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Real-World Evidence in Heart Failure: Data Quality and Evidence Validity

Short title: Real-World Evidence in Heart Failure

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Abstract

Objective: Quantitatively evaluate the quality of data underlying real-world evidence (RWE) in heart failure (HF).

Design: Retrospective comparison of accuracy in identifying HF patients and phenotypic information was made using traditional (i.e., structured query language applied to structured EHR data) and advanced (i.e., AI applied to unstructured EHR data) RWE approaches. The performance of each approach was measured by the harmonic mean of precision and recall (F1 score) using manual annotation of medical records as a reference standard.

Setting: EHR data from a large academic healthcare system in North America between 2015 and 2019, with an expected catchment of approximately 500,000 patients.

Population: 4288 encounters for 1155 patients aged 18 to 85 years, with 472 patients identified as having HF.

Outcome measures: HF and associated concepts, such as comorbidities, left ventricular ejection fraction, and selected medications.

Results: The average F1 scores across 19 HF-specific concepts were 49.0% and 94.1% for the traditional and advanced approaches, respectively (P<0.001 for all concepts with available data). The absolute difference in F_1 score between approaches was 45.1% (98.1% relative increase in F_1 score using the advanced approach). The advanced approach achieved superior F1 scores for HF presence, phenotype, and associated comorbidities. Some phenotypes, such as HFpEF, revealed dramatic differences in extraction accuracy based on technology applied, with a 4.9% F_1 score when using natural language processing (NLP) alone and a 91.0% F_1 score when using NLP plus AI-based inference.

Conclusions: A traditional RWE generation approach resulted in low data quality in HF patients. While an advanced approach demonstrated high accuracy, the results varied dramatically based on extraction techniques. For future studies, advanced approaches and accuracy measurement may be required to ensure data are fit-for-purpose.

Strengths and limitations of this study

- Using RWE for HF patients requires demonstrating that the data source and technologies result in accurate data.
- Natural language processing alone lacked context from the longitudinal record, limiting phenotype identification and study validity.
- Findings suggest that advanced methods can enable high-validity RWE for heart failure patients.
- The use of data from a single healthcare system may limit generalizability to other populations.

INTRODUCTION

Heart failure (HF) is a major public health problem with significant associated morbidity, mortality, and cost.[1,2] Despite the availability of novel drugs and devices, morbidity and mortality in HF rivals many malignancies, with a 5-year survival rate as low as 50%.[3-8] Randomized controlled trials (RCTs) have traditionally been used to assess the safety and efficacy of new therapies and represent a cornerstone for regulatory approval. However, RCTs are frequently conducted in highly selected populations, typically younger, healthier, and less diverse than patients treated in clinical practice. Furthermore, such trials often include patients with an established HF diagnosis, receiving guideline-directed medical therapy at tertiary centers, and may not represent the broader HF population. In contrast, registry data usually offers additional insights into more inclusive populations. Even with this, there is potential bias based on inclusion and exclusion criteria. Because HF is a clinically heterogeneous syndrome with numerous etiologies and phenotypes, studying this population can be particularly difficult.

Real-world evidence (RWE) has held promise as a potential means to assess therapeutic benefit outside of clinical trials, with sufficient power to characterize therapeutic impact in HF subgroups. Accordingly, RWE can complement RCTs, extending the findings to patient populations that may have been excluded from or insufficiently enrolled in pivotal trials. To accelerate these and similar precision medicine goals, the 21st Century Cures Act was passed in 2016, which required the United States Food and Drug Administration (FDA) to develop guidance supporting the use of

RWE in new drug indications and post-marketing surveillance.[9] In addition, payors have increasingly utilized RWE to inform reimbursement decisions and are increasingly demanding credible evidence.[10]

Not surprisingly, the quality of RWE hinges on how well real-world data are collected, processed[11], and used to inform study questions. Such is the case in HF, where accurate identification of patients in administrative and other structured data sets is an ongoing focus.[12-14] Artificial intelligence (AI) applied to unstructured data represents a novel method of analyzing the electronic health record (EHR). Because of the importance of data reliability in RWE and the potential to use unstructured data to achieve data enrichment[15], we sought to better understand differences in accuracy between traditional RWE methods and advanced AI approaches for a range of HF-specific data elements.

METHODS

Varied data sources and applied technologies were used to assess data reliability in patients with risk factors for HF. Leveraging manual chart abstraction as the reference standard, comparisons were made between the two methods. The first method used structured EHR data (e.g., diagnosis codes and problem lists) and standard query techniques, defined as the 'traditional approach'. The second used unstructured EHR data (e.g., narratives from primary care and specialty notes) and AI techniques, described as the 'advanced approach' (Figure 1). The primary objective was measurement of the accuracy of identified HF-specific elements using traditional and advanced approaches. We hypothesized that the advanced approach would better

identify key HF-specific elements than the traditional approach. Data were deidentified before study initiation, and the study was determined not to be human subjects research. Both natural language processing (NLP) and machine-learned inference technologies used in the advanced approach were provided by Verantos, Inc. (Menlo Park, CA, USA). The core of AI is a deterministic NLP layer. This layer is built on top of the GATE NLP architecture.[16] The architecture is used to construct a flexible pipeline for processing incoming text against English language syntactical rules augmented with a lexicon based on a clinical vocabulary. The AI-based inference was applied during data processing. Millions of machine-learned and manually curated associations enable disambiguation and identification of clinically relevant concepts. As an example of AI-based inference, a patient with HF on the problem list and a narrative encounter describing “EF 60%” would not be interpreted by NLP as having HF with preserved ejection fraction (HFpEF) since the text does not have sufficient information to identify this condition. On the other hand, AI-based inference would infer HFpEF based on disparate information in the record.

EHR Data Source and Processing

EHR data from primary care encounters between 2011 and 2018 were deidentified and securely transferred to a cloud-based server for analysis. The data set consisted of both structured data (e.g., medical conditions, procedures performed, medications, and problem lists) and unstructured data (e.g., narrative notes from primary care providers and specialists, telephone visits, and other narrative text) (Figure 1).

As the study aimed to test the accuracy of different RWE approaches and not treatment effectiveness, the cohort was enriched for patients with suspected HF based on comorbidities and medications. Specifically, the following filters were applied: records containing both narrative and structured components; narrative length 1,000 characters or more; and at least one of the following problems or medications in structured or unstructured data: myocardial infarction, congestive heart failure, or carvedilol.

A prespecified set of clinical concepts pertinent to patients with HF was extracted using traditional and advanced techniques (Table 1). Problem lists were mapped to Systematized Nomenclature of Medicine (SNOMED) ontology, and unadjudicated claims were mapped to ICD-10 codes. Standard sets of individual codes were used to represent each concept. With the advanced approach, inference incorporating pattern recognition was utilized to identify potentially missing or ignored concepts within the text (e.g., HF being likely in patients with dyspnea and pitting edema on a diuretic). Specifically, no narrative coding took place before the AI algorithm was used; instead, it was applied directly to the narrative text and then mapped by the algorithm to the SNOMED ontology. Next, manual chart abstraction using the same SNOMED code set

was used as a reference to assess the accuracy of the coding by the AI algorithm. Engineers were blinded to validation data and its corresponding chart abstraction.

Study End Points and Statistical Analysis

The primary endpoint was the F_1 score for traditional and advanced approaches. The F_1 score is an accuracy measure that combines recall and precision; more specifically, it is the weighted harmonic mean of these two measures. Secondary endpoints were recall (i.e., the proportion of patients correctly identified as having the condition, akin to sensitivity) and precision (i.e., the proportion of patients with HF and its subtypes correctly identified divided by the total number of patients identified in each cohort akin to positive predictive value)[17,18] for the traditional and advanced approaches. The reference standard used to evaluate accuracy of the traditional and advanced approaches was manual chart abstraction. For each encounter, two independent clinical annotators labeled each concept and all metadata for that concept. Annotators were blinded to each other's annotations, and inter-rater agreement was measured by Cohen's kappa score. Further description of the reference standard methodology is provided in the Supplemental Material. Results were summarized using descriptive statistics, and percentages were calculated for categorical variables. Differences in F_1 scores between traditional and advanced approaches were analyzed using the chi-square test; associated *P*-values were reported.

RESULTS

A total of 4288 encounters for 1155 patients were examined, of which 472 patients with HF were identified. Of these, 382 had HF with reduced ejection fraction (HFrEF), 35 had HF with mildly reduced ejection fraction (HFmrEF), and 55 had HF with preserved ejection fraction (HFpEF). The reference standard Cohen's kappa score was 0.95, suggesting high validity.

Supplementary Table 1 reports the F_1 score, recall, and precision results achieved with both approaches. Figure 2 graphically presents F_1 scores for HF diagnoses and Figure 3 includes F_1 scores for symptoms, medications, and comorbid conditions. Overall, accuracy was significantly greater for the advanced approach (AI applied to unstructured EHR data) than for the traditional approach (structured query language applied to structured EHR data) (Supplementary Table 1; Figure 2; Figure 3), with an absolute difference of 45.1%.

With the traditional approach, recall for any HF diagnosis was 46.9% (i.e., 53.1% of patients with HF were missed entirely) and precision was 95.4%, resulting in an F_1 score of 62.9% (P<0.001). In contrast, with the advanced approach, recall for any HF diagnosis was 96.0% and precision was 94.7%, resulting in an F_1-score of 95.3% (P<0.001 when F_1 scores for the two approaches were compared) (Supplementary Table 1; Figure 2). Among HF phenotypes, recall with the advanced approach was highest with HFrEF, followed by HFpEF and HFmrEF; precision was 100% for all phenotypes. With the traditional approach, F_1 scores could not be calculated for HFrEF, HFmrEF, and HFpEF because only less granular HF codes were used (Supplementary Table 1).

Accuracy in identifying left ventricular ejection fraction (LVEF) was similarly high with the advanced approach, with an F_1 score of 96.7%. Data could not be extracted for LVEF with the traditional approach because no such codes were available within the EHR, nor did a mechanism to encode LVEF within the problem list or unadjudicated claims exist (Supplementary Table 1; Figure 2).

Accurate identification of HF symptoms was greater with the advanced approach (*P*<0.001) (Supplementary Table 1; Figure 3A). Whereas identification of commonly prescribed HF medications was high with both approaches (Supplementary Table 1; Figure 3B), identification of cardiovascular comorbidities was higher in all cases with the advanced approach (*P*<0.001) (Supplementary Table 1; Figure 3C).

