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Research paper

Clinical predictors of improvement in left ventricular ejection fraction in U. S. veterans with heart failure

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ABSTRACT

Background: Our understanding of the factors associated with improvement of LVEF and a heart failure with improved EF (HFimpEF) phenotype remains incomplete.

Methods: We conducted a retrospective study using a national database of patients followed in the Veterans Affairs (VA) health system with serial assessment of left ventricular ejection fraction (LVEF) by echocardiography. We identified US veterans with a new diagnosis of heart failure with: (i) LVEF of <40 % in the 12 months prior to diagnosis, and (ii) follow-up LVEF assessment at least 6 months after their diagnosis. We defined HFimpEF as a final LVEF of ≥40 %.

Results: Among the 106,414 US veterans with an initial LVEF of <40 % in this analysis, 39,994 (37.6 %) had a final EF of >40 % after a median follow up of 5 years. Multivariate regression analysis identified several factors that were independently associated with LVEF improvement including female sex, younger age, higher BMI, and a history of specific comorbid conditions such as hypertension, valve disease, atrial fibrillation, connective tissue disease, liver disease, and malignancy ($p < 0.001$). Conversely, a history of ischemic heart disease and peripheral arterial disease, as well as specific racial backgrounds (Black and Hispanic) were associated with lower rates of LVEF improvement. The model c-statistic for predicting LVEF improvement was 0.70.

Conclusions: This large, detailed dataset facilitated an analysis of a large number of variables that significantly associated with HFimpEF; however, their combined discriminatory value for LVEF improvement remained modest, underscoring the complexity of the gene-environment-treatment interactions that govern LV function.

1. Introduction

Heart failure (HF), a heterogeneous clinical syndrome with diverse etiologies, accounts for more medical expenditure than any other diagnosis in the US [1]. HF has traditionally been classified as heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF); however, recent data indicates that left ventricular ejection fraction (LVEF) is dynamic and the prospect of reverse remodeling and recovery of LV function exists. In a longitudinal, community-based cohort of over 1200 patients with HF, approximately 40 % of patients with HFpEF and HFrEF had a LVEF of <50 % and ≥50 % respectively at some point during 5 year follow up [2]. A growing body of evidence now indicates that patients with a depressed LVEF who demonstrate an improvement in LV function exhibit a different prognosis and clinical course [3–5]. As such, heart failure with recovered EF, which has recently been renamed as heart failure with improved EF (HFimpEF) to more accurately reflect longitudinal LVEF trends in HF [6,7], has emerged as a distinct clinical entity that warrants further study. In this context, developing a more comprehensive understanding of the clinical predictors and determinants of myocardial recovery holds the potential to facilitate a more personalized approach to the care of patients with HF.

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Currently, our understanding of the factors that predict LVEF improvement remains incomplete. Several retrospective and prospective analyses have suggested a variety of clinical factors determine likelihood of LVEF improvement, though these are often inconsistent across studies [2,3,8–16]. A potential reason for the inconsistencies in these studies may be small sample size; the majority of studies included only a few hundred patients [2,3,8–11]. The largest investigations of HFimpEF to date included 700–800 patients with LVEF recovery [17,18]. In these investigations, female sex, younger age, and non-ischemic etiology of heart failure were positive predictors of LVEF improvement. In this study, we aimed to leverage a large national database of patients with serial assessment of LVEF in the Veterans Affairs (VA) health system constructed using a bioinformatics approach [19]. We sought to determine factors associated with those individuals with an initial LVEF <40 % that improves to over 40 %.

2. Methods

2.1. Patient identification and study population

We identified patients with an inpatient or outpatient encounter with a new diagnosis for heart failure from 1/1/2009 to 1/1/2017. New HF was defined as no prior diagnosis of heart failure in the previous 4 years (2005–2008). Inpatient data included those hospitalized at non-VA facilities where the VA paid for care.

2.2. Left ventricular ejection fraction determination

We used LVEF data from a national database that used a previously validated Natural Language Processing (NLP) algorithm (EchoExtractor) that leverages a custom dictionary built to process clinical language used in VA echocardiography reports and clinic notes [19]. We then identified patients who met all of the following criteria: (i) a new diagnosis of HF (as defined above); (ii) a documented LVEF of <40 % by TTE in the 12 month period prior to their diagnosis of HF; and (iii) a follow-up LVEF assessment at least 6 months after the initial TTE. In cases where there were more than one follow up echocardiograms, the EF from the last available TTE was used for the final LVEF. Those patients with a final LVEF of ≥40 % were classified as improved LVEF (HFimpEF). Those with a final LVEF of <40 % were classified as having persistent heart failure with reduced EF (HFrEF).

2.3. Baseline characteristics

Baseline demographic, anthropometric, and vital signs data were collected through the VA Corporate Data Warehouse (CDW). Race was self-reported. For laboratory values, vital signs, and body mass index (BMI), we extracted values in the prior six months and used the value closest to the index echocardiogram. The presence of baseline medical conditions was determined using diagnostic codes from encounter data (hospitalization or outpatient) in the two years prior to the diagnosis date (see Supplemental Appendix for details of ICD-9/ICD-10 codes used). Available information on goal directed medical therapy (GDMT) with angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and beta blockers was derived from VA pharmacy data on prescriptions filled in the 6 month period after the initial diagnosis of new HF.

