



# Evaluation of claims-based computable phenotypes to identify heart failure patients with preserved ejection fraction

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## Abstract

The purpose of this analysis was to develop and validate computable phenotypes for heart failure (HF) with preserved ejection fraction (HFpEF) using claims-type measures using the Rochester Epidemiology Project. This retrospective study utilized an existing cohort of Olmsted County, Minnesota residents aged  $\geq 20$  years diagnosed with HF between 2007 and 2015. The gold standard definition of HFpEF included meeting the validated Framingham criteria for HF and having an LVEF  $\geq 50\%$ . Computable phenotypes of claims-type data elements (including ICD-9/ICD-10 diagnostic codes and lab test codes) both individually and in combinations were assessed via sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with respect to the gold standard. In the Framingham-validated cohort, 2,035 patients had HF; 1,172 (58%) had HFpEF. One in-patient or two out-patient diagnosis codes of ICD-9 428.3X or ICD-10 I50.3X had 46% sensitivity, 88% specificity, 84% PPV, and 54% NPV. The addition of a BNP/NT-proBNP test code reduced sensitivity to 35% while increasing specificity to 91% (PPV = 84%, NPV = 51%). Broadening the diagnostic codes to ICD-9 428.0, 428.3X, and 428.9/ICD-10 I50.3X and I50.9 increased sensitivity at the expense of decreasing specificity (diagnostic code-only model: 87% sensitivity, 8% specificity, 56% PPV, 30% NPV; diagnostic code and BNP lab code model: 61% sensitivity, 43% specificity, 60% PPV, 45% NPV). In an analysis conducted to mimic real-world use of the computable phenotypes, any one in-patient or out-patient code of ICD-9 428/ICD-10 150 among the broader population ( $N = 3,755$ ) resulted in lower PPV values compared with the Framingham cohort. However, one in-patient or two out-patient instances of ICD-9 428.0, 428.9, or 428.3X/ICD-10 150.3X or 150.9 brought the PPV values from the two cohorts closer together. While some misclassification remains, the computable phenotypes defined here may be used in claims databases to identify HFpEF patients and to gain a greater understanding of the characteristics of patients with HFpEF.

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## KEYWORDS

Administrative Data, Algorithm, Electronic Health Records, Heart failure

## 1 | INTRODUCTION

Chronic heart failure (HF) affects over 6.5 million adults in the United States.<sup>1</sup> In approximately half of HF patients, the left ventricular ejection fraction (LVEF) is reduced (below 50%) (HFpEF).<sup>2</sup> Patients with LVEF  $\geq$  50% are described as having preserved ejection fraction (HFpEF).<sup>3</sup> Both HFpEF and HFpEF patients exhibit increased morbidity and mortality, but while there are effective guidelines for treatment of HFpEF, therapies for those with HFpEF remain limited.<sup>4,5</sup> In order to develop urgently needed new therapies for HFpEF, a better understanding of patient characteristics for HFpEF patients is needed.

Large claims databases are often utilized to gain a better understanding of the demographic and clinical characteristics of patients with specific conditions. However, the condition of interest needs to be precisely identified in order to effectively use claims data. Algorithms have been previously developed to broadly identify HF patients using claims data<sup>6-8</sup> but utilizing such data for more narrow indications, such as HFpEF, has several challenges. Complex indications require a wide variety of lab results and clinical characteristics in order to provide an accurate diagnosis, but often the needed elements are not systematically or reliably captured and vary in accuracy across administrative databases.<sup>9</sup> Likely because of these reasons, to date there are very few published algorithms to identify HFpEF patients in administrative databases. In this study, we identified and tested several different combinations of administrative data codes, also known as computable phenotypes, to identify patients with HFpEF using an established community-based epidemiologic cohort of patients with validated HF.

