Electronic health record characterization and outcomes of heart failure with preserved ejection fraction

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Background Electronic health record (EHR)-based identification of heart failure with preserved ejection fraction (HFpEF) in the clinical setting may facilitate screening for clinical trials by improving the understanding of its epidemiology and outcomes; yet, previous data have yielded variable results. We sought to characterize groups identified with HFpEF by different EHR screening strategies and their associated long-term outcomes across a large and diverse population.

Methods We retrospectively analyzed 116,499 consecutive patients from an academic referral center who underwent echocardiography, and 9,263 patients who underwent echocardiography within 6 months of right heart catheterization (RHC), between 2008 and 2018. EHR-based screening strategies identified patients with HFpEF using 1) International Classification of Diseases (ICD)-9/10 codes, 2) H_2FpEF score $\geq$6 and ejection fraction (EF) $\geq$50%, or 3) RHC wedge pressure $\geq$15 mmHg and EF $\geq$50%, when available. Primary outcomes were 1) cumulative incident heart failure hospitalization (HFH), and 2) death, over 10 years.

Results There were 33,461 (29%) patients who met either ICD or H_2FpEF-HFpEF definition, of whom 5,310 (16%) met both criteria. Compared to ICD-HFpEF, patients with H_2FpEF-HFpEF were more likely older (median age 72 vs 67), White (78% vs 64%), and had atrial fibrillation (97% vs 41%). Among those also with RHC, 6,353 (69%) patients met any HFpEF criteria, of whom only 783 (12%) satisfied all three criteria. Female sex was more common among RHC-HFpEF (55%) compared to other methods (H_2FpEF-HFpEF, 47%; ICD-HFpEF, 43%). Atrial fibrillation was substantially higher among HFpEF identified by the H_2FpEF score (97%) compared to other methods (49% for ICD and 47% for RHC). Across HFpEF screening methods, 10-year cumulative incidence rates for HFH was 32% to 45% for echocardiography only and 43% to 52% for echocardiography and RHC populations; 10-year risk of death was 54% to 56% for echocardiography only and 52% to 57% for echocardiography and RHC populations.

Conclusions Different EHR-based HFpEF definitions identified cohorts with modest overlap and varying baseline characteristics. Yet, long-term risk for HFH and death were similarly high for cohorts identified among both populations undergoing echocardiography only or echocardiography and RHC. These data aid in identifying relevant subgroups in clinical trials of HFpEF. (Am Heart J 2023;263:1–14.)

Background

Heart failure with preserved ejection fraction (HFpEF) affects over 3 million adults in the US with increasing prevalence each year.[1] HFpEF is a heterogeneous clinical syndrome with hallmark symptoms of breathlessness and poor cardiac pump reserve despite having a left ventricular ejection fraction (EF) of $\geq$ 50%.[2] Further, it is associated with ageing, hypertension, and obesity, and other comorbidities.[3] The ability to accurately identify HFpEF from the electronic health record (EHR) may improve the understanding of the epidemiology, outcomes, and treatment response of representative patient populations with HFpEF, and can facilitate the planning and conduct of clinical research.

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Abbreviations: HFpEF, heart failure with preserved ejection fraction; EF, ejection fraction; EHR, electronic health record; HFH, heart failure hospitalization; ICD, International Classification of Diseases; NPV, negative predictive value; NT-proBNP, N-terminal pro-brain natriuretic peptide; PPV, positive predictive value; RHC, right heart catheterization.

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The reference standard for diagnosing HFpEF is invasive hemodynamic testing,[4-6] which may not be performed during an initial diagnostic evaluation due to risk and availability. Several clinical diagnostic scores, including H_2FpEF and HFA-PEFF scores, have been applied using EHR-derived parameters in the diagnosis of HFpEF among at-risk populations.[7-11] These scores have yielded varying patient characteristics with varying short-term outcomes among hospitalized and ambulatory populations.[4,9,10] The addition of concomitant loop diuretic use and natriuretic peptide level to these screening measures have also offered uncertain diagnostic potential when applied to a large population undergoing both echocardiography and cardiac catheterization.[12]

In the present study, we sought to characterize HFpEF cohorts identified by different EHR-based screening strategies and associated long-term outcomes across a large, diverse, and unrestricted population undergoing echocardiography, as well as those who underwent echocardiography within six months of invasive hemodynamics. We also aimed to understand how the addition of loop diuretics and natriuretic peptide levels may influence the agreement of HFpEF screening algorithms to HFpEF diagnosed by invasive hemodynamics.

Methods

Study design and populations

This retrospective cohort study identified and characterized patients meeting varying HFpEF definitions using clinical data collected as part of routine clinical care in a large tertiary care referral health system between January 1st, 2008 and December 31st, 2018. Data sources included the electronic health record for clinical characteristics and comorbidities, echocardiography core laboratory database for standardized echocardiography data, and cardiac catheterization database for invasive hemodynamics. An overall "echo" population consisted of adult patients who had a first-time (index) echocardiogram during the study period. A "cath" population consisted of adult patients who underwent echocardiography within 6 months of an index right heart catheterization (RHC) with available pulmonary capillary wedge pressure data.

HFpEF electronic screening definitions

Patients were screened using various HFpEF definitions which required meeting the combination of appropriate clinical and imaging data within 6 months of their index imaging study: (1) International Classification of Diseases (ICD)-9/10 codes for HF with preserved or unspecified EF within a 6-month time window of index procedure; (2) H_2FpEF score $\geq$6 and an EF of $\geq$50%; and (3) RHC with pulmonary capillary wedge pressure $\geq$15 mmHg and an EF $\geq$50%. Diagnostic codes used to identify HFpEF are listed in Supplementary Table I and were derived from the EHR data repository (primary or secondary) that was closest to index study. The H_2FpEF score was derived using a validated point estimate for body mass index >30 kg/m^2 (2 points), using $\geq$2 antihypertensive medications (1 point), presence of atrial fibrillation (3 points), Doppler echocardiographic estimated pulmonary artery systolic pressure >35 mmHg (1 point), age >60 years (1 point), and Doppler Echocardiography E/e' >9 (1 point)[7]; respective comorbidities used to derive a H_2FpEF score were obtained from diagnostic codes and are listed in Supplementary Table II. Invasive pulmonary artery wedge pressure was measured in the resting supine position; invasive exercise hemodynamics were infrequently obtained (<1%) and thus excluded.

Covariates

Patient demographics, clinical history, vitals, laboratory studies, and medication use were obtained from encounters within six months of the index procedure (Supplementary Table 2). N-terminal pro-brain natriuretic peptide (NT-proBNP) was categorized as normal, if $\leq$225 pg/mL, and abnormal, if >225 pg/mL, based on local laboratory criteria. Use of loop diuretic medications from the EHR (i.e. furosemide, bumetanide, torsemide, or ethacrynic acid) was also recorded.

Outcomes

Outcomes of interest included all-cause mortality and heart failure hospitalization (HFH). All-cause mortality was based on documented deaths recorded in the DUHS health records (eg, in-hospital deaths and deaths reported by family members), as well as deaths from the Social Security Death Master File provided by the National Technical Information Service, and from North Carolina death certificates. HFH was determined from a heart failure diagnosis at discharge (primary or secondary) associated with distinct hospital admissions, with event date occurring as the date of hospital admission. For all HFH, a 30-day blanking period was implemented from the time of index procedure to recording of event to minimize misclassification of hospitalizations triggered by the imaging results as "clinical events."