2.4. Statistics

Baseline data are reported as proportions or means with standard deviations. Baseline clinical characteristics were compared by HF subtype (HFrEF vs HFimpEF) in unadjusted analyses using either analysis of variance for continuous variables or χ^2 test for categorical variables (Mantel-Haenzsel χ^2 test for trend for evaluation over time). For multivariate analyses, we imputed rare (<1 %) and non-rare continuous variables using the mean. For rare (<1 %) and non-rare missing categorical variables, we used the most common value. We used logistic regression to determine baseline patient characteristics that independently associated with an improvement in LVEF to >40 % at follow-up. We report adjusted odds ratios with 95 % confidence intervals. We determined the c-statistic, pseudo R^2 score and Hosmer-Lemeshow *p*-value as measures of logistic model discrimination. Variables used in the logistic regression included the demographic, comorbidity, clinical and laboratory characteristics and findings noted in Table 1. Continuous laboratory values were converted to categories to account for potential non-linearity between lab value and LVEF improvement. A p value <0.05 was considered statistically significant. All analyses were conducted using SAS 9.2, Cary NC.

3. Results

3.1. Study population and HF classification

In this study, we identified a total of 335,956 eligible patients with a new diagnosis of heart failure and at least two LVEF assessments six months apart during the study period (Fig. 1). Of these patients, 229,542 (68.0 %) were excluded based on an initial TTE with LVEF>40 %. Among the 106,414 patients with a new diagnosis of HF and an initial LVEF <40 % included in the cohort, 39,994 (37.6 %) had an LVEF ≥40 % reported on their last available echocardiogram and were classified as HFimpEF. The remaining 66,420 (62.4 %) patients had persistent LV dysfunction with an LVEF <40 % on their last available echocardiogram. These patients were classified as HFrEF. The initial LVEF at the time of the index echocardiogram in the HFimpEF group was higher than the LVEF for the HFrEF group (32.3 % ± 7.7 % vs. 28.6 % ± 7.9 %; Table 1). As expected, the final LVEF was significantly higher in the HFimpEF group (49.6 % ± 8.2 % vs. 27.1 % ± 7.6 %; Table 1). The time between the index and the final echocardiogram ranged from <1 year up to 6 years across all patients. The median time between the index and the final echocardiogram was marginally longer for the HFimpEF group (4.4 ± 2.9 years) than for the HFrEF group (4.7 ± 2.8 years, $p < 0.0001$).

The baseline characteristics of the HFrEF and HFimpEF groups were significantly different by univariate analysis and are listed in Table 1. Patients with HFimpEF were younger and more likely to be female. Over half (51.7 %) of female veterans with a new diagnosis of HF demonstrated recovery of LVEF to >40 % on their final TTE. In contrast, only 37.3 % of male veterans with new HF had a final LVEF of >40 % (Fig. 2A). Information on race was available for 94 % of the study cohort. A higher percentage of patients in the HFimpEF were white compared to the HFrEF group (73.3 % vs. 70.1 %), but the racial composition of the two groups was otherwise similar (Fig. 2C). When we examined temporal trends of LVEF recovery in our cohort, we noted an increase in the rates of LVEF improvement to >40 % (HFimpEF phenotype) across the study period from 2009 to 2017 (Fig. 2D). Rates of LVEF recovery peaked in 2014 at 39.2 % and essentially plateaued in the subsequent years of the study (Fig. 2D). Cardiometabolic diseases such as chronic ischemic heart disease (IHD), peripheral artery disease (PAD), and diabetes were more common in the HFrEF cohort than in the HFimpEF group (Table 1), and veterans with these conditions showed lower rates of LVEF improvement (Fig. 2E). In contrast, patients in the HFimpEF group were more likely to have a history of atrial fibrillation, hypertension, valvular heart disease, malignancy, liver disease, connective tissue disorders, depression, and alcohol dependence (Fig. 2E). Other common conditions in veterans such as dementia had similar prevalence in the two groups. Our data also demonstrated significant differences in other baseline clinical parameters and laboratory studies. Patients with HFimpEF had higher baseline systolic and pulse pressures, higher body mass index but lower b-type natriuretic peptide (BNP), creatinine, and hemoglobin A1C levels (Table 1). When we examined trends in contact with the medical system, we observed that a greater proportion of patients in the HFimpEF group were either admitted to the

Table 1
Baseline patient characteristics by heart failure subtype.