## 2 | MATERIALS AND METHODS

This study was conducted in Olmsted County, Minnesota, which has age, sex, and ethnic characteristics similar to those of the state of Minnesota and upper Midwest region of the United States.<sup>10</sup> Olmsted County is relatively isolated from other urban centers, and only a few providers (mainly Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals) deliver most of the health care to local residents. The retrieval of nearly all healthcare-related events occurring in Olmsted County is possible via the resources of the Rochester Epidemiology Project (REP), a records linkage system that links medical records as well as billing information from each institution.<sup>11</sup> The records include demographics, diagnostic codes, surgical procedure codes, drug prescriptions, and laboratory results from all in-patient and out-patient visits that are available from participating institutions. The linked records are available to researchers to abstract data and validate events. This record linkage system encompasses

## Key Points

1. Therapies for heart failure with preserved ejection fraction (HFpEF) are limited, and in order to develop urgently needed new therapies, a better understanding of patient characteristics for HFpEF patients is needed.
2. One way of characterizing patients with a specific condition is through large claims (administrative) databases but this is only possible when the condition can be precisely identified.
3. Using a combination of claims-type data elements (including ICD-9 and ICD-10 diagnostic codes and lab test codes) a series of computable phenotypes were developed that had acceptable levels of sensitivity, specificity, and positive predictive value to identify patients with HFpEF.
4. Although prone to some misclassification, computable phenotypes were identified that may be used in commercially available claims databases to gain a deeper understanding of the characteristics of the HFpEF population.

more than 6 million person-years of follow-up in over 500000 unique individuals from 1966 to the present and enables virtually complete capture of outcomes and healthcare utilization in Olmsted County residents.<sup>11</sup> The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved this study.

Patient and clinical characteristics needed to identify HFpEF patients were previously collected within a retrospective cohort study of patients with incident HF in Olmsted County, Minnesota (hereafter called "HF cohort").<sup>2</sup> To develop the HF cohort, patients with International Classification of Disease (ICD) codes from revisions 9 and 10 for HF (ICD-9 code 428 and ICD-10 code I50) were identified and all medical records were reviewed to validate the HF diagnoses using the Framingham criteria.<sup>12</sup> For this study, eligible patients were those diagnosed with incident HF between 1 January 2007 and 31 December 2015, who were 20 years of age or older at the date of HF diagnosis and had a measurement of LVEF within 1 year before or after the HF diagnosis. The 1 year time window for LVEF was used to optimize the number of people who had an available LVEF to characterize the type of HF; however, 90% of the echocardiograms occurred within the 3 months before or after HF diagnosis. When multiple values of LVEF were available, the value closest to the HF date was used; when multiple values were available on the same day, the average value was used. Patients meeting these criteria who further had LVEF  $\geq$  50% were considered to meet the gold standard definition of HFpEF. The remaining patients were considered to have heart failure with reduced ejection fraction (HFpEF; LVEF < 50%).

Clinical characteristics were collected from the medical records by trained nurse abstractors or code-based clinical diagnoses. Body mass index ( $\text{kg}/\text{m}^2$ ) was calculated using the last weight before HF diagnosis and earliest adult height. Heart rate closest to the time of HF diagnosis was abstracted by trained nurse abstractors. Smoking was dichotomized as ever vs never. Comorbidities were characterized using the Charlson Comorbidity Index<sup>13</sup> and required the presence of two codes separated by at least 30 days within the 5 years prior to the HF diagnosis. Medication prescriptions at the time of HF diagnosis, B-type natriuretic peptide (BNP), and N-terminal pro B-type natriuretic peptide (NT-proBNP) values (closest value within 1 year prior to HF diagnosis), diagnosis codes within 1 year prior to HF diagnosis (using ICD-9 and ICD-10 codes; see Table S1), and out-patient visits and hospitalizations within 1 year prior to HF diagnosis were obtained electronically.

To characterize the patient population, demographic and clinical measures were summarized for the HF cohort meeting the gold standard definition for HFpEF and for comparison, also for HFrfEF patients. Patient characteristics were summarized with mean (SD) for continuous variables and n (%) for categorical variables. Characteristics were compared between patients with HFpEF and HFrfEF using t-tests and chi-square tests, as appropriate.