Statistical analysis

Patient characteristics at time of index imaging procedure were summarized for the overall Echo and Cath populations by each of the HFpEF screening definitions. Continuous variables were presented as median (interquartile range), and categorical variables were summarized by reporting frequencies and percentages. Missing data were excluded from all denominators. To characterize agreement among the HFpEF definitions, cross-tabulations of each HFpEF definition was developed, and estimates of sensitivity, specificity, positive predictive value, and negative predictive value were reported

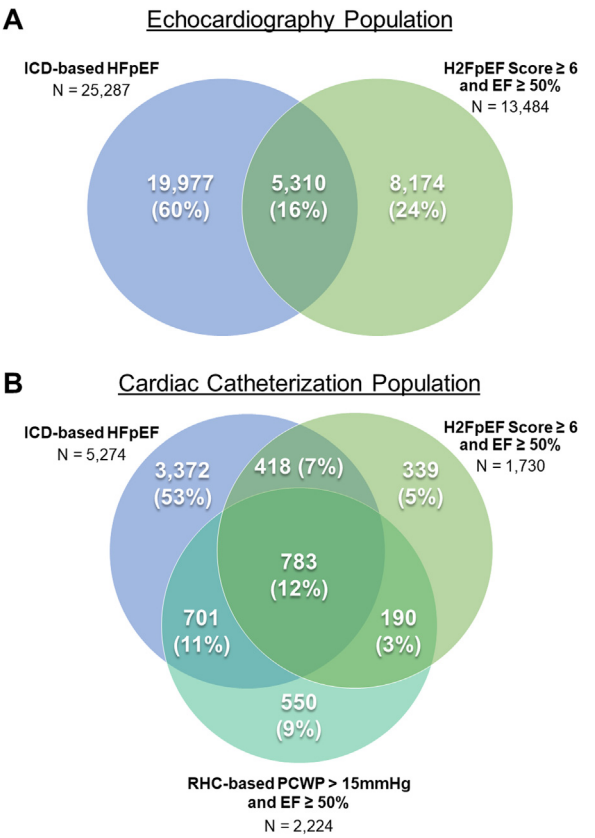
with 95% confidence intervals and then stratified by normal/abnormal NT-proBNP level and use of loop diuretics within six months of index RHC, with HFpEF defined by RHC as the reference gold standard. To distinguish the timing of clinical events, cumulative event rates and 95% confidence intervals were estimated as a function of follow-up time by each HFpEF screening definition with use of the Kaplan-Meier method for all-cause mortality and by a nonparametric cumulative incidence function estimator for first HFH.[13,14] In addition, the total number of events were reported for patients in each HFpEF group. Since patients may have satisfied multiple HFpEF definitions, analyses were descriptive only. To summarize recurrent heart failure hospitalizations, average event rate estimates (per 100 patient-years of follow-up) were reported with 95% confidence intervals from fitting a Poisson model using generalized estimating equations with a robust variance estimate to account for possible over-dispersion. An offset variable (log of follow-up time) was included in the model to account for differential lengths of patient follow-up time. Additional analyses were conducted by repeating the analyses described above, however, stratified by the following subgroups: (1) sex, (2) loop diuretic use at baseline, and (3) patients satisfying only a single HFpEF definition (mutually exclusive groups). For the latter, the associated p-value from Gray's test or the log-rank test was calculated and presented.[15] All analyses have been completed using SAS v9.4 (Cary, NC).

Results

Echocardiography population

Of the 116,499 patients with a first-time echocardiogram between 2008 and 2018, a total of 33,461 (28.7%) unique patients met at least one HFpEF screening definition: 13,484 (11.6%) met the H_2FpEF definition, and 25,287 (21.7%) met the ICD-based definition (Supplementary Figure 1). Among the overlapping cohorts, when compared to HFpEF identified by ICD definition, patients in the H_2FpEF-based HFpEF were older (median 72 [65-79] vs 67 [56-76] years), mostly white (78.5% vs 64.3%), and more frequently had atrial fibrillation (96.6% vs 40.7%) and hypertension (83.6% vs 79.4%). Use of diuretics were lower for mineralocorticoid antagonists (12.4% vs 25.1%) and loop diuretics (67.3% vs 76.5%), as was NT-proBNP level (1,694 [599-4,332] vs 2,494 [781-6,967] pg/mL) among those identified by H_2FpEF score compared to by ICD diagnoses. Patients in the ICD-based cohort had worse RV contractile function and LV end-diastolic diameter by echocardiogram, while the H_2FpEF cohort had worse left atrial size. Average EF was lower in the ICD-based cohort (44.4% vs 54.3%), owing to the fact that we included all patients with available ICD codes regardless of EF in index echocardiogram (Table I).

Figure 1



Overlapping Populations of HFpEF Identified by Screening Methods among Patients with an Echocardiogram and with or without a Right Heart Catheterization. Overlap varied among HFpEF cohorts identified by ICD-9/10 codes for HFpEF, H_2FpEF score $\geq$ 6 and EF $\geq$ 50%, and RHC-derived pulmonary capillary wedge pressure $>$ 15 mmHg and EF $\geq$ 50%. Abbreviations: EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, International Classification of Diseases codes; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization.

Agreement in definitions

Overlap was low among those who met at least one definition. Among patients identified as having HFpEF, 5,310 (15.9%) met both definitions for HFpEF, whereas 8,174 (24.4%) met only the H_2FpEF definition, and 19,977 (59.7%) met only the ICD-based definition (Figure 1).

Incident heart failure hospitalization and mortality

Kaplan-Meier incident event rates (95% CI) at 1, 5, and 10-years are displayed in Table II. At 10 years, cumulative incident HFH was 44.7% (44.0-45.4) for ICD-based HFpEF over median 4.1 years and 31.8% (30.8-32.7) for H_2FpEF-based HFpEF over median 3.7 years.

Table I. Baseline characteristics of the echocardiography population by electronic-based HFpEF screening method.