Data concept extraction with the advanced approach greatly depended upon the technology used. For example, NLP, which ends at the sentence boundary, was only able to identify HFpEF with an F_1 score of 4.9% because "HFpEF" or "heart failure with preserved ejection fraction" was rarely written. Conversely, inference, which can find related items from the longitudinal record, was able to identify both "HF" and "normal ejection fraction" as separate annotations for HFpEF with an F_1-score of 91.0% (Supplementary Table 1; Figure 2).

DISCUSSION

The utilization of RWE has grown substantially in recent years, driven in part by its perceived value by clinicians, regulators, and payors. As RWE is increasingly used to refine care standards through clinical, regulatory, and reimbursement pathways, its

accuracy has come under increased scrutiny. This is particularly important for complex medical conditions, such as HF. Accordingly, we used chart abstraction to quantitatively evaluate traditional and advanced approaches to define HF-specific data elements. This allowed us to rigorously evaluate whether commonly used techniques are sufficiently accurate for observational studies, comparative effectiveness research, and post-approval safety studies.

In this study, we demonstrated that: 1) the use of an advanced, AI-based approach consistently identified HF phenotypes (i.e., HFrEF, HFmrEF, and HFpEF) more accurately than a traditional approach; 2) common HF symptoms and comorbid conditions were consistently and accurately identified using an advanced approach; and 3) medications for HF were accurately identified using both advanced and traditional approaches. While studies have previously leveraged an AI-based approach to identify patients with HF,[19-22] our study highlights the discrepancy between traditional EHR query methods and an AI-based approach standardized against a manual reference. Given that the accuracy of the data set and appropriateness of the applied technology are not tested in many RWE studies, there is a high potential for error.[23,24] The current findings highlight this while also reinforcing the impact that specific AI technologies (e.g., NLP vs. NLP plus inference) can have on phenotype generation and study validity.

Accurate phenotyping is paramount in any RWE study that includes HF patients. With varying etiologies and multiple phenotypes, HF is a clinically diverse syndrome, with outcomes that may vary between subgroups. In addition, HF patients may have different

trajectories, highlighting some of the limitations of using structured data. For example, LVEF may fluctuate throughout a patient's disease course, with some patients experiencing recovery of their LVEF with the use of guideline-directed medical therapy. Accordingly, accurate phenotyping of HF patients usually requires the incorporation of data that crosses clinical encounters. In addition, although symptoms are an essential reflection of clinical status, they are poorly captured in structured data. Suboptimal recognition of comorbidities like valvular heart disease can also impact disease trajectory and risk for future cardiovascular events.

Our findings represent an important advance for RWE studies that include HF patients. Notably, the only way to ascertain comparative accuracy between data sources and technologies in a domain is to test it. Accuracy consists of both recall and precision, and in the case of many health conditions, recall can fall below 50% when one relies solely upon the problem list.[25,26]

In the current study, we were able to focus on both precision and recall through use of the F_1 score. Despite availability of SNOMED codes for HFrEF and HFpEF, along with a similar code for HFmrEF, such codes were rarely included. Documentation of a HF code using structured data was only found 46.9% of the time when there was clear evidence of HF in the chart. We postulate that the low accuracy of structured data for disease subtypes at least partially relates to how the data is likely to be used. A physician may look within notes to understand HF subtype. Information entered into problem lists and claims may be more to provide a high-level understanding of disease burden. Granular billing codes may be a low priority for physicians if claims are reimbursed with the non-

granular HF code. Furthermore, because addition of diagnoses to the problem list is not a requirement, the problem list may not be specific or updated. This contrasts with clinical notes, where detailed documentation is usually performed to communicate a care plan and is a medical-legal requirement.

When low-accuracy and non-granular data are utilized, there are several potential consequences. Missingness can result in selection bias, particularly if sicker patients have more frequent encounters, higher rates of specialty care, and more complete documentation. Depending on the study question, use of structured data alone to identify certain subgroups may be inadvisable, since these data have a low recall for specific clinical concepts such as ST-elevation myocardial infarction and HFrEF.[27] Even advanced approaches (e.g., NLP) may result in poor accuracy, as illustrated in this study, where HFpEF required AI-based inference for proper identification. Collectively, this highlights that not all data sources and technologies are the same; therefore, accuracy testing may be required for rigorous RWE generation. Furthermore, given the growth in RWE to support new drug indications, post-marketing surveillance, and decision-making regarding reimbursement, such inaccuracies may have a profound impact on large numbers of patients.

Even though standard dictionaries and clinical terms related to cardiovascular medicine were used, there is a need to test the two analytic methods using different EHRs across a broader set of community and referral practices. With numerous EHRs available and practitioner-to-practitioner variability in documentation accuracy, efforts like the one described here represent an important means of strengthening data quality.

Importantly, this study has several limitations. First, we used data from a single health system, with results that may not be generalizable to other populations. Second, the study protocol required the selection of patients enriched with cardiovascular disease to make the study feasible, with manual chart abstraction conducted to ensure the accuracy of results. While selection criteria were applied to both structured and unstructured data, it is possible that this could have biased results in a way that favored structured data since a larger proportion of patients with HF on the problem list may have been included than if the sample had been created randomly. In addition, the specific filters used likely led to a higher-than-expected proportion of HFrEF patients (compared to those with HFmrEF and HFpEF). Second, the study required laborious manual annotation of thousands of records. Such a sample size is adequate for high-prevalence conditions, but would likely require adjustment for low-prevalence conditions with low concept occurrence rates. Finally, the study did not include clinical outcome assessment; rather, it was designed to compare data sources and processing methods.

Conclusion

As RWE is increasingly used to analyze patient subgroups, inform clinical decision-making, and influence regulatory and reimbursement decisions, data reliability and evidence validity are of critical importance. Use of a traditional approach was associated with low data accuracy. While much greater accuracy was observed with AI-based methods, it depended upon the technology utilized. These findings highlight the importance of using data fit-for-purpose to the research question posed. In addition, they suggest that accuracy testing should be part of any EHR-based study that includes

HF patients. Finally, unstructured data and a technology-based approach to data extraction may be required in some studies to achieve sufficient accuracy, depending upon the clinical assertion being tested.

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Contributors

ARG and DR drafted the manuscript. ARG, KLM, RED, DR, and TJG critically reviewed the manuscript. ARG, RED, DR, and TJG provided clinical insight.

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Competing interests

KLM and RED are employees and stockholders of Amgen Inc. DR is an employee and stockholder of Verantos, Inc. ARG has received research support from Abbott and TJG has no competing interests to declare.

Ethics Approval

This study has been independently reviewed and accepted for exemption in accordance with 45 CFR 46.101(b)(4ii).

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data are available.

Supplemental Materials

Supplemental Methods

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Table 1. Prespecified heart failure–specific concepts extracted from the electronic health record.

High Priority Conditions	Comorbidities	Symptoms	Findings	Medications
Congestive HF HF with reduced EF HF with mid-range EF HF with preserved EF	Myocardial infarction Atrial fibrillation Aortic regurgitation Mitral regurgitation Tricuspid regurgitation	Angina Chest pain Dyspnea Fatigue Palpitations	LVEF	Carvedilol Lisinopril Metoprolol Furosemide

HF, heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction.

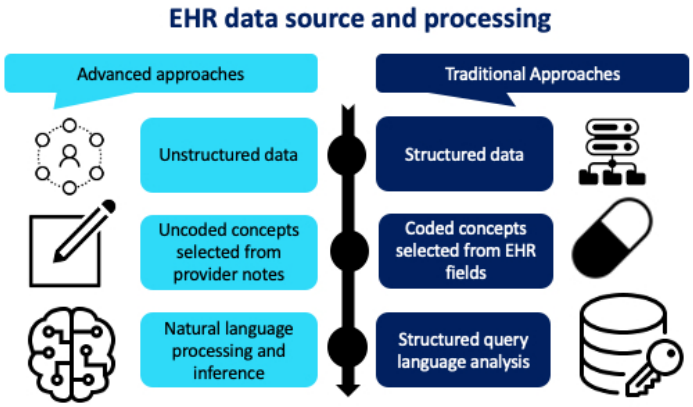

Figure 1. Comparison of traditional and advanced real-world evidence approaches. EHR, electronic health record.

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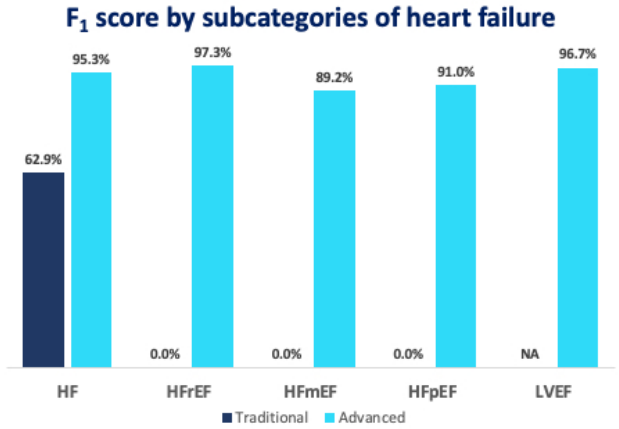

Figure 2. F1 scores for heart failure diagnoses. *F1-score could not be calculated due to lack of data for precision. †Structured data recall is not applicable for ejection fraction because no code was available within the problem list. HF, heart failure; HFmrEF, heart failure with mildly-reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 0% reflects a measured value and indicates the availability of the diagnosis code in the EHR dropdown versus N/A, not applicable, which refers to a diagnosis without available code in the relevant codeset.

338x190mm (54 x 54 DPI)

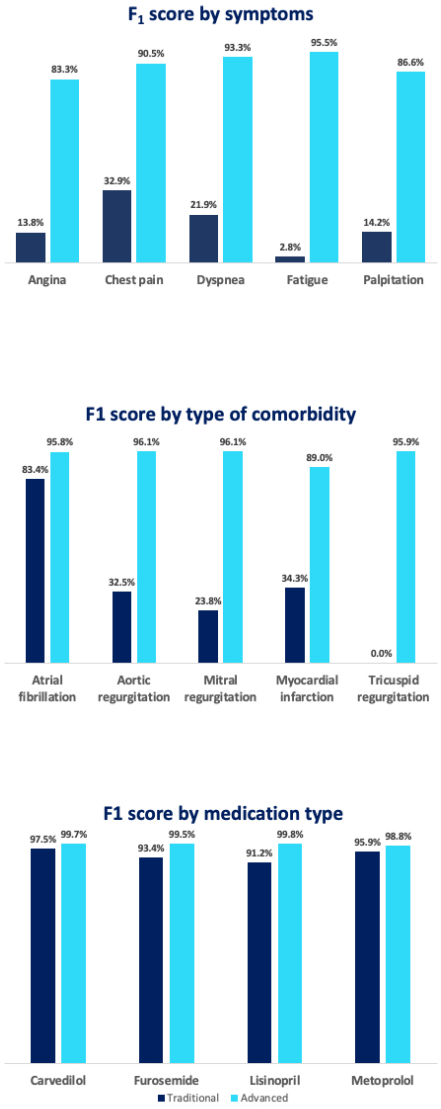

Figure 3. F1 scores for (A) symptoms, (B) medications, and (C) comorbid conditions. *F1 score could not be calculated due to a lack of data for precision. N/A, not applicable.

