

Original Article

The outcome of heart failure in women: a study from a tertiary heart function clinic

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Abstract: Background: Women have unique risk factors for heart disease and a higher risk of cardiovascular mortality. Heart failure (HF) prevalence in women is affected by age, pregnancy, and menopause. More understanding of HF etiology, management, and outcome in women is needed. Method: a retrospective study of women diagnosed with HF following at a heart function clinic (HFC) in a tertiary cardiac center. Results: A total of 1988 HF patients were screened. Women accounted for 561 (28.2%). The mean age at first HF presentation was 47.7 ± 17.9 years. The most common diagnosis was HF with reduced ejection fraction (HFrEF $\leq 40\%$) 473 (84%). The most frequent cause of HF was dilated cardiomyopathy (DCM) in 304 patients (54.2%). Prevalence of diabetes (DM) was 272 (48.5%), hypertension (HTN) 267 (47.6%), and body mass index (BMI) ≥ 30 was 332 (59%). Adverse pregnancy events included miscarriages 151 (38.6%), preeclampsia 15 (3.8%), and spontaneous coronary dissection 3 (0.8%). Left ventricle recovery to EF $\geq 50\%$ occurred in 116 (20.7%) patients, while death occurred in 32 (5.7%) patients during follow-up. Women living with chronic HF were 240 (42.8%). The use of beta-blockers occurred in (96%), renin-angiotensin enzyme inhibitors (86.6%), mineralocorticoids (55.4%), and sodium-glucose cotransporter 2 inhibitors (31.6%). Women who had a heart transplant were 19 (3.75%). Conclusion: Referral to specialized heart function clinics remains low for women. There is high burden of obesity among women and the majority of women have chronic HF but advanced HF therapy consideration is low in women.

Keywords: Heart disease in women, cardiomyopathy, transplant, heart function clinic

Introduction

Cardiovascular disease in women carries a high mortality and morbidity [1, 2]. The clinical presentation and severity of cardiac diseases are significantly different in women compared to men [1-4]. Men and women both share the cardiovascular disease risk factors, such as diabetes (DM), hypertension (HTN), dyslipidemia, and obesity [5]. In addition, women have unique cardiovascular risk factors, such as hypertensive disorders of pregnancy, gestational diabetes, and menopause [5]. Moreover, Cardiomyopathy has unique etiologies in women such as peripartum cardiomyopathy (PPCM), stress-induced cardiomyopathy, and chemotherapy-induced cardiomyopathies [4-7]. Obesity, in women, is associated with an increased risk of heart failure (HF), up to 5-fold compared to men [6, 8]. The metabolic syndrome of diabe-

tes, hypertension, and obesity has a higher risk of HF in women compared to men [9].

The multiparity is a risk for cardiovascular disease [2, 10]. Women who have > 5 live births have a higher risk of developing HFrEF [10]. There is a strong association between maternal risk for HF and adverse pregnancy outcomes such as preterm birth, hypertensive disorders of pregnancy, and gestational diabetes [11]. The PPCM is a form of HF that affects women during pregnancy or within 6 months of post-delivery [7, 12, 13]. Risk factors include advanced age, primigravida, multigravida, twin pregnancy, and comorbidities such as hypertension, diabetes, and anemia [7, 12, 13]. PPCM is associated with high maternal morbidity and mortality [13].

Women with HF have an atypical presentation and late diagnosis compared to men [14, 15].

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The diagnostic thresholds for women with cardiomyopathy differ from men, leading to late diagnosis. Cardiomyopathies such as amyloid and hypertrophic cardiomyopathy will present in the late stages [16, 17]. Literature has reported that the female gender is one of the limitations of optimizing medical therapy [18]. In addition, the enrollment of women for left ventricle assist device (LVAD) therapy is only 21%, in transplant listing is 25% [19-21].

The national HF registry “Heart Function Assessment Registry Trial in Saudi Arabia” (HEARTS) had a low representation of women [22, 23]. The HF patients in this region have a younger age and advanced disease [23]. This observational study aims to highlight the challenges associated with managing women living with HF and identify their clinical characteristics and outcomes at a tertiary heart function clinic (HFC).

Objectives

Describe the clinical characteristics of HF among women in association with cardiovascular risk factors and obstetric history. Understand the degree of cardiac interventions and HF outcomes among women at a tertiary cardiac center.