Characteristic	All Echo Patients (N=116,499)	H_2FpEF Definition (N=13,484)	ICD-9/-10 Definition (N=25,287)
Demographics			
Age (years)			
N	116,499	13,484	25,287
Median (Q1, Q3)	62 (50, 72)	72 (65, 79)	67 (56, 76)
Female Sex	59,425/116,498 (51.0%)	6,514/13,484 (48.3%)	11,695/25,287 (46.2%)
Race			
White	75,625/113,454 (66.7%)	10,491/13,369 (78.5%)	16,062/24,963 (64.3%)
Black	31,283/113,454 (27.6%)	2,411/13,369 (18.0%)	7,738/24,963 (31.0%)
Other	6,546/113,454 (5.8%)	467/13,369 (3.5%)	1,163/24,963 (4.7%)
Hispanic/Latino Ethnicity	1,896/111,775 (1.7%)	100/13,210 (0.8%)	280/24,721 (1.1%)
Vitals			
Systolic Blood Pressure (mmHg)			
N	104,931	12,564	23,010
Median (Q1, Q3)	126 (113, 140)	128 (115, 142)	124 (110, 140)
Diastolic Blood Pressure (mmHg)			
N	104,496	12,482	22,830
Median (Q1, Q3)	73 (64, 81)	70 (61, 79)	70 (61, 79)
Heart Rate (bpm)			
N	104,814	12,518	22,898
Median (Q1, Q3)	77 (67, 88)	75 (65, 87)	78 (68, 89)
Body Mass Index (kg/m^2)			
N	105,516	12,433	22,814
Median (Q1, Q3)	28 (24, 33)	29 (25, 34)	29 (25, 35)
Weight (kg)			
N	108,657	12,791	23,596
Median (Q1, Q3)	82 (69, 98)	86 (71, 102)	85 (71, 102)
Comorbidities			
Chronic Pulmonary Disease	28,740/116,499 (24.7%)	4,941/13,484 (36.6%)	10,970/25,287 (43.4%)
Atrial Fibrillation/Flutter	24,396/116,499 (20.9%)	13,025/13,484 (96.6%)	10,301/25,287 (40.7%)
Hypertension	71,876/116,499 (61.7%)	11,278/13,484 (83.6%)	20,067/25,287 (79.4%)
Coronary Disease	37,893/116,499 (32.5%)	6,417/13,484 (47.6%)	14,706/25,287 (58.2%)
Diabetes Mellitus	29,725/116,499 (25.5%)	4,568/13,484 (33.9%)	10,214/25,287 (40.4%)
Obesity (body mass index ≥30 kg/m^2)	42,121/105,516 (39.9%)	5,800/12,433 (46.7%)	10,179/22,814 (44.6%)
Chronic Kidney Disease Stage ≥ 3	19,390/116,499 (16.6%)	3,391/13,484 (25.1%)	8,548/25,287 (33.8%)
Obstructive Sleep Apnea	10,270/116,499 (8.8%)	2,192/13,484 (16.3%)	3,910/25,287 (15.5%)
Concomitant Medications			
Mineralocorticoid Antagonist	10,806/116,499 (9.3%)	1,666/13,484 (12.4%)	6,345/25,287 (25.1%)
Diuretics	60,684/116,499 (52.1%)	11,255/13,484 (83.5%)	20,910/25,287 (82.7%)
Loop Diuretics	43,033/116,499 (36.9%)	9,075/13,484 (67.3%)	19,340/25,287 (76.5%)
Beta Blockers	61,145/116,499 (52.5%)	11,753/13,484 (87.2%)	19,960/25,287 (78.9%)
ACEI/ARB	46,974/116,499 (40.3%)	7,873/13,484 (58.4%)	15,729/25,287 (62.2%)
Calcium Channel Blockers	37,200/116,499 (31.9%)	8,698/13,484 (64.5%)	10,920/25,287 (43.2%)
Hydralazine	19,850/116,499 (17.0%)	3,921/13,484 (29.1%)	7,397/25,287 (29.3%)
Nitrates	7,027/116,499 (6.0%)	1,148/13,484 (8.5%)	4,019/25,287 (15.9%)
Labs			
NT-proBNP (pg/mL)			
N	26,905	4,595	12,777
Median (Q1, Q3)	1,046 (223, 4,009)	1,694 (599, 4,332)	2,494 (781, 6,967)
BNP (pg/mL)			
N	3,259	666	1,840
Median (Q1, Q3)	253 (75, 748)	318 (137, 644)	479 (179, 1,180)
eGFR (mL/min/1.73m^2)			
N	101,015	13,007	23,903
Median (Q1, Q3)	76 (53, 96)	64 (45, 83)	59 (38, 82)
BUN (mg/dL)			
N	99,578	12,979	23,856
Median (Q1, Q3)	15 (11, 22)	18 (13, 26)	19 (13, 30)
Sodium (mmol/L)			

(*continued on next page*)

Table I. (*continued*)

Characteristic	All Echo Patients (N=116,499)	H_2FpEF Definition (N=13,484)	ICD-9/-10 Definition (N=25,287)
N	99,631	12,981	23,869
Median (Q1, Q3)	138 (136, 140)	138 (136, 140)	138 (136, 140)
ALT (U/L)			
N	87,239	11,623	21,978
Median (Q1, Q3)	22 (16, 32)	21 (16, 31)	22 (16, 33)
AST (U/L)			
N	86,052	11,522	21,833
Median (Q1, Q3)	26 (21, 36)	27 (21, 36)	27 (21, 39)
ALP (U/L)			
N	85,119	11,438	21,769
Median (Q1, Q3)	70 (56, 91)	70 (55, 91)	73 (57, 96)
Bilirubin (mg/dL)			
N	85,602	11,465	21,818
Median (Q1, Q3)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Red Cell Distribution Width (%)			
N	96,474	12,729	23,401
Median (Q1, Q3)	14 (13, 16)	14 (14, 16)	15 (14, 16)
Hemoglobin (g/dL)			
N	92,290	12,353	22,711
Median (Q1, Q3)	12 (10, 14)	12 (10, 13)	12 (10, 13)
Echocardiographic Parameters			
Right Ventricular Size			
Moderately Enlarged	3,521/116,499 (3.0%)	683/13,484 (5.1%)	1,785/25,287 (7.1%)
Severely Enlarged	1,185/116,499 (1.0%)	204/13,484 (1.5%)	729/25,287 (2.9%)
Right Ventricular Contractile Function			
Moderate Global Decrease	3,717/116,499 (3.2%)	456/13,484 (3.4%)	2,223/25,287 (8.8%)
Severe Global Decrease	1,212/116,499 (1.0%)	107/13,484 (0.8%)	833/25,287 (3.3%)
Right Ventricular Systolic Pressure (mmHg)			
N	47,019	7,790	13,449
Median (Q1, Q3)	31 (25, 42)	37 (30, 48)	40 (30, 52)
TAPSE (cm)			
N	57,510	6,566	11,246
Median (Q1, Q3)	2 (2, 3)	2 (2, 2)	2 (1, 2)
E/e' Ratio			
N	116,363	13,462	25,223
Median (Q1, Q3)	8 (8, 8)	8 (8, 8)	8 (8, 10)
Left Atrium Size			
Moderately Enlarged	10,682/116,499 (9.2%)	2,597/13,484 (19.3%)	4,903/25,287 (19.4%)
Severely Enlarged	3,371/116,499 (2.9%)	1,036/13,484 (7.7%)	1,634/25,287 (6.5%)
Left Ventricular End-diastolic Diameter (cm)			
N	110,695	12,615	23,749
Median (Q1, Q3)	4.5 (4.1, 5.0)	4.5 (4.0, 4.9)	4.8 (4.2, 5.5)
Left Ventricular Ejection Fraction (%)			
N	116,320	13,484	25,234
Median (Q1, Q3)	55 (55, 55)	55 (55, 55)	50 (35, 55)

Results are presented as number of total data available (percentage) or median (interquartile range).

Cumulative mortality was 56.1% (55.3-56.9) for ICD-based HFpEF and 54.3% (53.2-55.5) for H_2FpEF-based HFpEF (Figure 2A). Cumulative incident mortality or HFH were higher among ICD-based HFpEF (73.1% [72.4-73.8]) compared to H_2FpEF-based HFpEF (66.8% [65.7-67.8]; Supplementary Table 3). When stratified by sex, mortality, and incident HFH rates were similar among men and women for both ICD-based and H_2FpEF-based HFpEF (Supplementary Table 4).