Next, a series of computable phenotypes using combinations of claims-type data (i.e. billing data) were created to test for identification of HFpEF patients in relation to the gold standard definition of HFpEF. Multiple computable phenotypes, first using individual claims-type measures and then using combinations of different claims-type measures, were developed using diagnostic codes, lab codes for BNP and NT-proBNP, and indicators for whether codes were assigned during in-patient versus out-patient visits. Within a computable phenotype, the included measures could occur in any time order within the 1 year prior to or after HF diagnosis. For the algorithms that required two or more out-patient diagnosis codes, the out-patient codes had to occur at least 30 days but not more than 365 days apart. In addition, no restrictions on the timing between the diagnostic code(s) and lab test code for BNP/NT-proBNP were imposed, except that the two criteria needed to be met within the 1 year window around the HF diagnosis. Finally, if a patient met the listed criteria for an algorithm, he/she was considered to be positive for the algorithm regardless of whether the patient also had a diagnostic code for HF that was not included in the algorithm definition.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each computable phenotype for evaluative purposes. Sensitivity is the proportion of HFpEF cases that are identified as having HFpEF by the algorithm (algorithm +/true +); specificity is the proportion of non-cases that are identified as not having HFpEF by the algorithm (algorithm -/true -). PPV is defined as the proportion of subjects identified as having HFpEF from the algorithm who are HFpEF cases (true +/algorithm +); NPV is the proportion of subjects who are identified as not having HFpEF from the algorithm who are non-cases (true -/algorithm -).

Next, an analysis was conducted to more closely mimic what real-world use of the computable phenotypes might be given that starting with a population selected by criteria outside of typical claims measures (such as Framingham) may not be available to all researchers or within existing large claims-only databases. This analysis was conducted among all REP patients who had at least one code of ICD-9 428 or ICD-10 I50 (which encompasses all patients who were screened to develop the HF cohort, rather than the subset of Framingham-validated HF patients). Within this broader population, PPV values were calculated in the same set of computable phenotype definitions for comparison. Because the starting population consists of patients with a HF code, values for sensitivity, specificity, and NPV cannot be calculated because the denominators are not available.

A sensitivity analysis was conducted limiting the population of HF patients to those who had a clinical diagnosis of HF rather than meeting the Framingham criteria and repeating the evaluation of sensitivity, specificity, PPV, and NPV for each computable phenotype. The clinical diagnosis of HF is a physician diagnosis that was captured at the time the HF cohort was created by reviewing the medical records. The date of clinical diagnosis was the date of the first physician diagnosis of HF in the medical record.

All statistical analyses were conducted using SAS/STAT software, version 9.4 (SAS Institute Inc Cary, NC).

### 3 | RESULTS

Between 1 January 2007 and 31 December 2015, 2,211 patients were identified with incident HF meeting Framingham criteria (gold standard population). Of these, 176 (8%) had no measures of LVEF within 1 year of the date of HF and were excluded, leaving a study population of 2,035 patients; 1,172 (58%) patients were identified as having HFpEF and 863 (42%) were identified as having HFrfEF.

The majority of the HF patients were Caucasian. HFpEF patients were older and more likely to be female, never smokers, and have a higher body mass index than the HFrfEF patients (Table 1). Mean LVEF among the HFpEF patients was 61.2% (range 50.0%-81.0%) while for the HFrfEF patients it was 33.7% (range 9.0%-49.7%). Mean resting heart rate was 85.5 and 96.4 for HFpEF and HFrfEF patients, respectively. Patients with HFpEF had a higher comorbidity burden as measured by the Charlson Comorbidity Index. In particular, they were more likely to have a history of peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, mild liver disease, and diabetes (data not shown). Patients with HFpEF had a higher number of diagnosis codes, hospitalizations, and out-patient visits within 1 year prior to the HF diagnosis. At the time of HF diagnosis, HFpEF patients were more likely to have been prescribed antilipemics (54.3% vs 47.2%,  $P < .01$ ), beta blockers (60.0% vs 50.4%,  $P < .01$ ), angiotensin II inhibitors (15.0% vs 9.5%,  $P < .01$ ), diuretics (58.5% vs 42.5%,  $P < .01$ ), and calcium channel blockers (34.1% vs 23.6%,  $P < .01$ ).