254x428mm (72 x 72 DPI)

Supplementary Table 1. Cohort identification of heart failure diagnoses, left ventricular ejection fraction, heart failure medications, symptoms, and comorbid cardiovascular conditions

	Traditional approach			Advanced approach					
	Recall, %	Precision, %	F_1 score, %	Recall, %	Precision, %	F_1 score, %	Concept occurrence	Encounter occurrence	*P*-value
HF diagnosis									
HF	46.9	95.4	62.9	96.0	94.7	95.3	265	155	<0.001
HFrEF	0	N/A*	N/A†	94.8	100.0	97.3	382	124	N/A§
HFmrEF	0	N/A*	N/A†	80.4	100.0	89.2	62	35	N/A§
HFpEF	0	N/A*	N/A†	83.5	100.0	91.0	103	55	N/A§
LVEF	N/A‡	N/A‡	N/A‡	93.7	100.0	96.7	677	238	N/A§
HF medications									
Carvedilol	95.1	100.0	97.5	99.7	99.7	99.7	407	141	<0.001
Furosemide	87.7	100.0	93.4	99.3	99.8	99.5	1572	371	0.116
Lisinopril	83.9	100.0	91.2	99.7	99.9	99.8	1068	386	<0.001
Metoprolol	92.2	100.0	95.9	97.7	100.0	98.8	1370	397	<0.001
Symptoms									

Angina	7.8	60.0	13.8	84.4	82.3	83.3	265	155	<0.001
Chest pain	21.4	70.8	32.9	95.4	86.1	90.5	2332	756	<0.001
Dyspnea	12.7	78.2	21.9	94.7	92.0	93.3	4474	832	<0.001
Fatigue	1.4	75.0	2.8	96.5	94.5	95.5	1711	371	<0.001
Palpitation	8.2	52.9	14.2	90.9	82.6	86.6	896	493	<0.001
Comorbid cardiovascular conditions									
Atrial fibrillation	72.2	98.7	83.4	93.0	98.7	95.8	1214	222	<0.001
Aortic regurgitation	19.4	100.0	32.5	92.5	100.0	96.1	153	90	<0.001
Mitral regurgitation	13.5	97.1	23.8	92.8	99.6	96.1	483	185	<0.001
Myocardial infarction	21.1	90.9	34.3	95.5	83.4	89.0	1220	578	<0.001
Tricuspid regurgitation	0	N/A*	N/A†	92.2	100.0	95.9	162	78	N/A§

*These elements did not occur when using the traditional approach. †F_1 scores could not be calculated due to a lack of data for precision. ‡Structured data recall is not applicable for ejection fraction because there was no code available within the problem list. §*P*-value could not be calculated due to the unavailability of F_1 scores for the traditional approach. *P*-values are derived from the chi-square test.

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; N/A, not applicable.

SUPPLEMENTAL MATERIAL

Reference Standard

Traditional and advanced approaches were tested against a reference standard for physician encounters. The reference standard consisted of an independent review, with manual annotation of relevant HF-specific features, including 19 unique HF-specific concepts. For each encounter, two independent clinical annotators labeled each concept and all metadata for that concept. For example, an annotator might mark the text "DOE over last month" as dyspnea on exertion, experienced = true, current = true, relative date = 1 month. Concept occurrence was defined as the sum of all concept occurrences, allowing for multiple occurrences per encounter. Encounter occurrence was defined as the number of encounters with at least one occurrence of the concept.

Given that many concepts, such as LVEF are specific to a point in time, concepts were tested at the encounter level. For example, if a patient had an LVEF of 30% in an encounter, the data extraction would only be annotated as correct if it identified "LVEF 30%" in that specific encounter. This reference standard was used to determine accuracy of automated extracted data and structured data. Specifically, this reference standard was used to calculate recall and precision for these individual features for traditional and advanced approaches.

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A Comparison of Traditional and Artificial-Intelligence Based Heart Failure Phenotyping to Enable Real-World Evidence

Short title: Real-World Evidence in Heart Failure

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Abstract

Objective: Quantitatively evaluate the quality of data underlying real-world evidence (RWE) in heart failure (HF).

Design: Retrospective comparison of accuracy in identifying HF patients and phenotypic information was made using traditional (i.e., structured query language applied to structured EHR data) and advanced (i.e., AI applied to unstructured EHR data) RWE approaches. The performance of each approach was measured by the harmonic mean of precision and recall (F1 score) using manual annotation of medical records as a reference standard.

Setting: EHR data from a large academic healthcare system in North America between 2015 and 2019, with an expected catchment of approximately 500,000 patients.

Population: 4288 encounters for 1155 patients aged 18 to 85 years, with 472 patients identified as having HF.

Outcome measures: HF and associated concepts, such as comorbidities, left ventricular ejection fraction, and selected medications.

Results: The average F1 scores across 19 HF-specific concepts were 49.0% and 94.1% for the traditional and advanced approaches, respectively (P<0.001 for all concepts with available data). The absolute difference in F_1 score between approaches was 45.1% (98.1% relative increase in F_1 score using the advanced approach). The advanced approach achieved superior F1 scores for HF presence, phenotype, and associated comorbidities. Some phenotypes, such as HFpEF, revealed dramatic differences in extraction accuracy based on technology applied, with a 4.9% F_1 score when using natural language processing (NLP) alone and a 91.0% F_1 score when using NLP plus AI-based inference.

Conclusions: A traditional RWE generation approach resulted in low data quality in HF patients. While an advanced approach demonstrated high accuracy, the results varied dramatically based on extraction techniques. For future studies, advanced approaches and accuracy measurement may be required to ensure data are fit-for-purpose.

Strengths and limitations of this study

- Using RWE for HF patients requires demonstrating that the data source and technologies result in accurate data.
- Natural language processing alone lacked context from the longitudinal record, limiting phenotype identification and study validity.
- Findings suggest that advanced methods can enable high-validity RWE for heart failure patients.
- The use of data from a single healthcare system may limit generalizability to other populations.

INTRODUCTION

Heart failure (HF) is a major public health problem with significant associated morbidity, mortality, and cost.[1,2] Despite the availability of novel drugs and devices, morbidity and mortality in HF rivals many malignancies, with a 5-year survival rate as low as 50%.[3-8] Randomized controlled trials (RCTs) have traditionally been used to assess the safety and efficacy of new therapies and represent a cornerstone for regulatory approval. However, RCTs are frequently conducted in highly selected populations, typically younger, healthier, and less diverse than patients treated in clinical practice. Furthermore, such trials often include patients with an established HF diagnosis, receiving guideline-directed medical therapy at tertiary centers, and may not represent the broader HF population. Because HF is a clinically heterogeneous syndrome with numerous etiologies and phenotypes, studying this population can be particularly difficult.

Real-world evidence (RWE) has held promise as a potential means to assess therapeutic benefit outside of clinical trials, with sufficient power to characterize therapeutic impact in HF subgroups. Accordingly, RWE can complement RCTs, extending the findings to patient populations that may have been excluded from or insufficiently enrolled in pivotal trials. To accelerate these and similar precision medicine goals, the 21st Century Cures Act was passed in 2016, which required the United States Food and Drug Administration (FDA) to develop guidance supporting the use of RWE in new drug indications and post-marketing surveillance.[9] In addition, payors have increasingly utilized RWE to inform reimbursement decisions and are increasingly demanding credible evidence.[10]

Not surprisingly, the quality of RWE hinges on how well real-world data are collected, processed[11], and used to inform study questions. Such is the case in HF, where accurate identification of patients in administrative and other structured data sets is an ongoing focus.[12-14] Traditional methods of identifying HF patients rely on querying diagnosis codes and structured data in the electronic health record (EHR) or medical claims. Conversely, artificial intelligence (AI) applied to unstructured data represents a novel method of analyzing the medical record. Because of the importance of data reliability in RWE and the potential to use unstructured data to achieve data enrichment[15], we sought to compare the accuracy achieved by traditional RWE methods versus advanced AI approaches in identifying a range of HF-specific data elements from the medical record.

METHODS

The study design is outlined in Figure 1. Varied data sources and applied technologies were used to assess data reliability in patients with risk factors for HF. Leveraging manual chart abstraction as the reference standard, comparisons were made between the two methods. The first method used structured EHR data (e.g., diagnosis codes and problem lists) and standard query techniques, defined as the 'traditional approach'. The second used unstructured EHR data (e.g., narratives from primary care and specialty notes) and AI techniques, described as the 'advanced approach' (Figure 1). The primary objective was measurement of the accuracy of identified HF-specific elements using traditional and advanced approaches. We hypothesized that the advanced approach would better identify key HF-specific elements than the traditional approach. Data were deidentified before study initiation, and the study was determined not to be human subjects research. Both natural language processing (NLP) and machine-learned inference technologies

used in the advanced approach were provided by Verantos, Inc. (Menlo Park, CA, USA). The core of AI is a deterministic NLP layer. This layer is built on top of the GATE NLP architecture.[16] The architecture is used to construct a flexible pipeline for processing incoming text against English language syntactical rules augmented with a lexicon based on a clinical vocabulary. The AI-based inference was applied during data processing. Millions of machine-learned and manually curated associations enable disambiguation and identification of clinically relevant concepts. As an example of AI-based inference, a patient with HF on the problem list and a narrative encounter describing "EF 60%" would not be interpreted by NLP as having HF with preserved ejection fraction (HFpEF) since the text does not have sufficient information to identify this condition. On the other hand, AI-based inference would infer HFpEF based on disparate information in the record.