Cardiac catheterization population

There were 9,263 patients who had both an echocardiogram and cardiac catheterization within 6 months of each other (Supplementary Figure 1). A total of 6,353

Table II. Cumulative incidence of all-cause mortality and heart failure hospitalizations by HFpEF screening methods in the echocardiography and cardiac catheterization populations.

Characteristic	Echocardiography population (N=116,499)		Cardiac catheterization population (N=9,263)		
	H_2FpEF definition (N=13,484)	ICD-9/-10 definition (N=25,077)	RHC definition (N=2,222)	H_2FpEF definition (N=1,730)s	ICD-9/-10 definition (N=5,255)
Median follow-up time, years	3.69	4.07	3.70	3.52	3.77
All-cause mortality, No.*	5,741	11,470	864	739	2,288
K-M event rate (95% CI) at 1 year	19.6% (18.9%, 20.2%)	18.8% (18.3%, 19.3%)	15.4% (14.0%, 17.0%)	17.6% (15.9%, 19.5%)	18.7% (17.7%, 19.8%)
K-M event rate (95% CI) at 5 years	38.4% (37.5%, 39.3%)	40.1% (39.4%, 40.7%)	36.0% (33.9%, 38.3%)	39.4% (36.9%, 41.9%)	39.9% (38.5%, 41.4%)
K-M Event Rate (95% CI) at 10 years	54.3% (53.2%, 55.5%)	56.1% (55.3%, 56.9%)	52.4% (49.3%, 55.6%)	57.5% (53.9%, 61.1%)	55.1% (53.2%, 57.1%)
Hospitalization for heart failure†					
Patients with ≥1 event through 1 year, No.	1,994	6,039	658	591	1,894
Cumulative incidence rate (95% CI)	14.8% (14.2%, 15.4%)	24.1% (23.6%, 24.6%)	29.6% (27.7%, 31.5%)	34.2% (31.9%, 36.4%)	36.0% (34.7%, 37.3%)
Patients with ≥1 event through 5 years, No.	3,149	9,268	840	712	2,442
Cumulative incidence rate (95% CI)	25.0% (24.2%, 25.7%)	38.4% (37.8%, 39.0%)	39.2% (37.1%, 41.3%)	42.5% (40.1%, 44.9%)	47.8% (46.4%, 49.2%)
Patients with ≥1 event through 10 years, No.	3,562	10,055	882	735	2,534
Cumulative incidence rate (95% CI)	31.8% (30.8%, 32.7%)	44.7% (44.0%, 45.4%)	43.5% (41.2%, 45.9%)	45.2% (42.7%, 47.8%)	51.6% (50.1%, 53.1%)
Total number of events	9,752	33,588	2,078	1,709	7,611
Average event rate, per 100 patient-years (95% CI)	16.4 (15.7, 17.2)	29.0 (28.2, 29.8)	21.2 (19.3, 23.4)	23.5 (21.1, 26.1)	33.2 (31.4, 35.1)

* Patients with death occurring prior to index catheterization date are excluded from outcomes analyses.

† Hospital admissions occurring at least 30 days after the index procedure date.Abbreviations: ICD, International Classification of Diseases codes; RHC, right heart catheterization.

(68.6%) unique patients met at least one of the HFpEF screening definitions: 2,224 (24.0%) met the RHC definition, 1,730 (18.7%) met the H_2FpEF, and 5,274 (56.9%) met the ICD code definition of HFpEF. Female sex was more common among RHC-based HFpEF (55.1%) compared to other methods (46.9% for H_2FpEF and 43.2% for ICD). Atrial fibrillation was substantial higher among HFpEF identified by the H_2FpEF score (97.2%) compared to other methods (48.7 for ICD and 46.9% for RHC). Compared to the H_2FpEF and ICD-based HFpEF, a higher percentage of patients in the RHC definition were also obese, had chronic pulmonary disease, had a higher pulmonary capillary wedge pressures, and with fewer use of loop diuretics (Table III).

Performance of H_2FpEF and ICD-based definitions compared to RHC for identifying HFpEF

Of those who met at least one HFpEF definition, there are 783 (12.3%) who met all 3 definitions for HFpEF (Figure 1). When compared to RHC-based HFpEF as a reference standard, the H_2FpEF and ICD-based definitions had varying performance (Figure 3). H_2FpEF had poor sensitivity of 43.8% (41.7-45.8); however, specificity was high of 89.2% (88.5-90.0). Positive predictive value (PPV) was 56.2% (53.9-58.6) and negative predictive value (NPV) of 83.4% (82.6-84.2). ICD-based HFpEF performed with higher sensitivity of 66.7% (64.8-68.7), yet with lower specificity of 46.2% (45.0-47.3). PPV was 28.1% (26.9-29.4), with an of NPV (81.4% [80.2-82.7]).

For those satisfying the H_2FpEF definition, when stratified by NT-proBNP, having normal NT-proBNP yielded sensitivity of 14.4% (8.7-20.1), and having abnormal NT-proBNP yielded an improved sensitivity of 54.0% (50.9-57.1). However, specificity remained greater than 89% among those with any NT-proBNP value. Loop diuretic use yielded similar changes in sensitivity, while specificity remained high (Figure 3).

For ICD-based HFpEF, the sensitivity was generally high but dropped to 52.1% (44.0-60.2) with normal NT-proBNP, and improved to 80.3% (77.9-82.8) with abnormal NT-proBNP. In contrast, specificity was poor: normal NT-proBNP: 67.6% (63.7-71.5); abnormal NT-proBNP:

Table III. Baseline Characteristics of the cardiac catheterization subpopulation by electronic-based HFpEF screening method.