	HFrEF (N = 863)	HFpEF (N = 1,172)	P-value
Age, Mean (SD)	72.3 (15.3)	76.9 (13.0)	<0.01
Female sex, n (%)	337 (39.0%)	700 (59.7%)	<0.01
Race, n (%)			
Black/African American	21 (2.4%)	25 (2.1%)	0.69
White	813 (94.2%)	1,102 (94.0%)	
Native Hawaiian/Pacific islander	1 (0.1%)	0 (0.0%)	
Asian	17 (2.0%)	25 (2.1%)	
Other	11 (1.3%)	20 (1.7%)	
Body mass index, kg/m <sup>2</sup> , Mean (SD)	29.6 (7.0)	31.1 (8.1)	0.01
Smoking status			
Never	332 (38.2%)	538 (45.7%)	<0.01
Ever	537 (61.8%)	640 (54.3%)	
Charlson Comorbidity Index, Mean (SD)	2.2 (2.4)	2.7 (2.5)	<0.01
Ejection Fraction (%), Mean (SD)	33.7 (9.9)	61.2 (6.1)	<0.01
Heart rate (beats per minute), Mean (SD)	96.4 (26.9)	85.5 (27.6)	<0.01
NT-pro BNP within 1 year <sup>a</sup>			
N with non-missing value	425	660	<0.01
Mean (SD)	7198.0 (8326.9)	4151.8 (8185.6)	
BNP within 1 year <sup>a</sup>			
N with non-missing value	87	142	<0.01
Mean (SD)	1140.4 (867.5)	624.0 (544.2)	
Number of diagnosis codes within 1 year <sup>a</sup>			
Mean (SD)	42.8 (23.8)	48.1 (25.8)	<0.01
Number of hospitalizations within 1 year <sup>a</sup>			
Mean (SD)	1.8 (1.7)	2.2 (2.1)	<0.01
Number of out-patient visits within 1 year <sup>a</sup>			
Mean (SD)	8.5 (9.4)	11.3 (11.4)	<0.01

Note: BNP, B-type natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation.

<sup>a</sup>Within the 1 year prior to diagnosis of Framingham-validated heart failure.

Definitions of the tested computable phenotypes are shown in Table 2. One in-patient diagnosis of ICD-9 428.3X or ICD-10 I50.3X had 42% sensitivity, 89% specificity, 84% PPV, and 53% NPV for HFpEF compared to the gold standard Framingham definition. Requiring either one in-patient code<sup>a</sup> or two out-patient codes of ICD-9 428.3X or ICD-10 I50.3X increased the sensitivity of the algorithm to 45% while the specificity, PPV, and NPV were similar. Using the aforementioned one in-patient or two out-patient diagnosis codes with the addition of one BNP/NT-proBNP lab test code resulted in a reduced sensitivity of 35% while the specificity increased to 91% (PPV = 84%, NPV = 51%). Expanding the diagnostic codes to one in-patient or two out-patient codes of ICD-9 428.0, 428.9, and 428.3X or ICD-10 I50.3X and I50.9 increased the sensitivity while

lowering the specificity (diagnostic code-only definition: 87% sensitivity, 8% specificity, 56% PPV, 30% NPV; diagnostic code plus BNP/NT-proBNP code: 61% sensitivity, 43% specificity, 60% PPV, 45% NPV).

A broader population of HF patients defined as having any one code (in-patient or out-patient) of ICD-9 428/ICD-10 I50 (N = 3,755) was included to provide estimates of PPV from the computable phenotypes that might be expected in a real-world setting (Table 3). Compared with the Framingham-defined cohort, PPV values for the code-based cohort were generally lower when considering only ICD-9 code 428.3X/ICD-10 I50.3X. For example, one in-patient diagnosis of ICD-9 428.3X or ICD-10 I50.3X had a PPV of 37% in the broadly defined cohort compared with 84% in

**TABLE 1** Descriptive characteristics including mean (standard deviation [SD]) and N (%) of patients with Framingham-validated heart failure patients by reduced (<50%) vs preserved (≥50%) left ventricular ejection fraction