Characteristic	HFrEF (n = 66,420)	HFimpEF (n = 39,994)	P value (Chi-Square)
Demographics			
Age (years, mean ± SD)	68.5 ± 11.4	67.5 ± 11.3	<0.0001
Sex			<0.0001
Women	977 (1.5 %)	1044 (2.6 %)	
Men	65,443 (98.5 %)	38,948 (97.4 %)	
Race			0.049
White	46,338 (70.1 %)	29,167 (73.3 %)	
Black	15,000 (22.7 %)	7848 (19.7 %)	
Hispanic	3008 (4.6 %)	1726 (4.3 %)	
Native American	637 (1.0 %)	408 (1.0 %)	
Pacific Islander	475 (0.7 %)	263 (0.7 %)	
Asian	456 (0.7 %)	260 (0.7 %)	
Declined	138 (0.2 %)	94 (0.2 %)	
Other	40 (0.06 %)	22 (0.06 %)	
Comorbidities (2 years prior)			
Ischemic heart disease	47,281 (71.2 %)	24,563 (61.4 %)	<0.0001
Acute Myocardial Infarction	10,491 (15.8 %)	5071 (12.7 %)	<0.0001
Peripheral arterial disease	19,799 (29.8 %)	9440 (23.6 %)	<0.0001
Hypertension	56,056 (84.4 %)	34,448 (86.1 %)	<0.0001
Valvular disease	9463 (14.3 %)	6149 (15.4 %)	<0.0001
Arrhythmia	39,203 (59.0 %)	21,690 (54.2 %)	<0.0001
Atrial fibrillation	22,323 (33.6 %)	14,554 (36.4 %)	<0.0001
Diabetes	31,523 (47.5 %)	18,709 (46.8 %)	0.031
Malignancy	10,087 (15.2 %)	6401(16.0 %)	0.0004
Liver disease	4669 (7.0 %)	3069 (7.7 %)	<0.0001
COPD	24,317 (36.6 %)	15,463 (38.7 %)	0.001
Connective Tissue Disease	1757 (2.7 %)	1322 (3.3 %)	<0.0001
Dementia	1991 (3.0 %)	1165 (2.9 %)	0.430
Depression	19,522 (29.3 %)	13,385 (33.5 %)	<0.0001
Psychiatric disorder	3168 (4.8 %)	2097 (5.2 %)	0.0006
Alcohol dependence	8189 (12.3 %)	5577 (13.9 %)	<0.0001
Medical contact (prior 1 year)			
Any ED visit	27,311 (41.1 %)	18,471 (46.2 %)	p < 0.0001
Inpatient admission (any reason)	5428 (8.2 %)	4471 (11.2 %)	p < 0.0001
Clinical parameters			
First LVEF (%)	28.6 ± 7.9	32.3 ± 7.7	<0.0001
Last LVEF (%)	27.1 ± 7.6	49.6 ± 8.2	<0.0001
Time between initial and final EF (yrs.)	4.4 ± 2.9	4.7 ± 2.8	<0.0001
Systolic blood pressure (mmHg)	126.7 ± 19.4	130.6 ± 20.0	<0.0001
Pulse pressure (mmHg)	52.4 ± 14.8	55.1 ± 15.7	<0.0001
Body mass index	29.1 ± 6.4	30.4 ± 7.1	<0.0001
Labs			
Sodium (mEq/L, mean ± SD)	138.7 ± 2.4	138.8 ± 2.3	<0.0001
Creatinine (mg/dL, mean ± SD)	1.40 ± 1.03	1.36 ± 1.08	<0.0001
BNP (pg/mL, mean ± SD)	1105 ± 3847	606 ± 2376	<0.0001
Hemoglobin A1C (%,mean ± SD)	6.7 ± 1.4	6.6 ± 1.3	<0.0001
WBC (x 10^9 cells/L, mean ± SD)	8.4 ± 35.6	8.2 ± 38.1	0.41
Hgb (g/dL, mean ± SD)	13.5 ± 1.6	13.5 ± 1.7	0.054

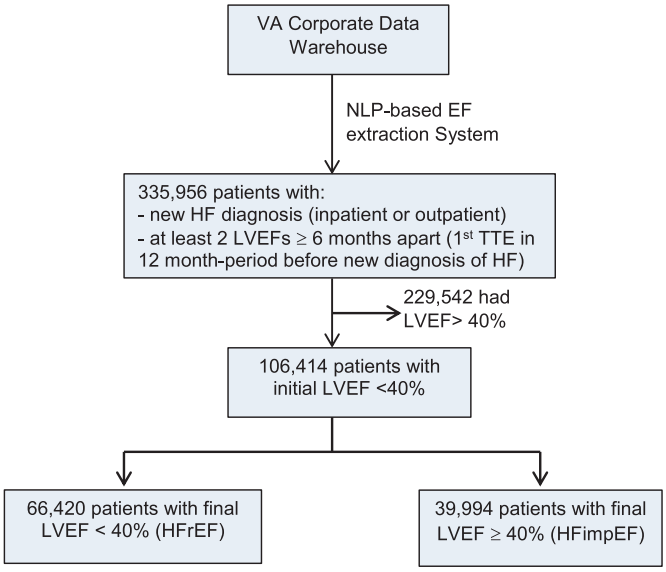

Fig. 1. Overview of study design and patient selection from VA Corporate Data Warehouse. HF- heart failure; LVEF- left ventricular ejection fraction; HFrEF- heart failure with reduced EF; HFimpEF- heart failure with improved EF; NLP- natural language processing.

hospital or had an Emergency Department visit in the 1 year prior to the new HF diagnosis.