Characteristic	All cath patients* (N=9,263)	RHC definition (N=2,224)	H_2FpEF definition (N=1,730)	ICD-9/-10 definition (N=5,274)
Demographics				
Age (years)				
N	9,263	2,224	1,730	5,274
Median (Q1, Q3)	64 (53, 71)	65 (55, 75)	70 (64, 78)	65 (54, 73)
Female sex	4,037/9,256 (43.6%)	1,225/2,224 (55.1%)	811/1,730 (46.9%)	2,280/5,274 (43.2%)
Race				
White	6,601/9,061 (72.9%)	1,585/2,185 (72.5%)	1,396/1,709 (81.7%)	3,555/5,211 (68.2%)
Black	2,101/9,061 (23.2%)	519/2,185 (23.8%)	259/1,709 (15.2%)	1,461/5,211 (28.0%)
Other	359/9,061 (4.0%)	81/2,185 (3.7%)	54/1,709 (3.2%)	195/5,211 (3.7%)
Hispanic/Latino	125/8,907 (1.4%)	26/2,139 (1.2%)	11/1,687 (0.7%)	57/5,143 (1.1%)
Vitals				
Systolic blood pressure (mm Hg)				
N	8,710	2,055	1,629	4,854
Median (Q1, Q3)	119 (107, 134)	124 (111, 140)	124 (111, 140)	118 (105, 134)
Diastolic blood pressure (mm Hg)				
N	8,641	2,035	1,615	4,803
Median (Q1, Q3)	69 (61, 78)	69 (60, 78)	68 (59, 76)	69 (60, 78)
Heart rate (bpm)				
N	8,707	2,052	1,627	4,849
Median (Q1, Q3)	82 (70, 94)	79 (68, 90)	76 (67, 88)	80 (70, 93)
Body mass index (kg/m^2)				
N	8,438	1,980	1,570	4,647
Median (Q1, Q3)	27 (24, 32)	29 (25, 35)	28 (25, 33)	28 (24, 33)
Weight (kg)				
N	8,710	2,051	1,627	4,854
Median (Q1, Q3)	81 (68, 96)	84 (70, 101)	83 (70, 97)	83 (70, 99)
Comorbidities				
Chronic pulmonary disease	6,156/9,263 (66.5%)	1,660/2,224 (74.6%)	1,209/1,730 (69.9%)	3,540/5,274 (67.1%)
Atrial fibrillation/Flutter	3,561/9,263 (38.4%)	1,042/2,224 (46.9%)	1,681/1,730 (97.2%)	2,571/5,274 (48.7%)
Hypertension	6,487/9,263 (70.0%)	1,664/2,224 (74.8%)	1,410/1,730 (81.5%)	4,165/5,274 (79.0%)
Coronary disease	5,220/9,263 (56.4%)	1,203/2,224 (54.1%)	1,116/1,730 (64.5%)	3,392/5,274 (64.3%)
Diabetes mellitus	3,210/9,263 (34.7%)	836/2,224 (37.6%)	660/1,730 (38.2%)	2,128/5,274 (40.3%)
Obesity (body mass index ≥30 kg/m^2)	2,793/8,438 (33.1%)	899/1,980 (45.4%)	618/1,570 (39.4%)	1,819/4,647 (39.1%)
Chronic kidney disease stage ≥ 3	2,841/9,263 (30.7%)	711/2,224 (32.0%)	636/1,730 (36.8%)	2,095/5,274 (39.7%)
Obstructive sleep apnea	1,406/9,263 (15.2%)	434/2,224 (19.5%)	336/1,730 (19.4%)	979/5,274 (18.6%)
Concomitant medications				
Mineralocorticoid antagonist	2,688/9,263 (29.0%)	538/2,224 (24.2%)	447/1,730 (25.8%)	2,196/5,274 (41.6%)
Diuretics	7,323/9,263 (79.1%)	1,866/2,224 (83.9%)	1,660/1,730 (96.0%)	4,845/5,274 (91.9%)
Loop diuretics	6,806/9,263 (73.5%)	1,725/2,224 (77.6%)	1,594/1,730 (92.1%)	4,662/5,274 (88.4%)
Beta blockers	6,458/9,263 (69.7%)	1,601/2,224 (72.0%)	1,532/1,730 (88.6%)	4,370/5,274 (82.9%)
ACEI/ARB	4,671/9,263 (50.4%)	1,058/2,224 (47.6%)	902/1,730 (52.1%)	3,318/5,274 (62.9%)
Calcium channel blockers	3,836/9,263 (41.4%)	1,135/2,224 (51.0%)	1,118/1,730 (64.6%)	2,358/5,274 (44.7%)
Hydralazine	2,606/9,263 (28.1%)	662/2,224 (29.8%)	634/1,730 (36.6%)	1,850/5,274 (35.1%)
Nitrates	1,119/9,263 (12.1%)	243/2,224 (10.9%)	189/1,730 (10.9%)	925/5,274 (17.5%)
Labs				
NT-proBNP (pg/mL)				
N	4,679	1,152	925	3,317
Median (Q1, Q3)	2,176 (534, 5,930)	1,755 (597, 4,375)	1,965 (753, 4,358)	2,801 (988, 7,062)
BNP (pg/mL)				
N	428	127	99	347
Median (Q1, Q3)	578 (209, 1,324)	486 (165, 1,109)	486 (250, 865)	675 (292, 1,451)
eGFR (mL/min/1.73m^2)				
N	9,223	2,215	1,729	5,268
Median (Q1, Q3)	70 (49, 90)	65 (43, 85)	64 (45, 82)	61 (42, 81)
BUN (mg/dL)				
N	9,205	2,211	1,729	5,263
Median (Q1, Q3)	17 (12, 25)	18 (13, 27)	19 (14, 26)	20 (14, 31)
Sodium (mmol/L)				

(*continued on next page*)

Table III. (*continued*)

Characteristic	All cath patients* (N=9,263)	RHC definition (N=2,224)	H_2FpEF definition (N=1,730)	ICD-9/-10 definition (N=5,274)
N	9,227	2,216	1,730	5,270
Median (Q1, Q3)	138 (136, 140)	139 (137, 140)	139 (137, 140)	138 (136, 140)
ALT (U/L)				
N	8,700	2,090	1,671	5,043
Median (Q1, Q3)	22 (16, 31)	20 (15, 28)	20 (15, 28)	22 (16, 33)
AST (U/L)				
N	8,690	2,085	1,671	5,038
Median (Q1, Q3)	26 (21, 35)	26 (21, 33)	26 (21, 33)	27 (21, 37)
ALP (U/L)				
N	8,691	2,087	1,671	5,039
Median (Q1, Q3)	70 (56, 91)	71 (56, 93)	69 (55, 89)	73 (57, 97)
Bilirubin (mg/dL)				
N	8,695	2,089	1,672	5,042
Median (Q1, Q3)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Red cell distribution width (%)				
N	9,198	2,205	1,729	5,258
Median (Q1, Q3)	15 (14, 16)	15 (14, 16)	15 (14, 16)	15 (14, 17)
Hemoglobin (g/dL)				
N	9,068	2,193	1,716	5,147
Median (Q1, Q3)	12 (11, 14)	12 (10, 13)	12 (10, 14)	12 (10, 14)
Echocardiographic parameters				
Right ventricular size				
Moderately enlarged	1,105/9,263 (11.9%)	255/2,224 (11.5%)	206/1,730 (11.9%)	731/5,274 (13.9%)
Severely enlarged	486/9,263 (5.2%)	130/2,224 (5.8%)	93/1,730 (5.4%)	352/5,274 (6.7%)
Right ventricular contractile function				
Moderate global decrease	1,161/9,263 (12.5%)	180/2,224 (8.1%)	145/1,730 (8.4%)	842/5,274 (16.0%)
Severe global decrease	478/9,263 (5.2%)	78/2,224 (3.5%)	47/1,730 (2.7%)	380/5,274 (7.2%)
Right ventricular systolic pressure (mm Hg)				
N	5,284	1,330	1,128	3,337
Median (Q1, Q3)	44 (32, 58)	49 (36, 65)	45 (35, 61)	46 (35, 60)
TAPSE (cm)				
N	5,311	1,242	985	2,909
Median (Q1, Q3)	2 (1, 2)	2 (2, 2)	2 (2, 2)	2 (1, 2)
E/e' Ratio				
N	9,229	2,217	1,726	5,254
Median (Q1, Q3)	8 (8, 11)	8 (8, 9)	8 (8, 10)	8 (8, 13)
Left Atrium Size				
Moderately enlarged	1,630/9,263 (17.6%)	481/2,224 (21.6%)	393/1,730 (22.7%)	1,246/5,274 (23.6%)
Severely enlarged	754/9,263 (8.1%)	226/2,224 (10.2%)	204/1,730 (11.8%)	521/5,274 (9.9%)
Left ventricular end-diastolic diameter (cm)				
N	8,790	2,095	1,631	5,024
Median (Q1, Q3)	4.7 (4.1, 5.5)	4.5 (4.0, 5.0)	4.4 (4.0, 5.0)	5.0 (4.2, 5.8)
Left ventricular ejection fraction (%)				
N	9,252	2,224	1,730	5,266
Median (Q1, Q3)	55 (35, 55)	55 (55, 55)	55 (55, 55)	50 (25, 55)
Pulmonary artery systolic pressure (mm Hg)				
N	9,151	2,195	1,713	5,210
Median (Q1, Q3)	43 (33, 58)	51 (42, 66)	46 (36, 61)	48 (37, 62)