EHR Data Source and Processing

EHR data from primary care encounters between 2011 and 2018 were deidentified and securely transferred to a cloud-based server for analysis. The data set consisted of both structured data (e.g., medical conditions, procedures performed, medications, and problem lists) and unstructured data (e.g., narrative notes from primary care providers and specialists, telephone visits, and other narrative text) (Figure 2).

As the study aimed to test the accuracy of different RWE approaches and not treatment effectiveness, the cohort was enriched for patients with suspected HF based on comorbidities and medications. Specifically, the following filters were applied: records containing both narrative and structured components; narrative length 1,000 characters or more; and at least one of the

following problems or medications in structured or unstructured data: myocardial infarction, congestive heart failure, or carvedilol (Figure 1).

A prespecified set of clinical concepts pertinent to patients with HF was extracted using traditional and advanced techniques (Table 1). Problem lists were mapped to Systematized Nomenclature of Medicine (SNOMED) ontology, and unadjudicated claims were mapped to ICD-10 codes. Standard sets of individual codes were used to represent each concept. With the advanced approach, inference incorporating pattern recognition was utilized to identify potentially missing or ignored concepts within the text (e.g., HF being likely in patients with dyspnea and pitting edema on a diuretic). Specifically, no narrative coding took place before the AI algorithm was used; instead, it was applied directly to the narrative text and then mapped by the algorithm to the SNOMED ontology. Next, manual chart abstraction using the same SNOMED code set was used as a reference to assess the accuracy of the coding by the AI algorithm. Engineers were blinded to validation data and its corresponding chart abstraction.

Study End Points and Statistical Analysis

The primary endpoint was the F_1 score for traditional and advanced approaches. The F_1 score is an accuracy measure that combines recall and precision; more specifically, it is the weighted harmonic mean of these two measures. Secondary endpoints were recall (i.e., the proportion of patients correctly identified as having the condition, akin to sensitivity) and precision (i.e., the proportion of patients with HF and its subtypes correctly identified divided by the total number of patients identified in each cohort akin to positive predictive value)[17,18] for the traditional and advanced approaches. The reference standard used to evaluate accuracy of the traditional and advanced approaches was manual chart abstraction. For each encounter, two independent clinical

annotators labeled each concept and all metadata for that concept. Annotators were blinded to each other's annotations, and inter-rater agreement was measured by Cohen's kappa score. Further description of the reference standard methodology is provided in the Supplemental Material. Results were summarized using descriptive statistics, and percentages were calculated for categorical variables. Differences in F_1 scores between traditional and advanced approaches were analyzed using the chi-square test; associated *P*-values were reported.

Patient and Public Involvement

Data were deidentified before study initiation, and the study was determined not to be human subjects research. As a result, no patients were recruited for study participation. The research question and study goal of highlighting methods for improving RWE use were driven by recognition that improvements in use of RWE to inform new drug indications, post-marketing surveillance, and reimbursement decisions would ultimately result in patient benefit.

RESULTS

A total of 4288 encounters for 1155 patients were examined, of which 472 patients with HF were identified. Of these, 382 had HF with reduced ejection fraction (HFrEF), 35 had HF with mildly reduced ejection fraction (HFmrEF), and 55 had HF with preserved ejection fraction (HFpEF). The reference standard Cohen's kappa score was 0.95, suggesting high validity.

Supplementary Table 1 reports the F_1 score, recall, and precision results achieved with both approaches. Figure 3 graphically presents F_1 scores for HF diagnoses and Figure 4 includes F_1 scores for symptoms, medications, and comorbid conditions. Overall, accuracy was significantly greater for the advanced approach (AI applied to unstructured EHR data) than for the traditional

approach (structured query language applied to structured EHR data) (Supplementary Table 1; Figure 3; Figure 4), with an absolute difference of 45.1%.

With the traditional approach, recall for any HF diagnosis was 46.9% (i.e., 53.1% of patients with HF were missed entirely) and precision was 95.4%, resulting in an F_1 score of 62.9% (P<0.001). In contrast, with the advanced approach, recall for any HF diagnosis was 96.0% and precision was 94.7%, resulting in an F_1-score of 95.3% (P<0.001 when F_1 scores for the two approaches were compared) (Supplementary Table 1; Figure 3). Among HF phenotypes, recall with the advanced approach was highest with HFrEF, followed by HFpEF and HFmrEF; precision was 100% for all phenotypes. With the traditional approach, F_1 scores could not be calculated for HFrEF, HFmrEF, and HFpEF because only less granular HF codes were used (Supplementary Table 1).

Accuracy in identifying left ventricular ejection fraction (LVEF) was similarly high with the advanced approach, with an F_1 score of 96.7%. Data could not be extracted for LVEF with the traditional approach because no such codes were available within the EHR, nor did a mechanism to encode LVEF within the problem list or unadjudicated claims exist (Supplementary Table 1; Figure 3).

Accurate identification of HF symptoms was greater with the advanced approach (P<0.001) (Supplementary Table 1; Figure 4A). Whereas identification of commonly prescribed HF medications was high with both approaches (Supplementary Table 1; Figure 4B), identification of cardiovascular comorbidities was higher in all cases with the advanced approach (P<0.001) (Supplementary Table 1; Figure 4C).

Data concept extraction with the advanced approach greatly depended upon the technology used. For example, NLP, which ends at the sentence boundary, was only able to identify HFpEF with an F_1 score of 4.9% because "HFpEF" or "heart failure with preserved ejection fraction" was rarely written. Conversely, inference, which can find related items from the longitudinal record, was able to identify both "HF" and "normal ejection fraction" as separate annotations for HFpEF with an F_1-score of 91.0% (Supplementary Table 1; Figure 3).

DISCUSSION

The utilization of RWE has grown substantially in recent years, driven in part by its perceived value by clinicians, regulators, and payors, particularly in light of the limitations of trial populations.[19] As RWE is increasingly used to refine care standards through clinical, regulatory, and reimbursement pathways, its accuracy has come under increased scrutiny. This is particularly important for complex medical conditions, such as HF.[20] Accordingly, in this analysis, chart abstraction was used to quantitatively evaluate traditional and advanced approaches to define HF-specific data elements. This enabled rigorous evaluation of whether commonly used techniques are sufficiently accurate for observational studies, comparative effectiveness research, and post-approval safety studies.

In this study, 1) the use of an advanced, AI-based approach consistently identified HF phenotypes (i.e., HFrEF, HFmrEF, and HFpEF) more accurately than a traditional approach; 2) common HF symptoms and comorbid conditions were consistently and accurately identified using an advanced approach; and 3) medications for HF were accurately identified using both advanced and traditional approaches. While studies have previously leveraged an AI-based approach to identify patients with HF,[21-24] the findings presented here highlight the discrepancy

between traditional EHR query methods and an AI-based approach standardized against a manual reference. Given that the accuracy of the data set and appropriateness of the applied technology are not tested in many RWE studies, there is a high potential for error.[25-28] The current findings highlight this while also reinforcing the impact that specific AI technologies (e.g., NLP vs. NLP plus inference) can have on phenotype generation and study validity.

Accurate phenotyping is paramount in any RWE study that includes HF patients. With varying etiologies and multiple phenotypes, HF is a clinically diverse syndrome, with outcomes that may vary between and even within subgroups.[29,30] In addition, HF patients may have different trajectories, highlighting some of the limitations of using structured data. For example, LVEF may fluctuate throughout a patient's disease course, with some patients experiencing recovery of their LVEF with the use of guideline-directed medical therapy. Accordingly, accurate phenotyping of HF patients usually requires the incorporation of data that crosses clinical encounters. In addition, although symptoms are an essential reflection of clinical status, they are poorly captured in structured data. Suboptimal recognition of comorbidities like valvular heart disease can also impact disease trajectory and risk for future cardiovascular events.

The findings presented here represent an important advance for RWE studies that include HF patients. Notably, the only way to ascertain comparative accuracy between data sources and technologies in a domain is to test it. Accuracy consists of both recall and precision, and in the case of many health conditions, recall can fall below 50% when one relies solely upon the problem list.[31,32]

In the current study, use of the F_1 score enabled analysis of both precision and recall. Despite availability of SNOMED codes for HFrEF and HFpEF, along with a similar code for HFmrEF,

such codes were rarely included. Documentation of a HF code using structured data was only found 46.9% of the time when there was clear evidence of HF in the chart. The low accuracy of structured data for disease subtypes may, at least partially, relate to how the data is likely to be used. A physician may look within notes to understand HF subtype. Information entered into problem lists and claims may be more to provide a high-level understanding of disease burden. Granular billing codes may be a low priority for physicians if claims are reimbursed with the non-granular HF code. Furthermore, because addition of diagnoses to the problem list is not a requirement, the problem list may not be specific or updated. This contrasts with clinical notes, where detailed documentation is usually performed to communicate a care plan and is a medical-legal requirement.

When low-accuracy and non-granular data are utilized, there are several potential consequences. Missingness can result in selection bias, particularly if sicker patients have more frequent encounters, higher rates of specialty care, and more complete documentation. Depending on the study question, use of structured data alone to identify certain subgroups may be inadvisable, since these data have a low recall for specific clinical concepts such as ST-elevation myocardial infarction and HFrEF.[33] Even advanced approaches (e.g., NLP) may result in poor accuracy, as illustrated in this study, where HFpEF required AI-based inference for proper identification. Collectively, this highlights that not all data sources and technologies are the same; therefore, accuracy testing may be required for rigorous RWE generation.[34] Furthermore, given the growth in RWE to support new drug indications, post-marketing surveillance, and decision-making regarding reimbursement, such inaccuracies may have a profound impact on large numbers of patients.

Even though standard dictionaries and clinical terms related to cardiovascular medicine were used, there is a need to test the two analytic methods using different EHRs across a broader set of community and referral practices. With numerous EHRs available and practitioner-to-practitioner variability in documentation accuracy, efforts like the one described here represent an important means of strengthening data quality.

Importantly, this study has several limitations. First, data from a single health system was used and results may not be generalizable to other populations. Second, the study protocol required the selection of patients enriched with cardiovascular disease to make the study feasible, with manual chart abstraction conducted to ensure the accuracy of results. While selection criteria were applied to both structured and unstructured data, it is possible that this could have biased results in a way that favored structured data since a larger proportion of patients with HF on the problem list may have been included than if the sample had been created randomly. In addition, the specific filters used likely led to a higher-than-expected proportion of HFrEF patients (compared to those with HFmrEF and HFpEF). Second, the study required laborious manual annotation of thousands of records. Such a sample size is adequate for high-prevalence conditions, but would likely require adjustment for low-prevalence conditions with low concept occurrence rates. Finally, the study did not include clinical outcome assessment; rather, it was designed to compare data sources and processing methods.