3.2. *Multivariable analysis of predictors of HFimpEF*

We performed a multivariate regression analysis to identify factors that are independently associated with improvement in LVEF (Table 2). Female sex demonstrated a robust association with a HFimpEF phenotype (Fig. 2A and Table 2). When stratified across age ranges, veterans with HF under the age of 40 years demonstrated the highest rates of LVEF recovery (45.1 %; Fig. 2B) while veterans older than 70 years had a statistically significant lower likelihood of demonstrating a HFimpEF phenotype after adjustment for the period of time between echocardiograms (Table 2). Although the racial composition of the HFimpEF and HFrEF groups was not significantly different in univariate analysis of baseline characteristics, adjustment for multiple variables revealed that Black and Hispanic race were associated with a lower likelihood of LVEF improvement (Table 2) and significantly lower rates of LVEF recovery (Fig. 2C). Other characteristics associated with a significant improvement in LVEF included a history of hypertension, valvular heart disease, connective tissue disorders, liver disease, and atrial fibrillation (Fig. 2C). Contact with the medical system through a hospitalization or emergency department visit in the year prior to the heart failure diagnosis was also positively associated with an improvement in LVEF to >40 %. Veterans with IHD and PAD demonstrated the lowest rates of LVEF improvement (Fig. 2C), and these conditions were negatively associated with HFimpEF on multivariate analysis (Table 2). Although a history of diabetes showed no significant association with changes in LVEF in our multivariate analysis over the follow up period, lower HgbA1C levels were associated with HFimpEF. Other laboratory values associated with an improvement in LVEF included a lower baseline BNP/NT-proBNP and serum creatinine.

Consistent with the observed association between a history of hypertension and LVEF recovery, a higher baseline systolic blood pressure and pulse pressure associated with LVEF improvement (Table 2). In addition, a higher BMI demonstrated a positive association with LVEF recovery. A lack of complete data on medications prevented a comprehensive analysis of the impact of goal-directed pharmacologic therapy on improvement in LV function. When we examined available pharmacy