(*continued on next page*)

Table III. (*continued*)

Characteristic	All cath patients* (N=9,263)	RHC definition (N=2,224)	H_2FpEF definition (N=1,730)	ICD-9/-10 definition (N=5,274)
Pulmonary artery diastolic pressure (mm Hg)				
N	9,153	2,200	1,715	5,215
Median (Q1, Q3)	20 (14, 26)	22 (18, 29)	20 (15, 25)	22 (15, 28)
Pulmonary capillary wedge pressure (mm Hg)				
N	9,240	2,224	1,728	5,264
Median (Q1, Q3)	14 (9, 21)	20 (17, 24)	16 (11, 22)	18 (12, 24)
Cardiac index (L/min/m^2)				
N	9,255	2,222	1,729	5,270
Median (Q1, Q3)	2 (2, 3)	3 (2, 3)	2 (2, 3)	2 (2, 3)
Pulmonary vascular resistance (Wood Units)				
N	9,189	2,201	1,714	5,225
Median (Q1, Q3)	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)

Results are presented as number of total data available (percentage) or median (interquartile range).

*Right heart catheterization patients who underwent an echocardiogram in the ± 6-month window around the qualifying right heart catheterization.

24.3% (22.7-25.8). With regard to loop diuretic use, the sensitivity remains higher compared to H_2FpEF. Patients on loop diuretics had sensitivity of 75.2% (73.2-77.2), yet those not on loop diuretics had low sensitivity of 37.5% (33.2-41.7). Specificity was lower compared to H_2FpEF regardless of loop diuretic use (Figure 3).

In general, the findings indicate that ICD-based HFpEF had a higher sensitivity for identifying patients who met RHC-based HFpEF compared to H_2FpEF score. On the other hand, H_2FpEF has a higher, and fairly strong, specificity for correctly distinguishing HFpEF from non-HFpEF compared with performance of ICD diagnosis codes. These trends persisted even when abnormal NT-proBNP or presence of loop diuretic use were added to the screen methods (Supplementary Figure 2).

Incident heart failure hospitalization and mortality

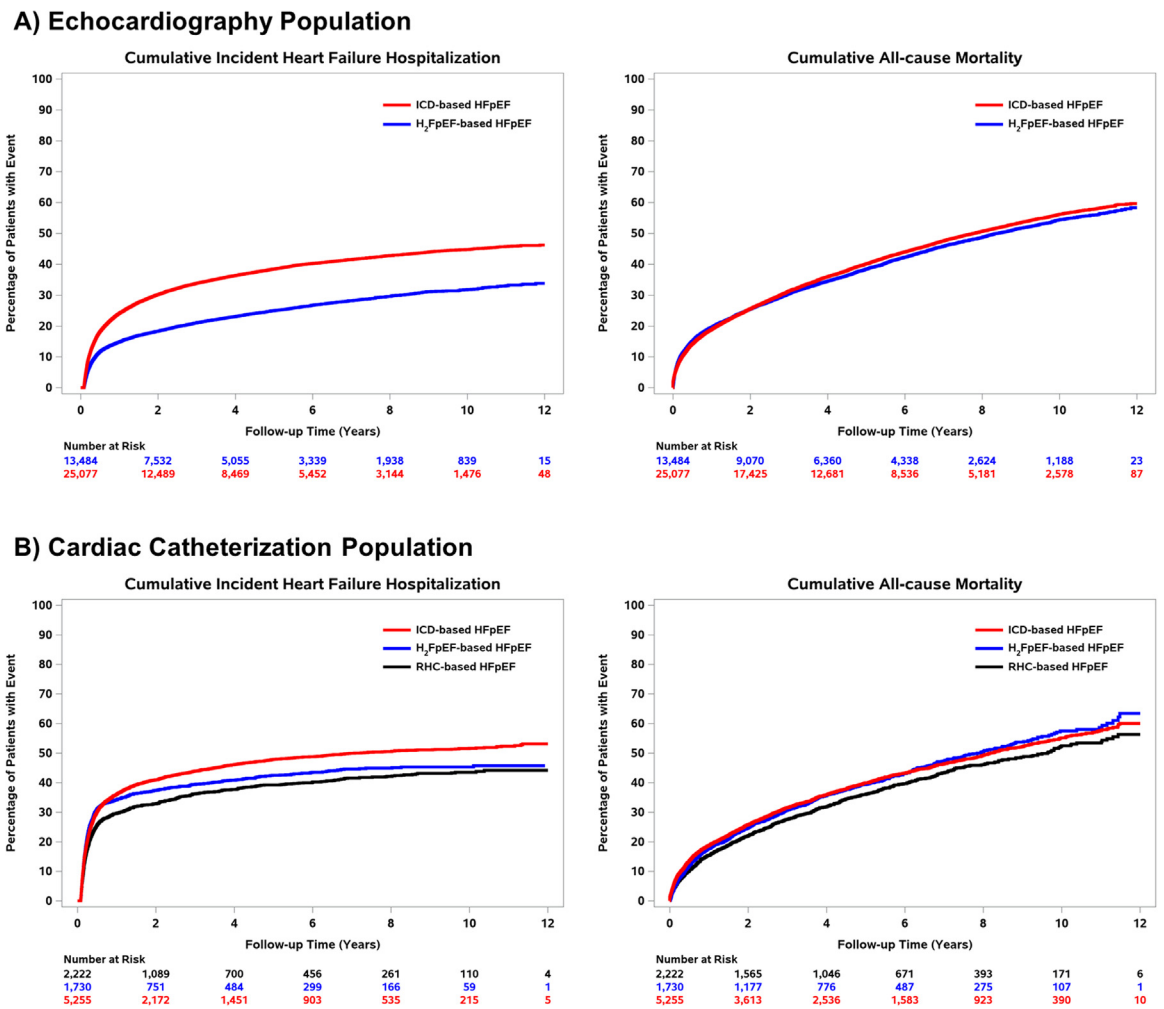
Kaplan-Meier incident event rates (95% CI) at 1, 5, and 10-years are displayed in Table II. At 10 years, cumulative incident HFH was 51.6% (50.1-53.1) over median 3.8 years for ICD-based HFpEF, 45.2% (42.7-47.8) over median 3.5 years for H_2FpEF-based HFpEF, and 43.5% (41.2-45.9) over median 3.7 years for RHC-based HFpEF. Cumulative mortality was 55.1% (53.2-57.1) for ICD-based HFpEF, 57.5% (53.9-61.1) for H_2FpEF-based HFpEF, and 52.4% (49.3-55.6) for RHC-based HFpEF (Figure 2B). Cumulative incident mortality or HFH were similar across HFpEF screening methods (Supplementary Table 5). When stratified by sex, mortality rates were slightly higher among men compared to women for all screening methods, whereas average HFH per 100 person-years differed by sex among screening methods: H_2FpEF-based HFpEF, women 26.0 (22.2-30.4) vs men 21.1 (18.4-24.3); ICD-based HFpEF, women 29.8 (27.3-32.5) vs men 36.0 (33.5-38.6) (Supplementary Table 6).