Conclusion

As RWE is increasingly used to analyze patient subgroups, inform clinical decision-making, and influence regulatory and reimbursement decisions, data reliability and evidence validity are of critical importance. Use of a traditional approach was associated with low data accuracy. While

much greater accuracy was observed with AI-based methods, it depended upon the technology utilized. These findings highlight the importance of using data fit-for-purpose to the research question posed. In addition, they suggest that accuracy testing should be part of any EHR-based study that includes HF patients. Finally, unstructured data and a technology-based approach to data extraction may be required in some studies to achieve sufficient accuracy, depending upon the clinical assertion being tested.

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Contributors

ARG and DR drafted the manuscript. ARG, KLM, RED, DR, and TJG critically reviewed the manuscript. ARG, RED, DR, and TJG provided clinical insight.

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Competing interests

KLM and RED are employees and stockholders of Amgen Inc. DR is an employee and stockholder of Verantos, Inc. ARG has received research support from Abbott and TJG has no competing interests to declare.

Ethics Approval

This study has been independently reviewed and accepted for exemption in accordance with 45 CFR 46.101(b)(4ii).

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data are available.

Supplemental Materials

Supplemental Methods

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Table 1. Prespecified heart failure–specific concepts extracted from the electronic health record.

High Priority Conditions	Comorbidities	Symptoms	Findings	Medications
Congestive HF HF with reduced EF HF with mid-range EF HF with preserved EF	Myocardial infarction Atrial fibrillation Aortic regurgitation Mitral regurgitation Tricuspid regurgitation	Angina Chest pain Dyspnea Fatigue Palpitations	LVEF	Carvedilol Lisinopril Metoprolol Furosemide

HF, heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction.

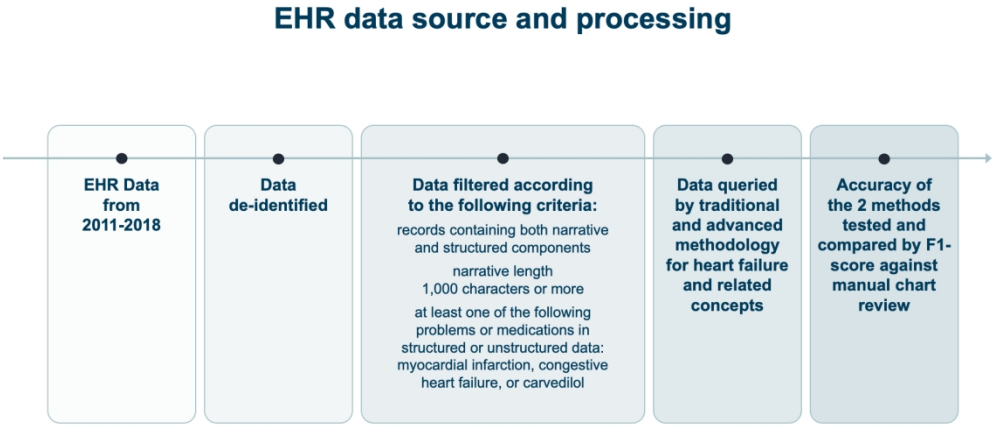


Figure 1: Electronic Health Record data source and processing.

338x190mm (144 x 144 DPI)

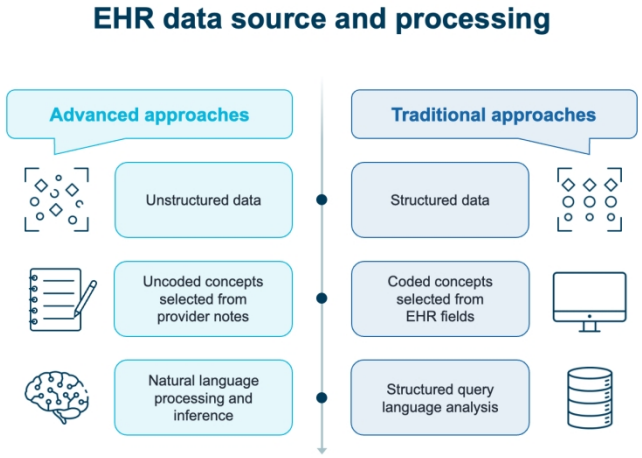


Figure 2: Comparison of traditional and advanced real-world evidence approaches. EHR, electronic health record.

338x190mm (144 x 144 DPI)

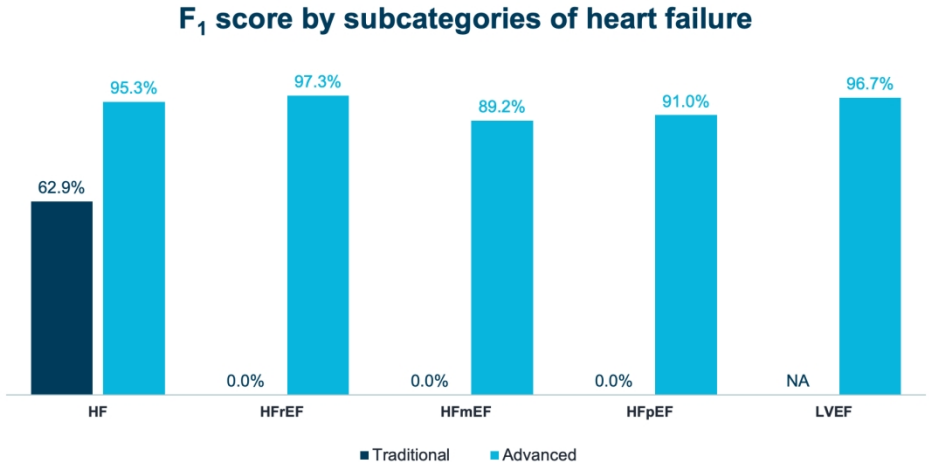
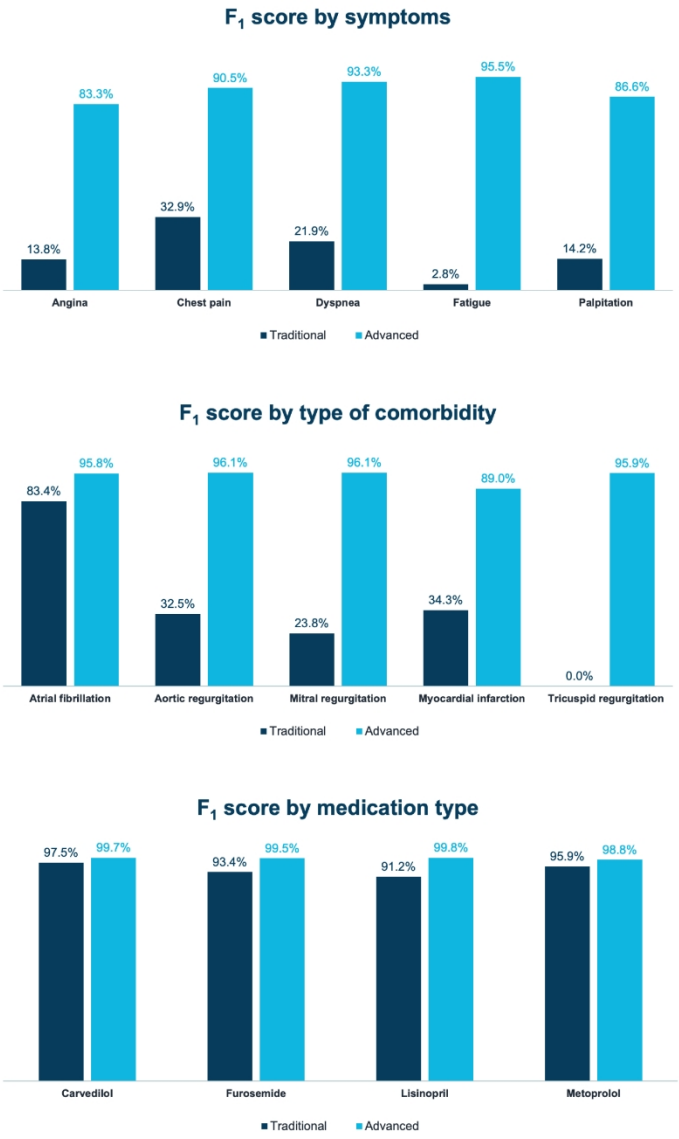


Figure 3: F1 scores for heart failure diagnoses. *F1-score could not be calculated due to lack of data for precision. †Structured data recall is not applicable for ejection fraction because no code was available within the problem list. HF, heart failure; HFmrEF, heart failure with mildly-reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 0% reflects a measured value and indicates the availability of the diagnosis code in the EHR dropdown versus N/A, not applicable, which refers to a diagnosis without available code in the relevant codeset.

338x190mm (144 x 144 DPI)



F1 scores for (A) symptoms, (B) medications, and (C) comorbid conditions. *F1 score could not be calculated due to a lack of data for precision. N/A, not applicable.

548x904mm (118 x 118 DPI)

Supplementary Table 1. Cohort identification of heart failure diagnoses, left ventricular ejection fraction, heart failure medications, symptoms, and comorbid cardiovascular conditions

	Traditional approach			Advanced approach					
	Recall, %	Precision, %	F_1 score, %	Recall, %	Precision, %	F_1 score, %	Concept occurrence	Encounter occurrence	*P*-value
HF diagnosis									
HF	46.9	95.4	62.9	96.0	94.7	95.3	265	155	<0.001
HFrEF	0	N/A*	N/A†	94.8	100.0	97.3	382	124	N/A§
HFmrEF	0	N/A*	N/A†	80.4	100.0	89.2	62	35	N/A§
HFpEF	0	N/A*	N/A†	83.5	100.0	91.0	103	55	N/A§
LVEF	N/A‡	N/A‡	N/A‡	93.7	100.0	96.7	677	238	N/A§
HF medications									
Carvedilol	95.1	100.0	97.5	99.7	99.7	99.7	407	141	<0.001
Furosemide	87.7	100.0	93.4	99.3	99.8	99.5	1572	371	0.116
Lisinopril	83.9	100.0	91.2	99.7	99.9	99.8	1068	386	<0.001
Metoprolol	92.2	100.0	95.9	97.7	100.0	98.8	1370	397	<0.001
Symptoms									

Angina	7.8	60.0	13.8	84.4	82.3	83.3	265	155	<0.001
Chest pain	21.4	70.8	32.9	95.4	86.1	90.5	2332	756	<0.001
Dyspnea	12.7	78.2	21.9	94.7	92.0	93.3	4474	832	<0.001
Fatigue	1.4	75.0	2.8	96.5	94.5	95.5	1711	371	<0.001
Palpitation	8.2	52.9	14.2	90.9	82.6	86.6	896	493	<0.001
Comorbid cardiovascular conditions									
Atrial fibrillation	72.2	98.7	83.4	93.0	98.7	95.8	1214	222	<0.001
Aortic regurgitation	19.4	100.0	32.5	92.5	100.0	96.1	153	90	<0.001
Mitral regurgitation	13.5	97.1	23.8	92.8	99.6	96.1	483	185	<0.001
Myocardial infarction	21.1	90.9	34.3	95.5	83.4	89.0	1220	578	<0.001
Tricuspid regurgitation	0	N/A*	N/A†	92.2	100.0	95.9	162	78	N/A§

*These elements did not occur when using the traditional approach. †F_1 scores could not be calculated due to a lack of data for precision. ‡Structured data recall is not applicable for ejection fraction because there was no code available within the problem list. §*P*-value could not be calculated due to the unavailability of F_1 scores for the traditional approach. *P*-values are derived from the chi-square test.