Method

Study designs

This is a single-center retrospective observational study, enrolling women diagnosed with HF following in the HFC at a tertiary cardiac center. Data are collected from the patient’s clinic notes and patients’ obstetric records.

Inclusion criteria

- All female patients with the diagnosis of HF who are following at the HFC.
- Diagnosis of HFrEF, HFpEF, HFmrEF, restrictive myopathies, hypertrophic myopathies, and congenital heart disease were included.

Exclusion criteria

- Male patients.

- Patients who never had an echocardiogram (ECHO) at the center.

Diagnostic criteria

- Diagnosis of HF is confirmed by ECHO. The left ventricle ejection fraction (LVEF) was measured by Simpson’s method on ECHO.

Data collection

- Demographic Variable: Age of onset, the age of first presentation with HF.
- Co-morbidity: Obesity described in BMI and grade of obesity, presence or absence of DM, HTN, and Dyslipidemia.
- The left ventricle ejection fraction (LVEF) was measured by Simpson’s method on ECHO. HF is categorized by LVEF to HFrEF, HFpEF, and HFmrEF.

- Guideline-directed medical therapy by class: Renin-angiotensin-aldosterone system inhibitor (RAASi), beta-blockers, mineralocorticoid receptor antagonist (MRA), and Sodium-Glucose Cotransporter 2 Inhibitors (SGLT-2i).

- Cardiac Intervention: Coronary artery revascularization by percutaneous intervention or surgical bypass graft. Valvular intervention is either: surgical replacement, surgical or percutaneous repair, as well as, type and number of valves. Device therapy with intracardiac defibrillator or resynchronization therapy. Ablation for cardiac arrhythmias.

Outcomes

- The HF outcomes on follow-up for HFrEF were defined as improved if LVEF reached $\geq 40\%$ after low EF $< 40\%$ or recovered LVEF $\geq 50\%$ with previously low EF $< 40\%$. Chronic HF was defined as no significant change in LVEF from the initial presentation. Transplant and left ventricle assist devices were considered as an outcome as they represent end-stage HF patients and death.
- Patients were considered lost follow-up if there were either no follow-up visits or no follow-up echo.

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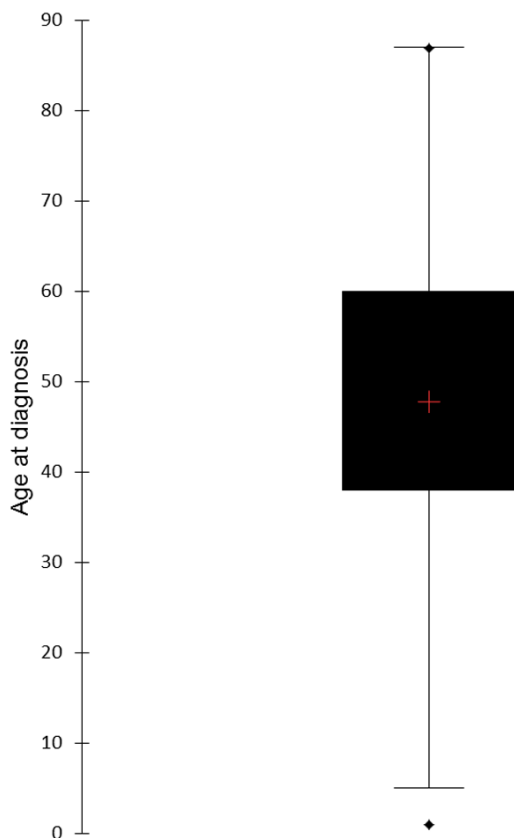


Figure 1. Age of onset of heart failure in women.

- For HFpEF, hypertrophic, and restrictive pathologies, the outcomes were reported as above, excluding improved and recovered LVEF.

Statistical analysis

The data were collected in a Microsoft EXCEL sheet. The data analysis was performed using XLSTAT life science version 2021.2.2.

The descriptive statistics reported the numerical variables as median and [interquartile range (IQR)], or mean \pm standard deviation (SD). Categorical variables are presented as numbers and percentages as appropriate.