Discussion

Across a large and diverse population of patients undergoing echocardiography, and subpopulation with right heart catheterization, patients identified with HFpEF by diagnostic codes, H_2FpEF score, and invasive hemodynamic-based criteria varied in prevalence and clinical characteristics. While clinical and imaging criteria for each screening method were obtained close to the occurrence of imaging studies, agreement between EHR-based HFpEF groups was modest in both populations. The inclusion of natriuretic peptide level and diuretic medication use provided varying improvements in sensitivity and specificity of ICD or H_2FpEF-based screening methods when compared to invasive hemodynamics as the reference standard. Regardless of screening method used to identify HFpEF, incident HFH and all-cause mortality occurred at exceedingly high rates across all HFpEF cohorts among both populations.

Accurately identifying HFpEF for patient selection in clinical trials can be challenging due to overlapping symptoms with other comorbidities.[2,3,16] Echocardiography is mainstay in HFpEF evaluation,[17] but screening by discrete echocardiography data alone is limited since HFpEF exhibits preserved systolic ventricular function.[2,3] Claims data have also yielded high risk for misclassification in community cohorts, with varying performance by EF.[18-20] Clinical diagnostic scores derived from cohorts undergoing invasive exercise studies intended to identify HFpEF also have varying performance,[7-11] and their comparison with other screening strategies has been lim-

Figure 2



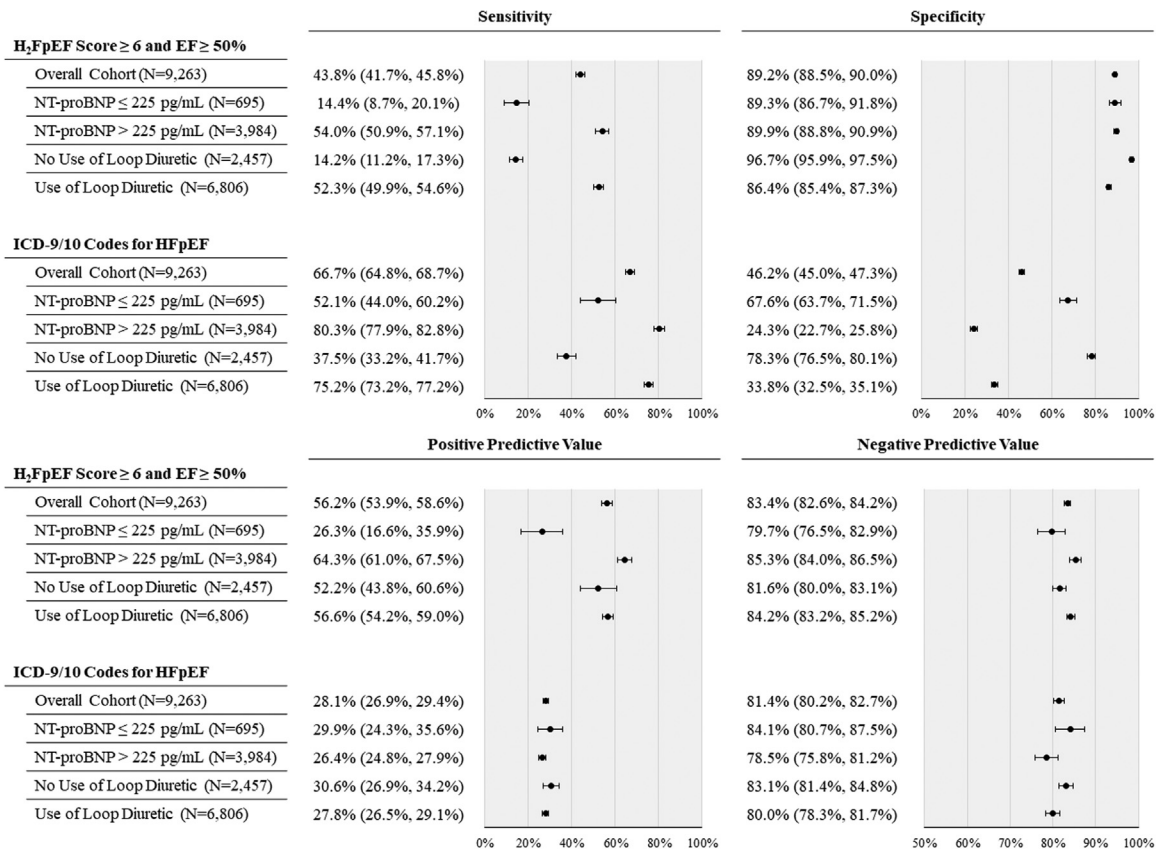
Cumulative Incidence Rates for Heart Failure Hospitalizations and All-Cause Mortality among Heart Failure with Preserved Ejection Fraction groups defined by ICD codes and H_2FpEF score. Cumulative incident heart failure hospitalizations were observed more among the HFpEF cohort identified by ICD-9/10 codes than those identified by H_2FpEF score $\geq$ 6 and ejection fraction $\geq$ 50%, whereas cumulative mortality was similar among both cohorts in the echocardiography population (Fig 2A). Cumulative incident outcomes were observed similarly among the HFpEF cohorts identified by ICD codes, H_2FpEF score, and those identified by RHC-derived pulmonary capillary wedge pressure $\geq$ 15 mmHg and EF $\geq$ 50% (Fig 2B). Abbreviations: EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, International Classification of Diseases codes; RHC, right heart catheterization.

ited.[16] Thus, characterizing screening methods following cardiovascular imaging studies may provide insight into identifying HFpEF through the EHR.

HFpEF screening among patients undergoing echocardiography

Nearly one-third of patients who underwent echocardiography had high probability of HFpEF based on diagnostic codes or H_2FpEF score in the present study. However, screening methods yielded a modest overlap (16%) who met both criteria. As such, clinical characteristics differed by screening method. ICD-based HFpEF identified patients who were younger, more often Black, with chronic lung disease, and with greater loop diuretic and mineralocorticoid use, with similar characteristics to other claims-derived community cohorts.[18-21] H_2FpEF-based HFpEF were often older and had hypertension, obesity, and atrial fibrillation, largely owing to the predictive variables included in the H_2FpEF score (obesity, atrial fibrillation, age >60 years, treatment with

Figure 3



Agreement between Electronic Screening Methods for HFpEF in Subpopulations with and without Concomitant Use of Loop Diuretics or NT-proBNP Levels. This figure displays the sensitivity, specificity, positive predictive value, and negative predictive value of the H_2FpEF score and ICD diagnosis code screening tools for HFpEF, with right heart catheterization-derived pulmonary capillary wedge pressure > 15 mmHg and EF ≥ 50% serving as the reference gold standard. The addition of NT-proBNP value or presence of loop diuretic use resulted in varying characteristics to identify HFpEF for each screening method. Abbreviations: EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, International Classification of Diseases; NT-proBNP, N-terminal-pro hormone brain natriuretic peptide.