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; N/A, not applicable.

SUPPLEMENTAL MATERIAL

Reference Standard

Traditional and advanced approaches were tested against a reference standard for physician encounters. The reference standard consisted of an independent review, with manual annotation of relevant HF-specific features, including 19 unique HF-specific concepts. For each encounter, two independent clinical annotators labeled each concept and all metadata for that concept. For example, an annotator might mark the text "DOE over last month" as dyspnea on exertion, experienced = true, current = true, relative date = 1 month. Concept occurrence was defined as the sum of all concept occurrences, allowing for multiple occurrences per encounter. Encounter occurrence was defined as the number of encounters with at least one occurrence of the concept.

Given that many concepts, such as LVEF are specific to a point in time, concepts were tested at the encounter level. For example, if a patient had an LVEF of 30% in an encounter, the data extraction would only be annotated as correct if it identified "LVEF 30%" in that specific encounter. This reference standard was used to determine accuracy of automated extracted data and structured data. Specifically, this reference standard was used to calculate recall and precision for these individual features for traditional and advanced approaches.

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A Retrospective Comparison of Traditional and Artificial-Intelligence Based Heart Failure Phenotyping in a US Health System to Enable Real-World Evidence

Short title: Real-World Evidence in Heart Failure

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Abstract

Objective: Quantitatively evaluate the quality of data underlying real-world evidence (RWE) in heart failure (HF).

Design: Retrospective comparison of accuracy in identifying HF patients and phenotypic information was made using traditional (i.e., structured query language applied to structured EHR data) and advanced (i.e., AI applied to unstructured EHR data) RWE approaches. The performance of each approach was measured by the harmonic mean of precision and recall (F1 score) using manual annotation of medical records as a reference standard.

Setting: EHR data from a large academic healthcare system in North America between 2015 and 2019, with an expected catchment of approximately 500,000 patients.

Population: 4288 encounters for 1155 patients aged 18 to 85 years, with 472 patients identified as having HF.

Outcome measures: HF and associated concepts, such as comorbidities, left ventricular ejection fraction, and selected medications.

Results: The average F1 scores across 19 HF-specific concepts were 49.0% and 94.1% for the traditional and advanced approaches, respectively (P<0.001 for all concepts with available data). The absolute difference in F_1 score between approaches was 45.1% (98.1% relative increase in F_1 score using the advanced approach). The advanced approach achieved superior F1 scores for HF presence, phenotype, and associated comorbidities. Some phenotypes, such as HFpEF, revealed dramatic differences in extraction accuracy based on technology applied, with a 4.9% F_1 score when using natural language processing (NLP) alone and a 91.0% F_1 score when using NLP plus AI-based inference.

Conclusions: A traditional RWE generation approach resulted in low data quality in HF patients. While an advanced approach demonstrated high accuracy, the results varied dramatically based on extraction techniques. For future studies, advanced approaches and accuracy measurement may be required to ensure data are fit-for-purpose.

Strengths and limitations of this study

- Using RWE for HF patients requires demonstrating that the data source and technologies result in accurate data.
- Natural language processing alone lacked context from the longitudinal record, limiting phenotype identification and study validity.
- Findings suggest that advanced methods can enable high-validity RWE for heart failure patients.
- The use of data from a single healthcare system may limit generalizability to other populations.

INTRODUCTION

Heart failure (HF) is a major public health problem with significant associated morbidity, mortality, and cost.[1,2] Despite the availability of novel drugs and devices, morbidity and mortality in HF rivals many malignancies, with a 5-year survival rate as low as 50%.[3-8] Randomized controlled trials (RCTs) have traditionally been used to assess the safety and efficacy of new therapies and represent a cornerstone for regulatory approval. However, RCTs are frequently conducted in highly selected populations, typically younger, healthier, and less diverse than patients treated in clinical practice. Furthermore, such trials often include patients with an established HF diagnosis, receiving guideline-directed medical therapy at tertiary centers, and may not represent the broader HF population. Because HF is a clinically heterogeneous syndrome with numerous etiologies and phenotypes, studying this population can be particularly difficult.

Real-world evidence (RWE) has held promise as a potential means to assess therapeutic benefit outside of clinical trials, with sufficient power to characterize therapeutic impact in HF subgroups. Accordingly, RWE can complement RCTs, extending the findings to patient populations that may have been excluded from or insufficiently enrolled in pivotal trials. To accelerate these and similar precision medicine goals, the 21st Century Cures Act was passed in 2016, which required the United States Food and Drug Administration (FDA) to develop guidance supporting the use of RWE in new drug indications and post-marketing surveillance.[9] In addition, payors have increasingly utilized RWE to inform reimbursement decisions and are increasingly demanding credible evidence.[10]

Not surprisingly, the quality of RWE hinges on how well real-world data are collected, processed[11], and used to inform study questions. Such is the case in HF, where accurate identification of patients in administrative and other structured data sets is an ongoing focus.[12-14] Traditional methods of identifying HF patients rely on querying diagnosis codes and structured data in the electronic health record (EHR) or medical claims. Conversely, artificial intelligence (AI) applied to unstructured data represents a novel method of analyzing the medical record. Because of the importance of data reliability in RWE and the potential to use unstructured data to achieve data enrichment[15], we sought to compare the accuracy achieved by traditional RWE methods versus advanced AI approaches in identifying a range of HF-specific data elements from the medical record.

METHODS

The study design is outlined in Figure 1. Varied data sources and applied technologies were used to assess data reliability in patients with risk factors for HF. Leveraging manual chart abstraction as the reference standard, comparisons were made between the two methods. The first method used structured EHR data (e.g., diagnosis codes and problem lists) and standard query techniques, defined as the 'traditional approach'. The second used unstructured EHR data (e.g., narratives from primary care and specialty notes) and AI techniques, described as the 'advanced approach' (Figure 1). The primary objective was measurement of the accuracy of identified HF-specific elements using traditional and advanced approaches. We hypothesized that the advanced approach would better identify key HF-specific elements than the traditional approach. Data were deidentified before study initiation, and the study was determined not to be human subjects research. Both natural language processing (NLP) and machine-learned inference technologies

used in the advanced approach were provided by Verantos, Inc. (Menlo Park, CA, USA). The core of AI is a deterministic NLP layer. This layer is built on top of the GATE NLP architecture.[16] The architecture is used to construct a flexible pipeline for processing incoming text against English language syntactical rules augmented with a lexicon based on a clinical vocabulary. The AI-based inference was applied during data processing. Millions of machine-learned and manually curated associations enable disambiguation and identification of clinically relevant concepts. As an example of AI-based inference, a patient with HF on the problem list and a narrative encounter describing "EF 60%" would not be interpreted by NLP as having HF with preserved ejection fraction (HFpEF) since the text does not have sufficient information to identify this condition. On the other hand, AI-based inference would infer HFpEF based on disparate information in the record.

EHR Data Source and Processing

EHR data from primary care encounters between 2011 and 2018 were deidentified and securely transferred to a cloud-based server for analysis. The data set consisted of both structured data (e.g., medical conditions, procedures performed, medications, and problem lists) and unstructured data (e.g., narrative notes from primary care providers and specialists, telephone visits, and other narrative text) (Figure 2).

As the study aimed to test the accuracy of different RWE approaches and not treatment effectiveness, the cohort was enriched for patients with suspected HF based on comorbidities and medications. Specifically, the following filters were applied: records containing both narrative and structured components; narrative length 1,000 characters or more; and at least one of the

following problems or medications in structured or unstructured data: myocardial infarction, congestive heart failure, or carvedilol (Figure 1).

A prespecified set of clinical concepts pertinent to patients with HF was extracted using traditional and advanced techniques (Table 1). Problem lists were mapped to Systematized Nomenclature of Medicine (SNOMED) ontology, and unadjudicated claims were mapped to ICD-10 codes. Standard sets of individual codes were used to represent each concept. With the advanced approach, inference incorporating pattern recognition was utilized to identify potentially missing or ignored concepts within the text (e.g., HF being likely in patients with dyspnea and pitting edema on a diuretic). Specifically, no narrative coding took place before the AI algorithm was used; instead, it was applied directly to the narrative text and then mapped by the algorithm to the SNOMED ontology. Next, manual chart abstraction using the same SNOMED code set was used as a reference to assess the accuracy of the coding by the AI algorithm. Engineers were blinded to validation data and its corresponding chart abstraction.

Study End Points and Statistical Analysis

The primary endpoint was the F_1 score for traditional and advanced approaches. The F_1 score is an accuracy measure that combines recall and precision; more specifically, it is the weighted harmonic mean of these two measures. Secondary endpoints were recall (i.e., the proportion of patients correctly identified as having the condition, akin to sensitivity) and precision (i.e., the proportion of patients with HF and its subtypes correctly identified divided by the total number of patients identified in each cohort akin to positive predictive value)[17,18] for the traditional and advanced approaches. The reference standard used to evaluate accuracy of the traditional and advanced approaches was manual chart abstraction. For each encounter, two independent clinical

annotators labeled each concept and all metadata for that concept. Annotators were blinded to each other's annotations, and inter-rater agreement was measured by Cohen's kappa score. Further description of the reference standard methodology is provided in the Supplemental Material. Results were summarized using descriptive statistics, and percentages were calculated for categorical variables. Differences in F_1 scores between traditional and advanced approaches were analyzed using the chi-square test; associated *P*-values were reported.