Correlation analysis is used to identify the risk of HF outcomes in relation to age, co-morbidity, medication, and pregnancy-related adverse events. The patients who lost follow-up were censored from the correlation analysis. The correlation of outcomes to age, BMI, LVEF, and the number of pregnancies was performed using chi-square and logistic regression. The

correlation of outcomes with causes of HF, DM, HTN, obesity, pregnancy adverse events, and GDMT was performed using chi-square, Fisher exact test, and logistic regression as appropriate. The regression analysis is reported with odds ratio (OR) and [confidence interval (C.I.)]. The correlation was considered significant if the p -value was < 0.05 .

Results

Age and etiology of heart failure

Patients following at the HFC from 2018-2022 were 1,988 HF patients, women accounted for 28.2% with 561 patients only. The median (IQR) for age at the initial HF diagnosis was 50 (38-60) years (**Figure 1**). Women who had HFrEF $\leq 40\%$ were 473 (84%). The mean LVEF at diagnosis in this cohort was $30.4 \pm 11.75\%$, while the mean LVEF in HFrEF patients was $26.6 \pm 7.9\%$. The most common HF etiology was DCM 304 (54.2%), followed by myocardial infarction 81 (14.4%), valvular heart disease (VHD) 44 (7.8%), PPCM 47 (8.8%), tachycardia-induced cardiomyopathy 18 (3.2%) and hypertrophic obstructive cardiomyopathy 8 (1.4%). The remaining HF etiologies are shown in (**Figure 2**).

Women with DM and HTN were 272 (48.5%), and 267 (47.6%), respectively. Obesity was prevalent in this cohort with a mean BMI of 31.2 ± 8.2 . Women with obesity grade II 99 (17.6%), and obesity grade III 75 (13.4%). The most common malignancy in this cohort is breast cancer 21 (3.7%). The baseline characteristics for this cohort are shown in **Table 1**.

The age for women with DCM was 51 (41-60) years old. The LVEF at the time of DCM diagnoses was $27 \pm 10\%$. History of breast cancer was present in 6 (1.9%) with DCM, however, the physician's records did not indicate if the HF was related to chemotherapy use. Moreover, patients with a documented diagnosis of chemotherapy-related cardiotoxicity were 19 (3.4%) most commonly due to breast cancer after treatment with monoclonal antibodies such as trastuzumab or pertuzumab. Myocardial infarction due to spontaneous coronary dissection occurred in 3 (0.77%). The HFpEF patients are underrepresented in this cohort due to the referral criteria to HFC at the center.

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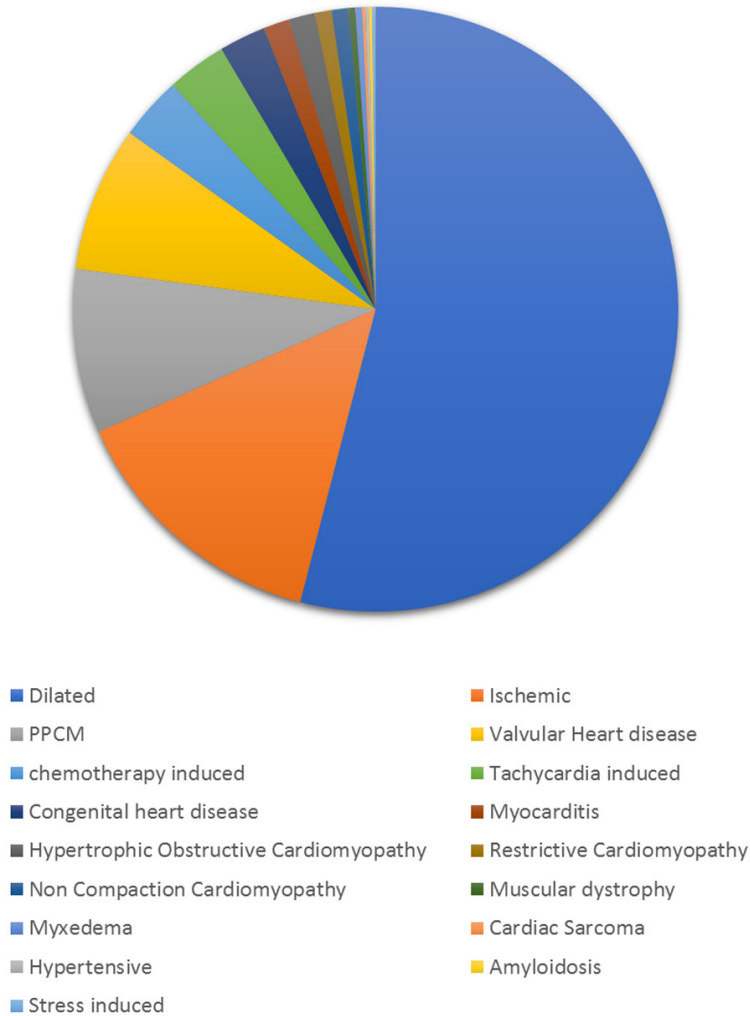


Figure 2. Etiologies of heart failure in women.