**TABLE 2** Computable phenotypes for HFpEF in a Framingham-validated heart failure cohort<sup>a</sup> (gold standard)

Computable Phenotype	N meeting criteria	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
<b>Codes only</b>					
1 IP diagnosis of 428.3X	591	42.2 (39.4, 45.1)	88.9 (86.8, 91.0)	83.8 (80.8, 86.7)	53.1 (50.5, 55.7)
1 IP or 2 OP diagnosis of 428.3X	636	45.6 (42.7, 48.4)	88.2 (86.0, 90.3)	84.0 (81.1, 86.8)	54.4 (51.8, 57.0)
1 IP diagnosis of 428.31 or 428.33	341	24.8 (22.4, 27.3)	94.2 (92.7, 95.8)	85.3 (81.6, 89.1)	48.0 (45.6, 50.4)
1 IP or 2 OP diagnosis of 428.31 or 428.33	358	26.0 (23.5, 28.5)	93.9 (92.3, 95.5)	85.2 (81.5, 88.9)	48.3 (45.9, 50.7)
1 IP diagnosis of 428.0, 428.9, or 428.3X	1,567	76.1 (73.7, 78.6)	21.8 (19.0, 24.5)	56.9 (54.5, 59.4)	40.2 (35.7, 44.6)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.3X	1,815	86.9 (84.9, 88.8)	7.7 (5.9, 9.4)	56.1 (53.8, 58.4)	30.0 (23.9, 36.1)
1 IP diagnosis of 428.0, 428.9, 428.31, or 428.33	1,504	71.0 (68.4, 73.6)	22.1 (19.4, 24.9)	55.3 (52.8, 57.8)	36.0 (31.9, 40.1)
1 IP or 2 OP diagnosis of 428.0, 428.9 or 428.31 or 428.33	1,750	81.4 (79.2, 83.6)	7.8 (6.0, 9.6)	54.5 (52.2, 56.9)	23.5 (18.6, 28.4)
<b>Codes + BNP/NT-proBNP</b>					
1 IP diagnosis of 428.3X and 1 BNP/NT-proBNP lab code	450	32.1 (29.4, 34.8)	91.4 (89.6, 93.3)	83.6 (80.1, 87.0)	49.8 (47.3, 52.2)
1 IP or 2 OP diagnosis of 428.3X and 1 BNP/NT-proBNP lab code	485	34.6 (31.9, 37.4)	90.9 (88.9, 92.8)	83.7 (80.4, 87.0)	50.6 (48.1, 53.1)
1 IP diagnosis of 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	281	20.5 (18.2, 22.8)	95.3 (93.8, 96.7)	85.4 (81.3, 89.5)	46.9 (44.5, 49.2)
1 IP or 2 OP diagnosis of 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	294	21.5 (19.2, 23.9)	95.1 (93.7, 96.6)	85.7 (81.7, 89.7)	47.2 (44.8, 49.5)
1 IP diagnosis of 428.0, 428.9, or 428.3X and 1 BNP/NT-proBNP lab code	1,053	54.0 (51.2, 56.9)	51.3 (48.0, 54.7)	60.1 (57.2, 63.1)	45.1 (42.0, 48.2)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.3X and 1 BNP/NT-proBNP lab code	1,205	61.2 (58.4, 64.0)	43.5 (40.2, 46.8)	59.5 (56.7, 62.3)	45.2 (41.8, 48.6)
1 IP diagnosis of 428.0, 428.9, 428.31, or 428.33 and 1 BNP/NT-proBNP lab code	1,015	50.9 (48.1, 53.8)	51.6 (48.2, 54.9)	58.8 (55.8, 61.9)	43.6 (40.6, 46.7)
1 IP or 2 OP diagnosis of 428.0, 428.9 or 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	1,165	57.9 (55.0, 60.7)	43.6 (40.3, 46.9)	58.2 (55.4, 61.0)	43.2 (39.9, 46.5)

BNP, B-type natriuretic peptide; CI, confidence interval; IP, in-patient; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; NT-proBNP, N-terminal pro B-type natriuretic peptide; OP, out-patient; PPV, positive predictive value.