Patient and Public Involvement

Data were deidentified before study initiation, and the study was determined not to be human subjects research. As a result, no patients were recruited for study participation. The research question and study goal of highlighting methods for improving RWE use were driven by recognition that improvements in use of RWE to inform new drug indications, post-marketing surveillance, and reimbursement decisions would ultimately result in patient benefit.

RESULTS

A total of 4288 encounters for 1155 patients were examined, of which 472 patients with HF were identified. Of these, 382 had HF with reduced ejection fraction (HFrEF), 35 had HF with mildly reduced ejection fraction (HFmrEF), and 55 had HF with preserved ejection fraction (HFpEF). The reference standard Cohen's kappa score was 0.95, suggesting high validity.

Supplementary Table 1 reports the F_1 score, recall, and precision results achieved with both approaches. Figure 3 graphically presents F_1 scores for HF diagnoses and Figure 4 includes F_1 scores for symptoms, medications, and comorbid conditions. Overall, accuracy was significantly greater for the advanced approach (AI applied to unstructured EHR data) than for the traditional

approach (structured query language applied to structured EHR data) (Supplementary Table 1; Figure 3; Figure 4), with an absolute difference of 45.1%.

With the traditional approach, recall for any HF diagnosis was 46.9% (i.e., 53.1% of patients with HF were missed entirely) and precision was 95.4%, resulting in an F_1 score of 62.9% (P<0.001). In contrast, with the advanced approach, recall for any HF diagnosis was 96.0% and precision was 94.7%, resulting in an F_1-score of 95.3% (P<0.001 when F_1 scores for the two approaches were compared) (Supplementary Table 1; Figure 3). Among HF phenotypes, recall with the advanced approach was highest with HFrEF, followed by HFpEF and HFmrEF; precision was 100% for all phenotypes. With the traditional approach, F_1 scores could not be calculated for HFrEF, HFmrEF, and HFpEF because only less granular HF codes were used (Supplementary Table 1).

Accuracy in identifying left ventricular ejection fraction (LVEF) was similarly high with the advanced approach, with an F_1 score of 96.7%. Data could not be extracted for LVEF with the traditional approach because no such codes were available within the EHR, nor did a mechanism to encode LVEF within the problem list or unadjudicated claims exist (Supplementary Table 1; Figure 3).

Accurate identification of HF symptoms was greater with the advanced approach (P<0.001) (Supplementary Table 1; Figure 4A). Whereas identification of commonly prescribed HF medications was high with both approaches (Supplementary Table 1; Figure 4B), identification of cardiovascular comorbidities was higher in all cases with the advanced approach (P<0.001) (Supplementary Table 1; Figure 4C).

Data concept extraction with the advanced approach greatly depended upon the technology used. For example, NLP, which ends at the sentence boundary, was only able to identify HFpEF with an F_1 score of 4.9% because "HFpEF" or "heart failure with preserved ejection fraction" was rarely written. Conversely, inference, which can find related items from the longitudinal record, was able to identify both "HF" and "normal ejection fraction" as separate annotations for HFpEF with an F_1-score of 91.0% (Supplementary Table 1; Figure 3).

DISCUSSION

The utilization of RWE has grown substantially in recent years, driven in part by its perceived value by clinicians, regulators, and payors, particularly in light of the limitations of trial populations.[19] As RWE is increasingly used to refine care standards through clinical, regulatory, and reimbursement pathways, its accuracy has come under increased scrutiny. This is particularly important for complex medical conditions, such as HF.[20] Accordingly, in this analysis, chart abstraction was used to quantitatively evaluate traditional and advanced approaches to define HF-specific data elements. This enabled rigorous evaluation of whether commonly used techniques are sufficiently accurate for observational studies, comparative effectiveness research, and post-approval safety studies.

In this study, 1) the use of an advanced, AI-based approach consistently identified HF phenotypes (i.e., HFrEF, HFmrEF, and HFpEF) more accurately than a traditional approach; 2) common HF symptoms and comorbid conditions were consistently and accurately identified using an advanced approach; and 3) medications for HF were accurately identified using both advanced and traditional approaches. While studies have previously leveraged an AI-based approach to identify patients with HF,[21-24] the findings presented here highlight the discrepancy

between traditional EHR query methods and an AI-based approach standardized against a manual reference. Given that the accuracy of the data set and appropriateness of the applied technology are not tested in many RWE studies, there is a high potential for error.[25-28] The current findings highlight this while also reinforcing the impact that specific AI technologies (e.g., NLP vs. NLP plus inference) can have on phenotype generation and study validity.

Accurate phenotyping is paramount in any RWE study that includes HF patients. With varying etiologies and multiple phenotypes, HF is a clinically diverse syndrome, with outcomes that may vary between and even within subgroups.[29,30] In addition, HF patients may have different trajectories, highlighting some of the limitations of using structured data. For example, LVEF may fluctuate throughout a patient's disease course, with some patients experiencing recovery of their LVEF with the use of guideline-directed medical therapy. Accordingly, accurate phenotyping of HF patients usually requires the incorporation of data that crosses clinical encounters. In addition, although symptoms are an essential reflection of clinical status, they are poorly captured in structured data. Suboptimal recognition of comorbidities like valvular heart disease can also impact disease trajectory and risk for future cardiovascular events.

The findings presented here represent an important advance for RWE studies that include HF patients. Notably, the only way to ascertain comparative accuracy between data sources and technologies in a domain is to test it. Accuracy consists of both recall and precision, and in the case of many health conditions, recall can fall below 50% when one relies solely upon the problem list.[31,32]

In the current study, use of the F_1 score enabled analysis of both precision and recall. Despite availability of SNOMED codes for HFrEF and HFpEF, along with a similar code for HFmrEF,

such codes were rarely included. Documentation of a HF code using structured data was only found 46.9% of the time when there was clear evidence of HF in the chart. The low accuracy of structured data for disease subtypes may, at least partially, relate to how the data is likely to be used. A physician may look within notes to understand HF subtype. Information entered into problem lists and claims may be more to provide a high-level understanding of disease burden. Granular billing codes may be a low priority for physicians if claims are reimbursed with the non-granular HF code. Furthermore, because addition of diagnoses to the problem list is not a requirement, the problem list may not be specific or updated. This contrasts with clinical notes, where detailed documentation is usually performed to communicate a care plan and is a medical-legal requirement.

When low-accuracy and non-granular data are utilized, there are several potential consequences. Missingness can result in selection bias, particularly if sicker patients have more frequent encounters, higher rates of specialty care, and more complete documentation. Depending on the study question, use of structured data alone to identify certain subgroups may be inadvisable, since these data have a low recall for specific clinical concepts such as ST-elevation myocardial infarction and HFrEF.[33] Even advanced approaches (e.g., NLP) may result in poor accuracy, as illustrated in this study, where HFpEF required AI-based inference for proper identification. Collectively, this highlights that not all data sources and technologies are the same; therefore, accuracy testing may be required for rigorous RWE generation.[34] Furthermore, given the growth in RWE to support new drug indications, post-marketing surveillance, and decision-making regarding reimbursement, it is imperative for clinicians to understand that such inaccuracies may have a profound impact on large numbers of patients.

Even though standard dictionaries and clinical terms related to cardiovascular medicine were used, there is a need to test the two analytic methods using different EHRs across a broader set of community and referral practices. With numerous EHRs available and practitioner-to-practitioner variability in documentation accuracy, efforts like the one described here represent an important means of strengthening data quality.

Importantly, this study has several limitations. First, data from a single health system was used and results may not be generalizable to other populations. Second, the study protocol required the selection of patients enriched with cardiovascular disease to make the study feasible, with manual chart abstraction conducted to ensure the accuracy of results. While selection criteria were applied to both structured and unstructured data, it is possible that this could have biased results in a way that favored structured data since a larger proportion of patients with HF on the problem list may have been included than if the sample had been created randomly. In addition, the specific filters used likely led to a higher-than-expected proportion of HFrEF patients (compared to those with HFmrEF and HFpEF). Second, the study required laborious manual annotation of thousands of records. Such a sample size is adequate for high-prevalence conditions, but would likely require adjustment for low-prevalence conditions with low concept occurrence rates. Finally, the study did not include clinical outcome assessment; rather, it was designed to compare data sources and processing methods.

Conclusion

As RWE is increasingly used to analyze patient subgroups, inform clinical decision-making, and influence regulatory and reimbursement decisions, data reliability and evidence validity are of critical importance. Use of a traditional approach was associated with low data accuracy. While

much greater accuracy was observed with AI-based methods, it depended upon the technology utilized. These findings highlight the importance of using data fit-for-purpose to the research question posed. In addition, they suggest that accuracy testing should be part of any EHR-based study that includes HF patients. Finally, unstructured data and a technology-based approach to data extraction may be required in some studies to achieve sufficient accuracy, depending upon the clinical assertion being tested.

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Contributors

ARG and DR drafted the manuscript. ARG, KLM, RED, DR, and TJG critically reviewed the manuscript. ARG, RED, DR, and TJG provided clinical insight.

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Competing interests

KLM and RED are employees and stockholders of Amgen Inc. DR is an employee and stockholder of Verantos, Inc. ARG has received research support from Abbott and TJG has no competing interests to declare.

Ethics Approval

This study has been independently reviewed and accepted for exemption in accordance with 45 CFR 46.101(b)(4ii).

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data are available.

Supplemental Materials

Supplemental Methods

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Table 1. Prespecified heart failure–specific concepts extracted from the electronic health record.

High Priority Conditions	Comorbidities	Symptoms	Findings	Medications
Congestive HF HF with reduced EF HF with mid-range EF HF with preserved EF	Myocardial infarction Atrial fibrillation Aortic regurgitation Mitral regurgitation Tricuspid regurgitation	Angina Chest pain Dyspnea Fatigue Palpitations	LVEF	Carvedilol Lisinopril Metoprolol Furosemide

HF, heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction.