≥2 antihypertensives, echocardiographic E/e' ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mmHg).[7] Of the two methods, the greatest proportion of patients identified were by ICD-based HFpEF, which was presumed to rely on the presence of clinical symptoms and preserved ejection fraction at the time of echocardiography.

These data uniquely show that despite their limited overlap, broadly applying non-invasive screening criteria for HFpEF did not discriminate clinical risk, with both cohorts exhibiting high short and long-term clinical risk for incident HFH and death through 10 years. Although the driving factors for each event could not be derived, the high prevalence of comorbid conditions, such as obesity, lung disease, diabetes, atrial fibrillation, renal dysfunction, and anemia,[16,22] may have either confounded HFpEF diagnosis or contributed to long-term clinical risk in this population.

HFpEF screening among patients undergoing echocardiography and catheterization

Invasive hemodynamic testing alongside echocardiography may occur for confirmatory diagnosis of HFpEF and/or in the evaluation of congestion.[16] While RHC with provocative testing is considered gold standard,[4-6] resting invasive hemodynamic testing is commonly performed due to its availability. Meanwhile, the performance of HFpEF screening methods among those with echocardiography and RHC is unclear. The present study showed nearly two-thirds of patients with echocardiography and RHC met any of the three HFpEF screening criteria, and only 12% met all three criteria. As observed

in the echocardiography only population, baseline characteristics differed by screening method.

When RHC-HFpEF was used as a reference, both ICD and H_2FpEF score-derived HFpEF had low sensitivity of ~50%, and only H_2FpEF score had high specificity in this subpopulation. When compared to other cohorts, H_2FpEF score identified 30% (n=187) of the Alberta HEART cohort as unlikely to be HFpEF, and 25.7% (n=160, including 43% of the 191 with clinically adjudicated HFpEF) as highly likely to be HFpEF.[23] When H_2FpEF score cutoff of >2 was applied, sensitivity increased to ~90%, and a H_2FpEF score <6 yielded specificity of 82% to rule out HFpEF in the Alberta HEART population.

Clinical outcomes were similar across all three screening methods. The limited overlap we observed between ICD, H_2FpEF, and RHC-derived HFpEF illustrated important and wide variations in HFpEF identification for clinical practice and research. As such, there is a growing need for developing gold standards for HFpEF in lieu of exercise invasive hemodynamics, as well as need for validation of EHR-based scores in large population cohorts. As such, future studies using larger cohorts are needed to validate the applicability of EHR-based screening tools to appropriately and consistently identify groups, or subgroups with common characteristics, of HFpEF.[11]

Leveraging EHR-based screening for clinical trial design

The present analysis lends insight into potential applications of EHR-based screening to improve identification and enrollment of patients with HFpEF into clinical trials. Imprecise recruitment of patients with HFpEF has been a challenge for clinical trial design due to lacking clearly defined features within the EHR, and prior HFpEF clinical trial enrollment algorithms have been based on expert opinion.[3] Our results suggest that broadly applying ICD or H_2FpEF score screening criteria across populations with echocardiography is feasible, acknowledging that each strategy may select HFpEF subpopulations with distinct characteristics. The advantage of ICD criteria includes a broad sampling of the population, but may require additional verification, especially given the high prevalence of non-cardiovascular comorbidities and patients with lower EF. Whereas, H_2FpEF may favorably enrich with subgroups with comorbid atrial fibrillation for whom clinical studies may be designed to determine therapeutic response to catheter ablation (ie, CABA-HFPEF trial; NCT05508256).

The application of natriuretic peptide level and/or loop diuretic use to HFpEF screening criteria may improve their performance in identifying patients with high probability of HFpEF.[16] Natriuretic peptides are well-established biomarkers for diagnosing HF with acute dyspnea,[24] and provided accurate prognostic information in patients with HFpEF.[25,26] However, prior validation studies of the H_2FpEF score among patients with unexplained dyspnea found no additional discrimination for HFpEF with the addition of natriuretic peptides.[7,9] The present study demonstrated that addition of abnormal natriuretic peptide levels provided variable changes to sensitivity and specificity for both ICD and H_2FpEF-based criteria in the catheterization population, particularly with disproportionate changes to sensitivity with ICD-based HFpEF. The variability in discriminating HFpEF when using invasive hemodynamics as reference highlights the challenge with interpreting natriuretic peptides in HFpEF, and particularly in obese-HFpEF.[27] Additionally, natriuretic peptides may not add incremental diagnostic information to variably selected screening measures in context of comorbidities, either by primarily clinical assessment (as with ICD-based HFpEF) or clinical and imaging based criteria (as with H_2FpEF score). Chronic diuretic use in HFpEF is associated with poor adverse outcomes,[28] yet the presence or absence of loop diuretic provided similar variability in HFpEF agreement between ICD or H_2FpEF score and invasive hemodynamics. Given that a significant proportion of patients enrolled in HFpEF trials, including TOPCAT and I-PRESERVE, had normal LV structure in absence of ventricular hypertrophy,[29,30] the utility of concomitantly abnormal NT-proBNP, loop diuretic use, and other markers of impaired vascular compliance or congestion as enrichment factors in clinical studies of HFpEF warrants further research.

Limitations

The results of this study should be interpreted in the context of the following limitations. The study population included consecutive patients who underwent echocardiography, and those with echocardiography within index RHC. Decision to obtain these imaging studies may provide referral bias, in particular for cardiac catheterization in which benefit/risk decision-making would meet a pretest probability for disease, limiting generalizability. Screening by ICD codes included diagnostic codes for HFpEF and unspecified HF, which may have contributed to the observed range of EF within this group. We additionally did not have access to signs and symptoms of heart failure at the time of index procedure, which limits the understanding of specific indications of imaging procedures in context of disease severity. Despite the large population size, the single center design may also limit generalizability among different patient populations at health centers across regions in the United States and worldwide. Since these data were derived from the EHR did not include full echocardiographic information that may be available in a research core lab setting, we were unable to apply other available HFpEF screening scores. Similarly, the absence of a control group and overlapping cohorts prevented us from directly comparing each screening method on popula-

tion characteristics and prognosis. Additionally, patients with infiltrative cardiomyopathies, such as cardiac amyloidosis, may have been underrepresented in the studied screening methods.

Conclusions

HFpEF was commonly identified through EHR-based screening tools using diagnostic codes and clinical and imaging characteristics. Despite having varying population characteristics and modest overlap across HFpEF screening methods, adverse risk of HFH and all-cause mortality remained exceedingly high. These data have implications for EHR screening for HFpEF for the purposes of clinical trial enrollment. Future research on EHR-based HFpEF cohorts and prognosis across multicenter populations is warranted.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.04.013.

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