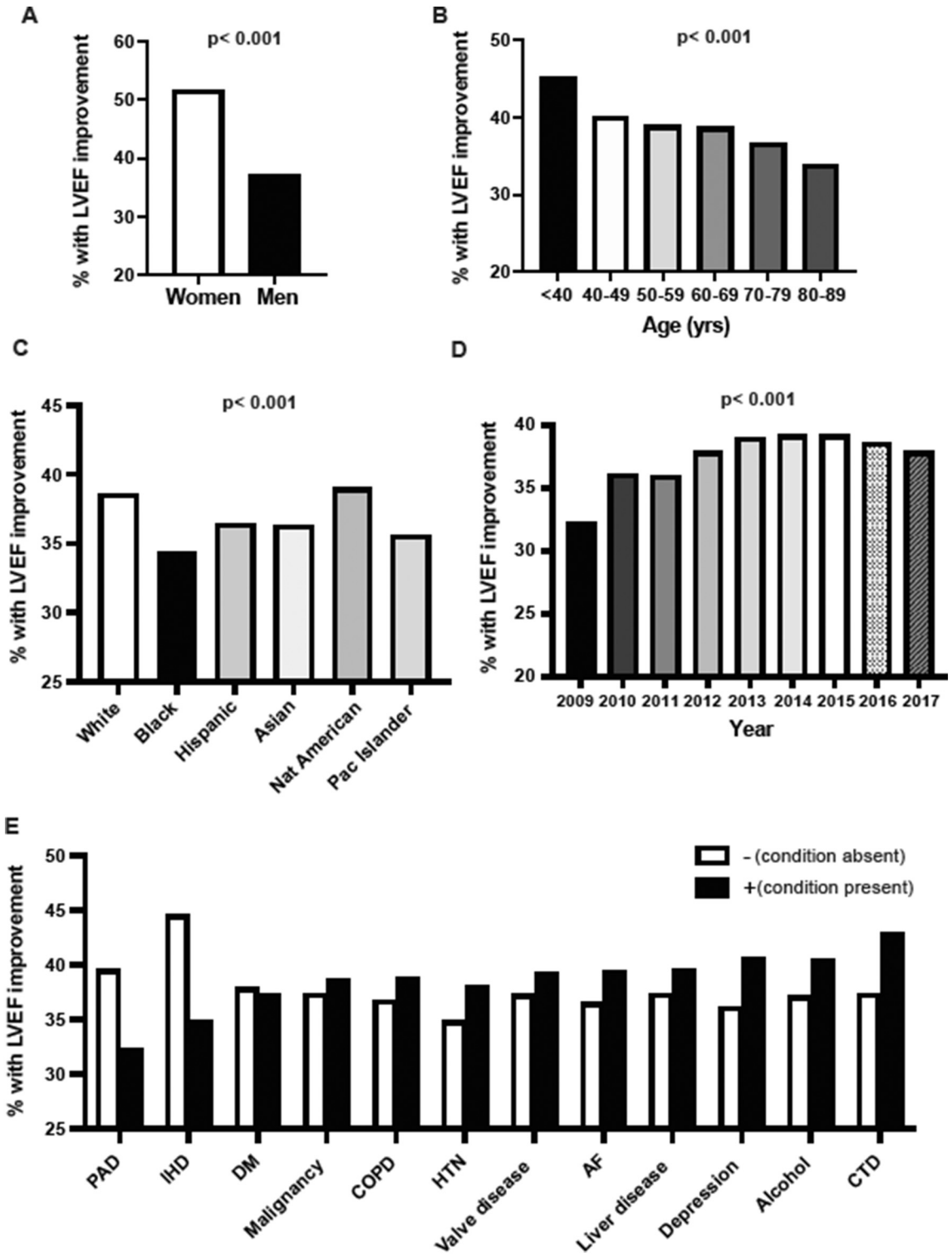

Fig. 2. Rates of improvement of LVEF across demographic and clinical parameters. A. Rates of improvement in LVEF (initial LVEF of <40 % and final LVEF >40 %) based on sex. B. Comparison of rates of improvement in LVEF across age ranges (<40 yrs. vs >40 yrs.). C. Variation in rates of improvement in LVEF by race. D. Temporal trends in LVEF recovery rates from 2009 to 2017. E. Rates of improvement in LVEF based presence or absence of cardiovascular and medical comorbidities. LVEF- left ventricular ejection fraction; HFimpEF- Heart failure with improved EF; HFrEF- Heart failure with reduced EF; IHD- ischemic heart disease; AF- atrial fibrillation; PAD- peripheral arterial disease; CTD- connective tissue disease; HTN- hypertension; COPD-chronic obstructive lung disease; alcohol-alcohol dependence.

data on angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), and beta blockers, we found that these medications did not significantly modify the association of other clinical factors positively or negatively associated with LVEF improvement (data not shown).

The overall c-statistic for the model was 0.70, demonstrating modest discriminatory capacity for predicting LVEF improvement based on the variables we examined in this study (Fig. 3). Consistent with this finding,

Table 2
Multivariate analysis of baseline patient characteristics and LVEF improvement[a].

Characteristic	Odds ratio	95 % CI	p-value
Age (yrs.)			<0.0001
18 vs 50	1.13	0.98–1.30	
40 vs 50	1.00	0.92–1.07	
60 vs 50	0.98	0.94–1.02	
70 vs 50	0.93	0.88–0.97	
80 vs 50	0.87	0.82–0.92	
Sex			
Women vs Men	1.43	1.30–1.58	<0.0001
Race			<0.0001
Hispanic vs White	0.89	0.83–0.95	
Black vs White	0.77	0.74–0.80	
Asian vs White	1.02	0.87–1.21	
Native American vs White	0.97	0.85–1.13	
Pacific Islander vs White	0.86	0.73–1.01	
Declined vs White	0.94	0.71–1.24	
Other vs White	1.03	0.86–1.23	
Comorbid conditions (Prior 2 years)			
Ischemic heart disease	0.65	0.63–0.67	<0.0001
Peripheral arterial disease	0.79	0.77–0.82	<0.0001
Valvular disease	1.23	1.18–1.30	<0.0001
Hypertension	1.11	1.06–1.15	<0.0001
Atrial fibrillation	1.53	1.47–1.59	<0.0001
Arrhythmia	0.70	0.68–0.73	<0.0001
Connective tissue disease	1.16	1.07–1.26	0.0002
COPD	1.08	1.05–1.14	<0.0001
Diabetes	0.98	0.94–1.02	0.22
Malignancy	1.08	1.04–1.12	<0.0001
Liver disease	1.07	1.02–1.13	0.0085
Depression	1.07	1.04–1.10	<0.0001
Dementia	1.06	0.98–1.15	0.14
Psychiatric Illness	1.03	0.96–1.09	0.42
Alcohol dependence	1.09	1.05–1.14	<0.0001
Clinical Features			
Ed visit within year of diagnosis	1.24	1.20–1.27	<0.0001
Admission within year of diagnosis	1.18	1.13–1.24	<0.0001
First EF (per 10 %)	1.74	1.70–1.77	<0.0001
Systolic BP (per 10 mmHg)	1.05	1.34–1.06	<0.0001
Pulse Pressure (per 10 mmHg)	1.07	1.05–1.08	<0.0001
Heart rate (per 10 bpm >60 bpm)	1.02	1.01–1.03	<0.0001
BMI (per 5 kg/m^2 above 25)	1.08	1.07–1.09	<0.0001
Laboratory studies			
BNP/NT-proBNP (pg/mL)			<0.0001
101–200/401–1000 vs 0–100/0–400	0.74	0.70–0.78	
201–700/1001–4000 vs 0–100/0–400	0.54	0.52–0.56	
701–1000/4001–6000 vs 0–100/0–400	0.38	0.36–0.41	
>1000/>6000 vs 0–100/0–400	0.28	0.27–0.30	
M[#] vs 0–100/0–400	0.64	0.61–0.66	
Sodium (mEq/L)			<0.0001
>135 to 136 vs ≤135	0.90	0.83–0.98	
>136 to 145 vs ≤135	1.00	0.94–1.06	
>145 vs ≤135	1.13	0.94–1.36	
M[#] vs ≤135	1.13	0.94–1.36	
Creatinine (mg/dL)			<0.0001
>0.8 vs <0.8	0.95	0.90–1.01	
>1.0 vs <0.8	0.89	0.84–0.94	
>1.5 vs <0.8	0.86	0.80–0.92	
≤2.0 vs <0.8	0.96	0.88–1.03	
M[b] vs >0.0	0.69	0.59–0.80	
Hemoglobin (g/dL)			<0.0001
10.0–12.0 vs ≤10	0.79	0.72–0.88	
>12–14.0 vs ≤10	0.68	0.61–0.74	
>14–15.0 vs ≤10	0.65	0.59–0.72	
>15 vs ≤10	0.65	0.59–0.72	
M[b] vs ≤10	0.60	0.52–0.70	
White Blood Count (×10^9 cells/L)			0.029
>6-≤7 vs ≤6	1.04	0.99–1.08	
>7-≤8 vs ≤6	1.05	1.00–1.09	
>8-≤10 vs ≤6	1.04	1.00–1.08	
>10 vs ≤6	1.06	1.01–1.11	
M[b] vs ≤6	0.80	0.65–0.98	
Hemoglobin A1c (%)			<0.0001
>6-≤7 vs ≤6	0.90	0.86–0.93	
>7-≤8 vs ≤6	0.87	0.83–0.92	
>8-≤10 vs ≤6	0.83	0.79–0.88	
>10 vs ≤6	0.74	0.67–0.82	
M[b] vs ≤6	0.84	0.80–0.89	
Time since diagnosis			<0.0001
1 yr. vs <6 months	1.14	1.08–1.21[b]	
2 yr. vs <6 months	1.26	1.19–1.34	
3 yr. vs <6 months	1.35	1.27–1.43	
4 yr. vs <6 months	1.36	1.28–1.45	
5 yr. vs <6 months	1.48	1.39–1.60	
6 yr. vs <6 months	1.40	1.33–1.47	