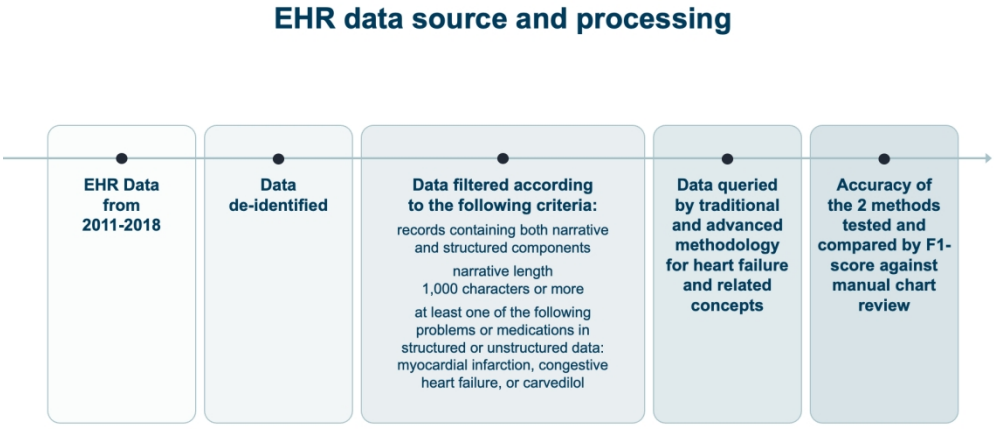


Figure 1: Electronic Health Record data source and processing.

338x190mm (144 x 144 DPI)

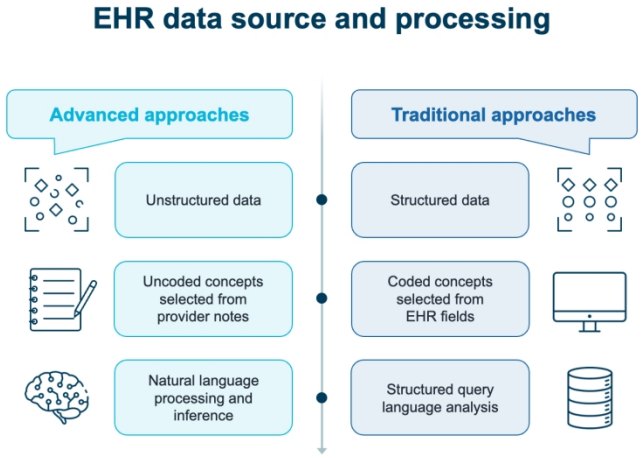


Figure 2: Comparison of traditional and advanced real-world evidence approaches. EHR, electronic health record.

338x190mm (144 x 144 DPI)

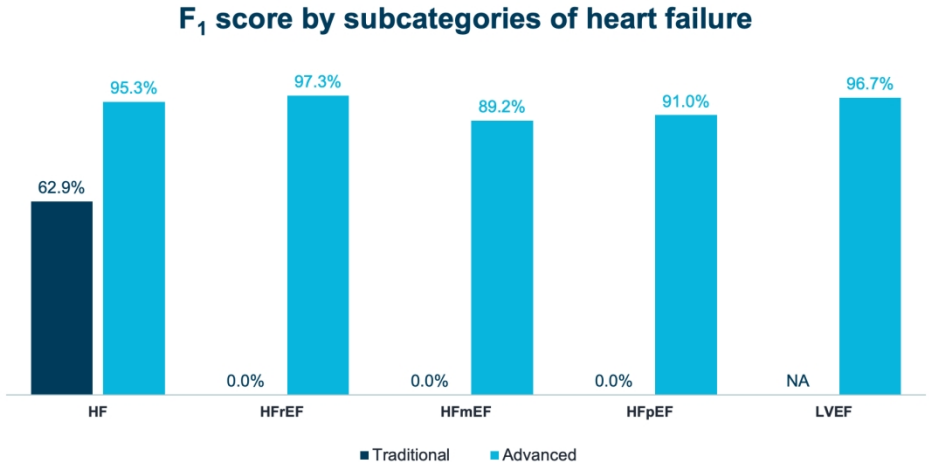
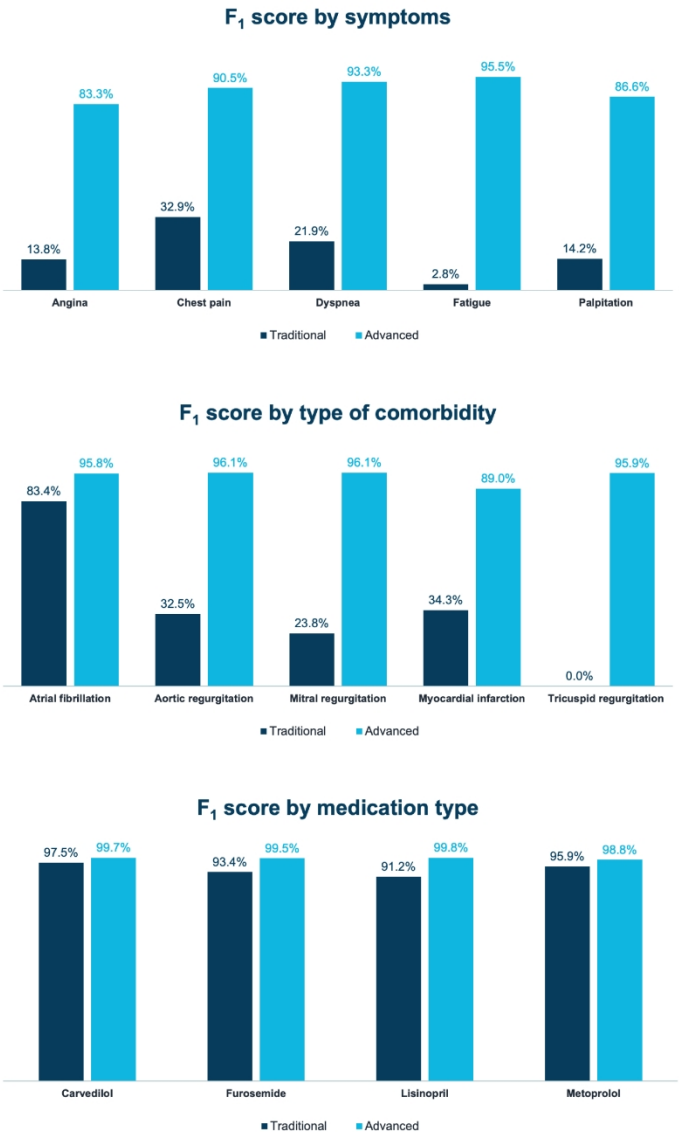


Figure 3: F1 scores for heart failure diagnoses. *F1-score could not be calculated due to lack of data for precision. †Structured data recall is not applicable for ejection fraction because no code was available within the problem list. HF, heart failure; HFmrEF, heart failure with mildly-reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 0% reflects a measured value and indicates the availability of the diagnosis code in the EHR dropdown versus N/A, not applicable, which refers to a diagnosis without available code in the relevant codeset.

338x190mm (144 x 144 DPI)



F1 scores for (A) symptoms, (B) medications, and (C) comorbid conditions. *F1 score could not be calculated due to a lack of data for precision. N/A, not applicable.

548x904mm (118 x 118 DPI)

Supplementary Table 1. Cohort identification of heart failure diagnoses, left ventricular ejection fraction, heart failure medications, symptoms, and comorbid cardiovascular conditions

	Traditional approach			Advanced approach					
	Recall, %	Precision, %	F_1 score, %	Recall, %	Precision, %	F_1 score, %	Concept occurrence	Encounter occurrence	*P*-value
HF diagnosis									
HF	46.9	95.4	62.9	96.0	94.7	95.3	265	155	<0.001
HFrEF	0	N/A*	N/A†	94.8	100.0	97.3	382	124	N/A§
HFmrEF	0	N/A*	N/A†	80.4	100.0	89.2	62	35	N/A§
HFpEF	0	N/A*	N/A†	83.5	100.0	91.0	103	55	N/A§
LVEF	N/A‡	N/A‡	N/A‡	93.7	100.0	96.7	677	238	N/A§
HF medications									
Carvedilol	95.1	100.0	97.5	99.7	99.7	99.7	407	141	<0.001
Furosemide	87.7	100.0	93.4	99.3	99.8	99.5	1572	371	0.116
Lisinopril	83.9	100.0	91.2	99.7	99.9	99.8	1068	386	<0.001
Metoprolol	92.2	100.0	95.9	97.7	100.0	98.8	1370	397	<0.001
Symptoms									

Angina	7.8	60.0	13.8	84.4	82.3	83.3	265	155	<0.001
Chest pain	21.4	70.8	32.9	95.4	86.1	90.5	2332	756	<0.001
Dyspnea	12.7	78.2	21.9	94.7	92.0	93.3	4474	832	<0.001
Fatigue	1.4	75.0	2.8	96.5	94.5	95.5	1711	371	<0.001
Palpitation	8.2	52.9	14.2	90.9	82.6	86.6	896	493	<0.001
Comorbid cardiovascular conditions									
Atrial fibrillation	72.2	98.7	83.4	93.0	98.7	95.8	1214	222	<0.001
Aortic regurgitation	19.4	100.0	32.5	92.5	100.0	96.1	153	90	<0.001
Mitral regurgitation	13.5	97.1	23.8	92.8	99.6	96.1	483	185	<0.001
Myocardial infarction	21.1	90.9	34.3	95.5	83.4	89.0	1220	578	<0.001
Tricuspid regurgitation	0	N/A*	N/A†	92.2	100.0	95.9	162	78	N/A§

*These elements did not occur when using the traditional approach. †F_1 scores could not be calculated due to a lack of data for precision. ‡Structured data recall is not applicable for ejection fraction because there was no code available within the problem list. §*P*-value could not be calculated due to the unavailability of F_1 scores for the traditional approach. *P*-values are derived from the chi-square test.

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; N/A, not applicable.

SUPPLEMENTAL MATERIAL

Reference Standard

Traditional and advanced approaches were tested against a reference standard for physician encounters. The reference standard consisted of an independent review, with manual annotation of relevant HF-specific features, including 19 unique HF-specific concepts. For each encounter, two independent clinical annotators labeled each concept and all metadata for that concept. For example, an annotator might mark the text "DOE over last month" as dyspnea on exertion, experienced = true, current = true, relative date = 1 month. Concept occurrence was defined as the sum of all concept occurrences, allowing for multiple occurrences per encounter. Encounter occurrence was defined as the number of encounters with at least one occurrence of the concept.

Given that many concepts, such as LVEF are specific to a point in time, concepts were tested at the encounter level. For example, if a patient had an LVEF of 30% in an encounter, the data extraction would only be annotated as correct if it identified "LVEF 30%" in that specific encounter. This reference standard was used to determine accuracy of automated extracted data and structured data. Specifically, this reference standard was used to calculate recall and precision for these individual features for traditional and advanced approaches.