The use of guideline-directed medical therapy (GDMT)

The guideline-directed medical therapy (GDMT) prescription was reviewed based on the recent HF guidelines. The beta-blockers were prescribed in 537 (95%), and the most common beta-blockers used was bisoprolol 266 (47%). The renin-angiotensin-aldosterone system inhibitors (RAASi) were prescribed in 486 (86.6%), and the most common (RAASi) prescribed was sacubitril/valsartan (ARNi) 217 (38.7%). The mineralocorticoid (MRA) use was 311 (55.4%), while the SGLT-2i was used only in 177 (31.6%).

Frequency of cardiac procedures

The cardiac intervention performed for coronary artery disease was 78 (13.9%), valvular 72

(12.8%), and device therapy 127 (22.6%). The most frequent valve intervention was surgical mitral valve replacement 27 (4.8%). The most frequent intracardiac device therapy was cardiac resynchronization therapy (CRTD) 65 (8.9%). Ablation of atrial tachycardia and premature ventricular contractions was performed in 11 (2%) of the patients. Advanced cardiac therapy remains low in this cohort despite the young age and severity of the disease. Heart transplantation was performed in 19 (3.75%) and left ventricle assist device in 5 (0.98%) patients.

Obstetric history and adverse pregnancy outcomes

On retrospective chart review, the obstetric history was available in 391 (69.7%) patients. The obstetric history showed that the majority of women were multiparous with a median (IQR) of 6 (3-9) live births. The majority of women were multiparous 130 (35%). Women who suffered from miscarriages defined as spontaneous pregnancy loss in the first trimester were 151 (38.6%), while intrauterine fetal death (IUFD) occurred in 3 (0.77), and preterm delivery was documented in 1 (0.26) only. The diagnosis of preeclampsia was documented in 15 (3.8%). There was low use of contraception methods 74 (18.9%). The details of the obstetric history are shown in **Table 2**.

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Heart failure outcomes

The majority of women 249 (49%) in this cohort had chronic HF, and patients who had improved LVEF and recovered LVEF were 94 (18.6%) and 107 (21%), respectively. Patients who lost follow-up were 55 (9.8%), and they were not included in the correlation analysis. Death occurred in this cohort in (6.3%), heart transplant in 19 (3.75%), and LVAD in 5 (0.98%) (**Table 3**).

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Table 1. Baseline characteristics of women with heart failure

Women with HF 561	
Age at HF Diagnosis	47.7 ± 17.9
Co-morbidity	n (%)
DM	272 (48.5)
HTN	267 (47.6)
BMI	31.2 ± 8.2
Obesity	
Grade I BMI ≥ 30	158 (28)
Grade II BMI ≥ 35	99 (17.6)
Grade III BMI ≥ 40	75 (13.4)
Cancer n (%)	37 (6.6)
Breast Cancer	21 (3.7)
Lymphoma	6 (1.2)
Uterine	4 (0.7)
Colon	2 (0.36)
Other Malignancies	4 (0.7)
Autoimmune disease n (%)	32 (5.7)
Rheumatoid	12 (2.1)
Lupus	3 (0.5)
Vasculitis	3 (0.5)
Other autoimmune disorders	14 (2.5)
Dialysis	30 (5.3)
Chemotherapy	29 (5.2)
Radiotherapy	17 (3)
Depression	22 (3.9)
Classification of HF	
HF _r EF ≤ 40%	473 (84)
HF _{mr} EF > 40-49%	38 (6.8)
HF _p EF ≥ 50%	50 (8.9)
Causes of HF	
Dilated	304 (54.2)
Ischemic	81 (14.4)
PPCM	47 (8.8)
Valvular heart disease	44 (7.8)
Chemotherapy	19 (3.4)
Tachycardia induced	18 (3.2)
Congenital heart disease	14 (2.5)
Myocarditis	8 (1.4)
Hypertrophic Obstructive Cardiomyopathy	8 (1.4)
Restrictive Cardiomyopathy	5 (0.9)
Non-Compaction Cardiomyopathy	5 (0.9)
Muscular dystrophy	2 (0.36)
Myxedema	2 (0.36)
Hypertensive	1 (0.18)
Amyloidosis	1 (0.18)
Stress-induced	1 (0.18)
Cardiac Sarcoma	1 (0.18)
EF at diagnosis	30.4 SD 11.75