[a] c-statistic 0.70.
[b] Missing values.

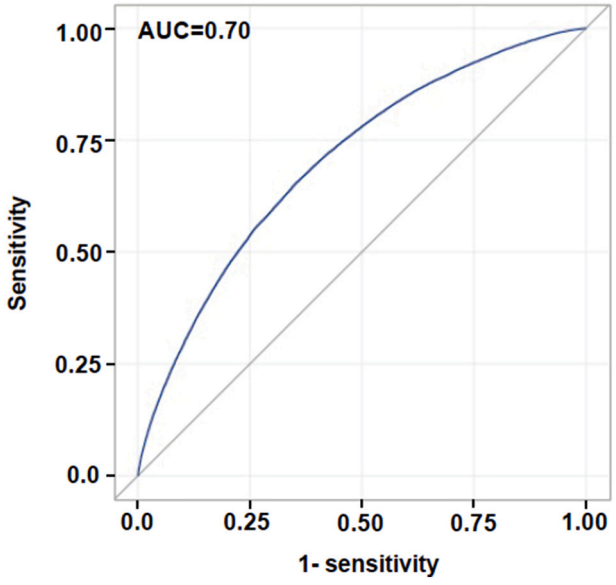

Fig. 3. Multivariate model for predicting LVEF recovery (final EF > 40 %). ROC curve for multivariate model for predicting HFimpEF.

the Pseudo R^2 goodness-of-fit assessment was only 0.07; however, the Hosmer-Lemeshow (HL) p value was significant at 0.003 (Supplemental Table 1). Given emerging evidence showing that patients with mildly reduced ejection fraction (EF 40–50 %) have a distinct prognosis [6,20], we also performed a sensitivity analysis focusing on patients with an improvement in LVEF to >50 % and found very similar results to the main findings summarized above (data not shown). We did find that diabetes, which was not associated with LVEF improvement in the initial multivariate analysis, emerged as a positive predictor of LVEF improvement (p = 0.04).

4. Discussion

Patients with reduced LVEF who experience an improvement in myocardial function demonstrate a distinct prognosis and clinical course when compared to patients with HFrEF and HFpEF [3,5]. As such, identifying patients with HFrEF who are likely to experience an improvement in LVEF may have important implications for developing tailored therapeutic approaches for this unique population. In the current analysis, we found that a significant portion (~38 %) of veterans with new HF and reduced EF demonstrated an improvement in LVEF to >40 % over the follow up period of the study. This observation is largely consistent with the two largest registry studies of HFimpEF to date which showed that approximately 1/3 of patients with HFrEF demonstrate LVEF recovery [17,18]. Our study confirmed previously reported associations between a HFimpEF phenotype and patient characteristics