<sup>a</sup>N = 2,035 patients with heart failure (1,172 patients with HFpEF and 863 HFREF). ICD codes are shown for Revision 9. Table S1 shows the conversion between ICD-9 and ICD-10.

the Framingham-defined cohort. Including additional ICD codes, however, brought the PPVs from the two cohorts closer together; the computable phenotype with one in-patient or two out-patient instances of ICD-9 428.0, 428.9, or 428.3X or ICD-10 I50.3X or I50.9 resulted in a PPV of 30% in the broader cohort and 56% in the Framingham-defined cohort.

As a way of assessing the robustness of the computable phenotypes, a sensitivity analysis was performed by limiting the population of HF patients to those with a clinical diagnosis of HF rather than meeting Framingham criteria. Of the 2,493 patients with a clinical HF diagnosis, 1,463 (59%) were identified as HFpEF and 1,030

(41%) were identified as HFREF. The same computable phenotypes evaluated in the Framingham-defined HF cohort were also evaluated in the clinically-defined HF cohort (Table 4). One in-patient diagnosis of ICD-9 428.3X or ICD-10 I50.3X had a lower sensitivity of 40% and NPV of 51% while specificity and PPV were similar to that of the Framingham-defined HF cohort. Similar to the Framingham-defined cohort, requiring either one in-patient or two out-patient diagnoses of 428.3X/I50.3X increased the sensitivity of the algorithm to 44% while the other measures were consistent. The addition of one BNP/NT-proBNP lab code to one in-patient or two out-patient codes of 428.3X/I50.3X reduced the sensitivity to 30% while the specificity

**TABLE 3** Computable phenotypes for HFpEF in patients with HF based on one or more instances of code ICD-9 428/ICD-10 I50<sup>a</sup> (gold standard)

Computable Phenotype	N meeting criteria	PPV % (95% CI)
Codes only		
1 IP diagnosis of 428.3X	1,289	37.1 (34.5, 39.7)
1 IP or 2 OP diagnosis of 428.3X	1,398	36.8 (34.3, 39.4)
1 IP diagnosis of 428.31 or 428.33	661	43.0 (39.2, 46.7)
1 IP or 2 OP diagnosis of 428.31 or 428.33	710	41.8 (38.2, 45.5)
1 IP diagnosis of 428.0, 428.9, or 428.3X	2,780	29.2 (27.5, 30.9)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.3X	3,127	29.1 (27.5, 30.7)
1 IP diagnosis of 428.0, 428.9, 428.31, or 428.33	2,593	29.4 (27.6, 31.1)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.31 or 428.33	2,964	29.0 (27.4, 30.6)
Codes + BNP/NT-proBNP		
1 IP diagnosis of 428.3X and 1 BNP/NT-proBNP lab code	709	42.9 (39.2, 46.5)
1 IP or 2 OP diagnosis of 428.3X and 1 BNP/NT-proBNP lab code	766	42.4 (38.9, 45.9)
1 IP diagnosis of 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	401	46.6 (41.8, 51.5)
1 IP or 2 OP diagnosis of 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	426	45.5 (40.8, 50.3)
1 IP diagnosis of 428.0, 428.9, or 428.3X and 1 BNP/NT-proBNP lab code	1,424	35.5 (33.0, 38.0)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.3X and 1 BNP/NT-proBNP lab code	1,568	36.1 (33.7, 38.5)
1 IP diagnosis of 428.0, 428.9, 428.31, or 428.33 and 1 BNP/NT-proBNP lab code	1,339	35.8 (33.2, 38.3)
1 IP or 2 OP diagnosis of 428.0, 428.9 or 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	1,494	36.0 (33.6, 38.4)

Note: ICD codes are shown for Revision 9. Table S1 shows the conversion between ICD-9 and ICD-10.

BNP, B-type natriuretic peptide; CI, confidence interval; ICD, International Classification of Diseases; IP, in-patient; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; OP, out-patient; PPV, positive predictive value.