Relation of age to heart failure diagnosis and outcomes

Women who had HF diagnosis at a younger age had lower LVEF (**Figure 3**). Age strongly predicted the cause of HF. Patients with DCM had a mean age of 49 (47-51) while patients with myocardial infarction had a mean age of 58 (55-68) and valvular heart disease at a mean age of 52.6 (48-57). PPCM occurred at the age of 34 (29-38). Restrictive cardiomyopathy had a wider range of presentation, for a mean age of 15 (2-29). Many women were living with chronic HF at age 46 (43.8-48) years old. However, LVEF improvement or recovery was noted in patients aged 49 (46-52). The death rate in this cohort was 6.3%, at a mean age of 58.7 (52.7-64.7) years old.

Relation of the co-morbidity to heart failure outcomes

There was a significant relationship between DM and HTN with HF outcome. The presence of HTN was correlated with better HF outcomes, and a higher probability of LVEF recovery ($P=0.001$), while DM had a worse prognosis and mortality ($P=0.005$). The initial EF at presentation was correlated with BMI ($P=0.049$) and grade of obesity ($P=0.008$). The regression analysis of BMI with LVEF is shown in **Figure 4**.

Relation of pregnancy-related adverse event to heart failure outcomes

The obstetric history did not have a significant correlation with HF outcomes. The number of pregnancies showed no significant correlation with the initial EF at the presentation ($P=0.13$). The number of pregnancies did not have a significant relation to the HF outcome. The likelihood of death in relation to the number of pregnancies had an OR=1 [CI 0.8-1.1] and OR=1 [CI 0.95-1.1] for LVEF recovery. The adverse pregnancy events did not have any significant relation with HF outcome. The miscar-

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Arrhythmia	
AF	74 (13)
Flutter	6 (1.2)
SVT	8 (1.4)
PVC	20 (3.6)
VT	16 (2.9)
Heart Block	6 (1.2)
Medication	
Betablockers	
Bisoprolol	266 (47)
Metoprolol	178 (32)
Carvedilol	93 (16)
Not on Betablockers	24 (4)
RAASi	
ACEi	147 (26.2)
ARB	122 (21.7)
ARNi	217 (38.7)
Not on RAASi	75 (13.4)
MRA	311 (55.4)
SGLT-2i	177 (31.6)
Hydralazine/Isosorbide	67 (11.9)
Anticoagulation	
Warfarin	63 (18.4%)
Novel Oral Anticoagulant	80 (23.4%)
Intervention	
Coronary Intervention	78 (13.9)
Percutaneous Coronary Intervention	66 (11.8)
Coronary Artery Bypass Graft	12 (2)
Valve Intervention	72 (12.8)
Percutaneous Edge to edge repair:	
○ 1 valve	26 (4.6)
○ 2 valves	2 (0.4)
Surgical Valve replacement or repair:	
○ 1 valve	26 (4.6)
○ 2 valves	16 (2.9)
○ > 2 valves	8 (1.4)
Intracardiac Device Therapy	127 (22.6)
Intra Cardiac Defibrillator	62 (8.5)
Cardiac Resynchronization Therapy	65 (8.9)
Permanent Pacemaker	11 (0.8)

riage had no significant relation with the cumulative outcome (P=0.2). The preeclampsia had no significant relation with the cumulative outcome (P=0.5).

Relation of the GDMT use to heart failure outcomes

Optimal medical therapy was associated with LV function improvement as well as recovery.

The overall interaction for RAASi was 0.049. However, the use of ARNi was significant for LV recovery to > 50% (P < 0.0001). The use of BB had a significant interaction with HF outcomes (P=0.001). The use of MRA and SGLT-2 was low in this cohort.