such as younger age [2,3,8–11,17,18], female gender [3,8–10,17,18,21], and a non-ischemic etiology of HF [2,3,8–10,17,18,21]. The large size of our study cohort (~40,000 patients with HFimpEF and >66,000 controls) and the deep clinical phenotypic data available through the centralized VA CDW allowed for the investigation of a number of clinical parameters and conditions not previously interrogated in context of recovery of LVEF in HF patients. We identified previously unreported positive predictors of HFimpEF including a history of valvular heart disease, connective tissue disorders, pre-existing liver disease, and malignancy. The biological basis of these associations remains unclear, but these observations raise the possibility that conditions associated with underlying adverse hemodynamics and/or inflammation may be associated with reversible LV dysfunction. The phenomenon of LVEF recovery with valvular disease may be related to the specific valvular lesion and timing of intervention. The availability of ICD 9/10 data on specific valve diseases as well as surgical and transcatheter procedural interventions available in VA CDW raise the possibility of leveraging our database further to conduct future studies that shed additional insight into LVEF improvement and prognosis. The higher likelihood of LVEF improvement in patients with a history of malignancy likely reflects unique, potentially reversible myocardial stressors such as cardiotoxic chemotherapy, as well as other cancer-related factors associated with transient LV dysfunction such as infection, sepsis, and DIC [22].

Prior investigations of HFimpEF showed conflicting data on the association between LVEF improvement and common conditions such as hypertension [3,9,10,14,15,17,18,21], diabetes [3,9–11,14–18,21], and atrial fibrillation [3,9,16–18,21]. Our analysis, which included over 90,000 patients with hypertension, identified a positive association between HTN and LVEF recovery. Consistent with this observation, patients with higher baseline BP and pulse pressure were more likely to show a significant increase in LVEF over the study period. Higher baseline blood pressures likely reflect a more favorable hemodynamic profile that facilitates initiation of GDMT and greater adherence to medications in HFrEF. The lack of complete and accurate data on medical therapy in the current analysis limits our ability to present a detailed comparison of GDMT stratified by BP or a diagnosis of hypertension, but this represents an important future avenue of investigation. Over 36,800 patients in the cohort had a history of AF and we found a modest positive association between AF and LVEF recovery. The acquisition of additional clinical data on average heart rates may facilitate a better understanding of the relative contribution of tachycardia-induced cardiomyopathy to LV dysfunction in AF and the likelihood of LVEF improvement. In addition, the timing of relevant rhythm control approaches, including direct current cardioversion, pulmonary view isolation and other catheter ablation therapies may provide relevant insight into the potential effect of rhythm control on LVEF improvement. When we examined over 50,200 patients in the cohort with diabetes, we found that a history of diabetes did not associate positively or negatively with LVEF recovery in multivariate analysis; however, lower hemoglobin A1C levels were independently associated with an increased likelihood of LVEF improvement. Collectively these findings suggest that severity of dysregulated glucose metabolism exerts a more significant impact on myocardial recovery than just a prior diagnosis of diabetes.

The majority of previous investigations of HFimpEF did not report detailed data on race, and the few studies that did examine the association of LVEF recovery with race reported conflicting findings on a very limited number of racial groups [3,9]. In the current analysis, we reported data for six major racial groups. We found no significant differences in the racial composition of the HFimpEF and HFrEF groups in unadjusted, univariate analysis of baseline characteristics (Table 1); however, after multi-variate adjustment, veterans who were black or hispanic were significantly less likely to experience improvement in LVEF, with the lowest rates of myocardial recovery observed in black patients. It is currently unclear to what extent fundamental biological differences contribute to the differential patterns of LV recovery noted across racial groups in this study. It is likely that social determinants of health such as access to care, income, and educational level disproportionately affect the racial groups with the lowest rates of LVEF recovery.

4.1. Clinical implications

The results of the current study may hold clinical implications for prognostication as well as selection of advanced device therapies in patients with HFrEF. Our analysis provides insight into the natural history of LV recovery in HFrEF. In our investigation of temporal trends, we found a near-linear increase in LVEF recovery until approximately 4 years from initial diagnosis, after which we observed a plateau in rates of significant LVEF improvement. The timeline and pattern of LVEF improvement observed in our large cohort raise important questions about current guideline recommendations on timing of device therapies such as implantation of ICD for primary prevention or CRT. It is possible that a subset of patients with HFrEF may experience LV recovery that obviates need for ICD or CRT over a longer timeframe than is currently considered in clinical guidelines. In addition, further analysis of medical therapy in our cohort may facilitate tailoring pharmacologic treatment for HF patients with improved EF. A recent study examining the impact of phased withdrawal of medical therapy leads to the recrudescence of LV dysfunction in over 40 % of patients with HFimpEF [23]. It is possible that deterioration of LVEF in patients with HFimpEF in response to withdrawal of therapy may be modified by the number of clinical predictors of recovery of LVEF that are present in individual patients. Patients with clinical characteristics that are associated with later improvement in LVEF may be more likely to maintain their recovered LVEF and may be the best candidates for future clinical trials of withdrawal of goal directed medical therapy. The rates of LVEF recovery increased from 2009 to 2014 and then essentially plateaued through 2017. Notably, clinical guidelines for treatment of HFrEF have been largely stable over the study period. The impact of recently approved treatments for heart failure such as angiotensin-receptor neprilysin inhibitors (ARNI) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) is not captured in our analysis. It is possible that the increased availability and use of these agents will exert important effects on LVEF recovery.

