía isquémica fueron reclutados y seguidos retrospectivamente. Se realizaron análisis sobre las características clínicas y ecocardiográficas basales de los pacientes, así como los factores de riesgo para un nuevo evento de HFpEF y un nuevo evento de HFrEF. Los criterios de exclusión fueron insuficiencia cardíaca conocida al inicio del estudio y aquellos que no tenían datos de ecocardiografía.

Resultados: Durante el período de seguimiento, la insuficiencia cardíaca se desarrolló en el 62,2% (61/98) de pacientes con cardiopatía isquémica con fracción de eyección ventricular izquierda preservada y en el 70,1% (92/130) de pacientes con cardiopatía isquémica con fracción de eyección ventricular izquierda reducida. No encontramos diferencias significativas entre HFrEF y HFpEF en el tiempo hasta la nueva aparición de insuficiencia cardíaca. La presión arterial sistólica, la presión arterial diastólica, la diabetes y las dimensiones de la aurícula iquierda y del ventrículo izquierdo en diástole tuvieron una asociación significativa con nuevos eventos de HFrEF en el análisis de regresión univariada. Mientras que un nuevo evento de HFpEF se asoció significativamente con la edad, el sexo, la presencia de hipertensión, la presión arterial sistólica y la dimensión ventricular izquierda diastólica. En el análisis de regresión de cox, la dimensión ventricular izquierda diastólica se asoció con HFpEF de nuevo inicio y HFrEF. La edad, la diabetes y la dimensión de la aurícula izquierda también se asociaron con HFrEF.

Conclusión: Este estudio de cohorte en pacientes con cardiopatía isquémica sugiere un papel clave para la dimensión ventricular izquierda diastólica, el tamaño de la aurícula izquierda, la diabetes, el sexo y la edad como predictores de un nuevo evento de HFrEF y HFpEF. Las estrategias dirigidas a la prevención y el tratamiento temprano de la diabetes, la dilatación del ventrículo izquierdo y la aurícula izquierda pueden prevenir una proporción considerable de HFrEF o HFpEF.

Palabras clave: ecocardiografía, cardiopatía isquémica, nuevo evento de insuficiencia cardíaca, fracción de eyección ventricular.