<sup>a</sup>N = 3,755 patients with heart failure.

increased to 92% (PPV = 84%; NPV = 48%). Including the diagnostic codes of ICD-9 428.0, 428.9, and 428.3X or ICD-10 I50.3X and I50.9 markedly increased the sensitivity while the specificity declined, similar to that observed in the Framingham-defined HF cohort. The computable phenotypes performed similarly on specificity, PPV, and NPV, but sensitivity was slightly higher (range 20.4%-86.4%) in the Framingham-defined HF cohort than in the clinically-defined cohort (range 16.0%-82.8%).

## 4 | DISCUSSION

In this study, we examined a series of claims-based computable phenotypes to identify patients with HFpEF within a linked medical record system. Using widely available claims data measures, we identified computable phenotypes with relatively high specificity and moderate sensitivity and PPV.

To date, very few studies have examined whether HF patients can be identified as having preserved or reduced ejection fraction using claims data. In a population of patients  $\geq 65$  years of age, Desai et al. linked Medicare claims data to electronic health records for two large healthcare provider networks in order to evaluate claims-based models to identify categories of ejection fraction.<sup>14</sup> The primary

computable phenotype identified in the study utilized 35 claims-based variables including demographic measures, diagnostic codes, and medication use, and found 97% sensitivity and 84% PPV for HFpEF, higher than in most of our models which utilized far fewer inputs. However, the population was limited to older adults (average age 77 years) which may have reduced heterogeneity and thus increased sensitivity and PPV. An earlier study attempted to identify the optimal LVEF cut-off between systolic and diastolic heart failure using claims data.<sup>15</sup> Codes used in this study were limited to those for systolic (ICD-9 428.2X) or diastolic heart failure (ICD-9 428.3X). The authors found a PPV of 72% and NPV of 81% for the optimal threshold cut-off for ejection fraction of 43.5%. While our study used the clinical cut-point of 50% to define HFpEF rather than the data-driven 43.5%, the observed PPV value of 72% is still well within the range observed in our study. However, none of our computable phenotypes had NPV values as high as 81%. Our study, though, was not limited to patients with a specific ICD code available for diastolic versus systolic heart failure which makes this comparison difficult as the specific code of 428.2X is often not readily used in the clinical setting.

There are some limitations with this study that should be noted. First, the HF cohort was composed of predominantly white individuals, and thus these results should be replicated in populations with different racial and ethnic compositions. Coding practices also differ