Discussion

HF in women has an atypical presentation and late diagnosis [15]. The HEARTS database has shown that HF patients have delayed recognition of the disease [22, 23]. In addition, patients of younger age have a worse disease at presentation [22, 23]. However, the majority of chronic HF patients in the HEARTS registry were men (70%) at a mean age of 55.6 ± 15.9 years [23]. The mean age of women in our cohort was 47.7 ± 17.9 years which is younger than what was reported in the registry.

Obesity is a risk factor for cardiovascular disease and HF in women [8]. Obesity among women was a significant finding in our cohort, as the mean BMI was 31.2 ± 8.2 and had a significant correlation with LVEF at diagnosis with a p-value of 0.049, while the mean BMI in HEARTS was 29 ± 5.8. A study from the United Kingdom evaluated mortality in HF patients above the age of 45 years [20]. The women with HF were 26,725 (47.8%) with a mean age of 79.9 ± 9.87 years [20]. Myocardial infarction (MI) was diagnosed in women (13.5%) compared to (26.3%) in men [20]. Women who had DM (21.3%), HTN (61.4%), AF (25.3%), and VHD (7.7%) [20]. Death was similar among men and women for ages 45-64 years

11.5% vs. 10.3%, respectively [20]. The difference was more pronounced between men and women for age 75-84 years 24.2% vs. 21.2%, respectively [20]. In our cohort, MI was prevalent in 81 (14.4%), VHD 44 (7.8%), DM 272 (48.5%), HTN 267 (47.6%), and AF only in 74 (13%).

The DIABETIC-IC cohort from Spain evaluated patients with DM and HF, 501 patients were

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Table 2. Obstetric history and adverse pregnancy outcomes in women with heart failure

Obstetric History	n (%)
Number of pregnancies	Median 6 (IQ 3:9)
Parity Groups	
Nulliparous	59 (15.1)
≥ 1-5	130 (33.25)
≥ 6-10	139 (35.6)
≥ 11-15	60 (15.3)
≥ 15	3 (0.8)
Pregnancy related complication	
Miscarriages	151 (38.6)
Preterm	1 (0.26)
IUFD	3 (0.77)
Preeclampsia	15 (3.8)
SCAD	3 (0.77)
GDM	10 (2.6)
Ectopic pregnancy	1 (0.26)
Molar pregnancy	1 (0.26)
Contraception	
Oral contraceptive use	36 (9.2)
Progesterone Injections	11 (2.8)
Intrauterine Contraception Device	21 (5.4)
Tubal Ligation	6 (1.5)
Other Treatments	
Hysterectomy	3 (0.8)
Hormonal replacement therapy	2 (0.5)

Table 3. Heart failure outcome in women

HF Outcome for Women	n (%)
Recovered ≥ 50%	107 (21)
Improved ≥ 40%	94 (18.6)
Chronic HF	249 (49)
Transplant	19 (3.75)
LVAD	5 (0.98)
Death	32 (6.3)

women [24]. This cohort showed that women had more HFpEF 15.2% [24]. Women were less optimized with GDMT, angiotensin-converting enzyme inhibitors (ACEi) were used in 26.2%, ARNi 6%, MRA 17.4%, and beta-blockers in 52.4% of [24]. Our population had similar use of ACEi but the use of ARNi was higher at 38.7%. The beta-blockers use was 96% and MRA 55.4%. A single-center study from HFC in Canada showed that 20% of patients were not optimized on the GDMT [18]. This cohort identi-

fied that the female gender was one of the limitations to optimizing medical therapy [18].

The referral and utilization of advanced HF therapies have been inconsistent in observational studies. A retrospective analysis of patients referred to the advanced HF program showed that the percentage of women referred to the program was 98 (23%) compared to men 331 (77%) [15]. Women who underwent advanced HF therapies compared to men were for LAVD implants (3% vs. 13%), and transplants (29% vs. 16%) [15]. However, women with advanced HF wait longer and have higher mortality on the transplant list [20, 25, 26]. Our cohort had fewer LVAD 5 (0.98%) and Transplants 19 (3.75%) compared to patients living with chronic HF 249 (49%) or who have died 32 (6.3%).

Conclusion

There are challenges in treating women with HF mainly associated with their unique risk factors, access to specialized HFC, and the opportunity to receive advanced HF therapies (**Figure 5**).