4.2. Strengths and limitations

In considering this investigation of clinical predictors of LVEF improvement, the size of our cohort and the spectrum of the clinical parameters examined represent the most significant strengths of our study. We employed a novel, previously validated NLP-platform [19] that extracted LVEF data from echocardiogram reports in the medical record and enabled the construction of the largest database used in the study of HFimpEF to date. While a large fraction of the patients were male, our analysis included over 2000 women and found a strong association between female sex and recovery of LVEF. In addition, our study is the largest to date to report on disparities in LVEF recovery across 6 racial groups.

Our study also has several potential limitations. The retrospective design and lack of a validation cohort may limit the general applicability of the main findings of the study. In addition, given the nature of our database, residual confounding remains as a notable limitation of our investigation. Assessment of LVEF by echocardiography is affected by issues related to measurement error and reproducibility [24,25]. Our study also did not account for LVEF assessed by alternative approaches such as magnetic resonance imaging (MRI) or single-photon emission computerized tomography (SPECT).

Prior investigations demonstrate that GDMT for HFrEF with beta blockers and ACEi/ARB is associated with improvements in LVEF [26]. Treatment with beta blockers such as carvedilol, metoprolol, and bisoprolol have been shown to increase LVEF ~5–10 % in both randomized control trials [27–30] and observational cohort studies [2,18,31,32]. A

systematic review of ACEi/ARB therapy in HFrEF demonstrated more modest improvements in LVEF of ~3–5 % in patients with HFrEF primarily in the post MI setting [33], while other studies of HFimpEF demonstrate ACEi/ARB were not positive predictors of LVEF improvement [17,18]. Collectively, these observations suggest that the clinical benefits of ACEi and ARB in HF are likely mediated through multiple mechanisms, including pathways that are independent of improvement in LVEF. We were not able to perform a complete analysis of the impact of disease-modifying medications (ACEi, ARB, and beta blockers) on LVEF recovery due to incomplete pharmacy data. An analysis of available data on ACEi/ARB and beta blocker therapy in the 6 months after the initial diagnosis of HF showed that these medications did not modify the association of key clinical variables (such as age, sex, comorbid conditions) with LVEF recovery. Complete capture of pharmacological treatments is challenging in observational studies in the US veteran population given fragmented medical care that is frequently received outside of the VA system. Beyond the issues surrounding missing pharmacy data, ACEi/ARB and beta blocker therapy represent time varying exposures that are difficult to control for in the veteran population.

Our study also does not include information on relevant procedural interventions in relation to serial LVEF assessments. Prior investigations demonstrate that cardiac resynchronization (CRT) augment LVEF ~5–10 % in patients with HFrEF [34–37]. Similarly, coronary revascularization [38–41], surgical or transcatheter valve repair/replacement [42–44], and direct current cardioversion [45–48] have all been shown to increase LVEF. The potential impact of these procedures was not accounted for in our multivariate analysis of clinical predictors of LVEF improvement but represents an important area of future investigation.

Overall, our investigation included over 50 clinical variables and expanded our understanding of positive and negative predictors of LVEF improvement in HF. Our multivariate logistic regression yielded a model with modest discriminatory capacity for predicting which patients with HFrEF are likely to experience recovery of LVEF. Although the HL p-value for the model was significant at 0.003, the overall c-statistic for was 0.70 with a pseudo R^2 score of 0.07. Although it is possible that the inclusion of other relevant data on medical therapy and procedures would augment performance of the model, it is likely that a complex, inter-connected network of genetic factors and environmental exposures will limit these improvements.

5. Conclusions

In summary, this large and detailed dataset facilitated an in-depth analysis of a significant number of factors associated with LVEF improvement. Despite the large number of variables identified, their combined predictive value for recuperation of LVEF in HF remained modest indicating that multiple other determinants of LVEF recovery exist and may include interactions between genetic and environmental factors, as well as medical and procedural therapies.

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CRediT authorship contribution statement

Dr. Nallamshetty and Dr. Heidenreich had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization: Nallamshetty, Heidenreich.

Acquisition, analysis, or interpretation of data: Nallamshetty, Castillo, Heidenreich.

Data Curation: Nallamshetty, Castillo, Nguyen, Heidenreich.

Critical revision of the manuscript for important intellectual content: All authors.

Formal Statistical analysis: Nallamshetty, Heidenreich.

Funding Acquisition: Nallamshetty.

Investigation: Nallamshetty, Heidenreich.

Validation: Nallamshetty, Haddad, Heidenreich.

Visualization: Nallamshetty, Castillo, Nguyen, Heidenreich.

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Role of the funder/sponsor

The funding agency had no role in the design of the study, analysis of data, or preparation of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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