**TABLE 4** Computable phenotypes for HFpEF in a clinically-defined heart failure cohort<sup>a</sup> (gold standard)

Computable Phenotype	N meeting criteria	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
<b>Codes only</b>					
1 IP diagnosis of 428.3X	691	39.9 (37.4, 42.4)	89.6 (87.8, 91.5)	84.5 (81.8, 87.2)	51.2 (48.9, 53.5)
1 IP or 2 OP diagnosis of 428.3X	752	43.7 (41.1, 46.2)	89.0 (87.1, 90.9)	85.0 (82.4, 87.5)	52.7 (50.3, 55.0)
1 IP diagnosis of 428.31 or 428.33	348	20.2 (18.2, 22.3)	95.0 (93.6, 96.3)	85.0 (81.3, 88.8)	45.6 (43.5, 47.7)
1 IP or 2 OP diagnosis of 428.31 or 428.33	367	21.3 (19.2, 23.4)	94.7 (93.3, 96.0)	85.0 (81.4, 88.7)	45.9 (43.7, 48.0)
1 IP diagnosis of 428.0, 428.9, or 428.3X	1,753	70.2 (67.9, 72.5)	29.5 (26.7, 32.3)	58.6 (56.3, 60.9)	41.1 (37.5, 44.6)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.3X	2,116	82.8 (80.8, 84.7)	12.1 (10.1, 14.1)	57.2 (55.1, 59.3)	33.2 (28.4, 37.9)
1 IP diagnosis of 428.0, 428.9, 428.31, or 428.33	1,634	62.5 (60.1, 65.0)	30.2 (27.4, 33.0)	56.0 (53.6, 58.4)	36.2 (33.0, 39.4)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.31 or 428.33	1,985	74.1 (71.9, 76.3)	12.5 (10.5, 14.6)	54.6 (52.4, 56.8)	25.4 (21.6, 29.2)
<b>Codes + BNP/NT-proBNP</b>					
1 IP diagnosis of 428.3X and 1 BNP/NT-proBNP lab code	482	27.6 (25.3, 29.8)	92.3 (90.7, 94.0)	83.6 (80.3, 86.9)	47.3 (45.1, 49.5)
1 IP or 2 OP diagnosis of 428.3X and 1 BNP/NT-proBNP lab code	525	30.1 (27.8, 32.5)	91.8 (90.2, 93.5)	84.0 (80.9, 87.1)	48.1 (45.9, 50.3)
1 IP diagnosis of 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	277	16.0 (14.1, 17.9)	95.8 (94.6, 97.1)	84.5 (80.2, 88.7)	44.5 (42.5, 46.6)
1 IP or 2 OP diagnosis of 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	291	16.9 (15.0, 18.8)	95.7 (94.5, 97.0)	84.9 (80.8, 89.0)	44.8 (42.7, 46.9)
1 IP diagnosis of 428.0, 428.9, or 428.3X and 1 BNP/NT-proBNP lab code	1,110	46.3 (43.7, 48.8)	58.0 (55.0, 61.0)	61.0 (58.1, 63.9)	43.2 (40.6, 45.8)
1 IP or 2 OP diagnosis of 428.0, 428.9, or 428.3X and 1 BNP/NT-proBNP lab code	1,317	54.0 (51.4, 56.6)	48.8 (45.8, 51.9)	60.0 (57.3, 62.6)	42.8 (39.9, 45.6)
1 IP diagnosis of 428.0, 428.9, 428.31, or 428.33 and 1 BNP/NT-proBNP lab code	1,046	42.2 (39.6, 44.7)	58.4 (55.3, 61.4)	59.0 (56.0, 62.0)	41.5 (39.0, 44.1)
1 IP or 2 OP diagnosis of 428.0, 428.9 or 428.31 or 428.33 and 1 BNP/NT-proBNP lab code	1,246	49.3 (46.7, 51.8)	49.0 (46.0, 52.1)	57.9 (55.1, 60.6)	40.5 (37.8, 43.2)

Note: ICD codes are shown for Revision 9. Table S1 shows the conversion between ICD-9 and ICD-10.

BNP, B-type natriuretic peptide; CI, confidence interval; IP, in-patient; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; NT-proBNP, N-terminal pro B-type natriuretic peptide; OP, out-patient; PPV, positive predictive value.

<sup>a</sup>N = 2,493 patients with heart failure; 1,463 patients with HFpEF

across institutions which is a limitation of developing algorithms in one population and applying in other populations. In addition, some of the data elements used in these algorithms may not be available across all administrative data, and almost certainly the starting point for defining the population of patients with Framingham-validated HF will not be widely available. Our analyses considering all patients with HF diagnosis codes and our sensitivity analysis using clinically-defined HF patients demonstrate to some degree the extent of this limitation, but results will likely vary across different data systems. Finally, the completeness and depth of data availability and accuracy in ascertaining incident HF may differ across databases,

which may result in differences in the performance of the algorithms. However, it should be noted that a major strength of this study is that the gold standard was manually validated HF which is key to the development of computable phenotypes.

Overall, these results demonstrate that widely available elements in claims data can be utilized to identify patients with HFpEF. The computable phenotypes presented here offer acceptable specificity and PPV with moderate sensitivity, indicating that these definitions could be used to identify HFpEF patients for further studies in administrative databases. Selection of a specific computable phenotype should be based on the research question at hand and on the appropriate

balance of sensitivity and specificity to answer that question. Work derived from such studies will ultimately be key to the development of targeted therapies for this population. More broadly, these results are informative for methodology that can be used to identify patients with other complex conditions using administrative databases.

## DISCLOSURES

Akeem Yusuf is an employee and stockholder of Amgen; Alanna M. Chamberlain is a coinvestigator on the REP; Sarah S. Cohen and Naimisha Movva are employees of EpidStrategies and received research contracts from Amgen, Inc for the conduct of this study.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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