Clinical prospective

There is a need to optimize cardiac disease prevention programs in obese women as they are at risk of developing HF. The pregnancy and obstetrics history should be part of the cardiovascular history for women with HF. Women with HF need to be referred to specialized HFCs for GDMT optimization. Advanced HF therapies should be considered in women with HF.

Limitation

This retrospective chart review is subjected to selection bias, confounders, and limitations with risk factor analysis.

Future research

Prospective research is required on pregnancy-related adverse events consequences on the incidence and prognosis of HF in women. In addition, cardiovascular risk factors screening and primary prevention should be encouraged to reduce the burden of HF in women.

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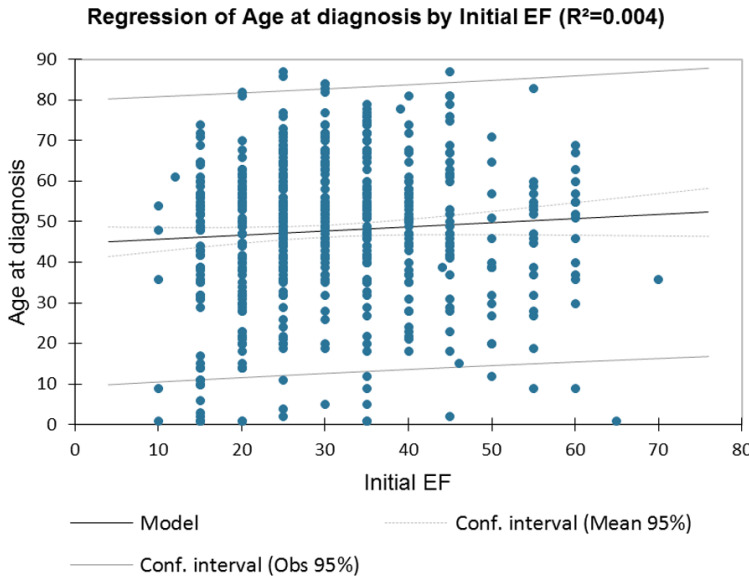


Figure 3. Regression analysis for age of onset of heart failure and the initial LVEF.

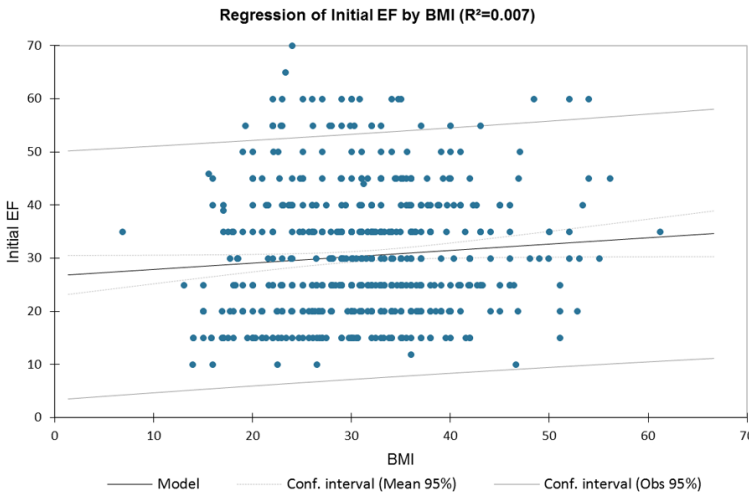


Figure 4. Regression analysis for BMI and the initial LVEF.

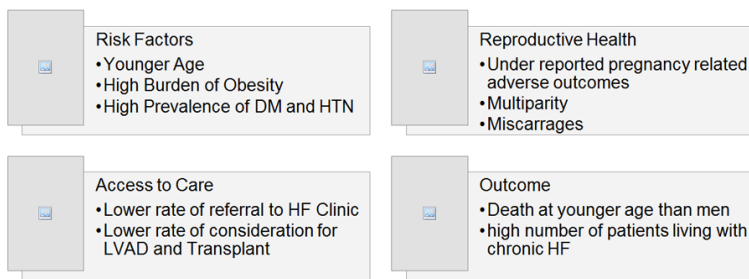


Figure 5. Challenges for women living with heart failure.

Disclosure of conflict of interest

None.

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