Abstract

Machine Learning models for diagnosis of Heart failure with preserved ejection fraction

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Introduction:

Diagnosis of Heart Failure with preserved Ejection Fraction (HFpEF) is difficult leading to delayed diagnosis and a high 23% 1-year mortality rate. The Heart Failure Association (HFA)-PEFF score is a multi-parameter approach to diagnose HFpEF. Currently, HFA-PEFF score use is limited to specialised HF units. Machine learning (ML) models were developed for a simple diagnosis of HFpEF even by a non-HF physician.

Methods:

ML models for HFpEF diagnosis were developed from a retrospective single center database of 418 hospitalized HFpEF patients over a 2-year (2019-20) period. The diagnostic performance of ML models - logistic regression (LR) and neural network (NN) has been compared with expert clinical diagnosis, HFA-PEFF score and in those with borderline HFA-PEFF score. Kappa statistic calculated to measure concordance between both scoring systems.

Results:

15 significant variables identified have been utilized for the generation of ML model. ML models were compared to the standard diagnosis by expert clinical opinion and both ML models showed good sensitivity and specificity – LR (0.76 and 73)and NN (0.81 and 0.73) respectively. HFA-PEFF score identified 291 of the 418 (70%) HFpEF patients as borderline suggesting further workup for diagnosis. Compared to HFA-PEFF score, ML models exhibited good sensitivity (LR 0.97; NN 0.90) and positive predictive accuracy (ML 0.85; NN 0.93) with modest negative predictive accuracy of (LR 0.50; NN 0.57). Concordance by kappa statistic for those with a definite diagnosis by HFA-PEFF was 0.46 and 0.56 for the ML based models. For those categorized as borderline by HFA-PEFF score, ML models could identify 211of the 291 (72.5%) and failed to categorize 27% of patients further demonstrating the superiority.

Conclusion:

Compared to the HFA-PEFF score, ML models could efficiently “rule-in” HFpEF with a good concordance. HFA-PEFF score conservatively identified 70% of patients as borderline. ML models exhibited better sensitivity, specificity, positive and negative predictive accuracy including in the group categorized as borderline by HFA-PEFF score. ML model based web app could be a good addition for the bedside diagnosis of HFpEF.

Introduction

Heart Failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterised by preserved cardiac systolic function and pathologically increased cardiac filling pressures either at rest or with exertion accompanied by classical HF symptoms or signs.[1] HFpEF is a common disease entity accounting for nearly 50% of those with HF and in people presenting with unexplained dyspnea the prevalence is estimated to be 20.4%.[2,3] In contrast to heart failure with reduced ejection fraction (HFrEF) with a left ventricular ejection fraction(LVEF) < 40%, in HFpEF the LVEF is > 50%. This binary classification of HF has therapeutic implications as HFrEF has established therapies whilst HFpEF does not have.[4] Over the past 2 decades, the incidence of HFrEF is decreasing but HFpEF is increasing and there is no difference in mortality between these two entities.[5] The diagnosis of HFrEF is fairly straightforward using echocardiography, while the diagnosis of HFpEF is difficult.

Over the last few years, three different scoring systems have been introduced for the diagnosis of HFpEF. The European Society of Cardiology (ESC) in its 2021 guidelines for the treatment of acute and chronic HF proposed to diagnose HFpEF based on clinical features, echocardiography and biochemical parameter – N-terminal pro-brain natriuretic peptide (NT-proBNP).[1] In 2018, the Mayo clinic introduced the H2PEF algorithm for the diagnosis of HFpEF based on six clinical characteristics and trans-thoracic echocardiography (TTE).[6] Subsequently, the Heart Failure Association (HFA) of the ESC in 2019, established the HFA-PEFF score, a 4-step score – Pretest Assessment (P), Diagnostic workup with echocardiogram and natriuretic peptide score (E), Advanced workup with functional testing in case of uncertainty (F), and Final etiological workup (F).[7] Both scoring systems took different approaches, the Mayo group took an invasive hemodynamic testing as the gold standard and modelled the H2PEFF score based on the

clinical and echocardiographic characteristics using logistic regression analyses whilst the ESC HFA proposed the 4-step PEFF score that was based on expert consensus recommendation by a writing committee comprising of leaders in the field. Both scoring systems suggested how a clinician can arrive at the "probability" of HFpEF diagnosis and suggested sophisticated tests for the confirmation of diagnosis. The need for sophisticated tests including advanced echocardiography parameters and they being non-dichotomous approach to diagnosis precluded the adaptation of these diagnostic models by the vast majority of physicians who work in clinical practice. Both these scores have been validated in recent studies which identified the limitations and lack of concordance suggesting the need for better diagnostic algorithms.[3,8,9]

Considering the limitations of the present scoring systems, in the current study we developed machine learning (ML) models for the diagnosis of HFpEF and assessed their efficiency in comparison with HFA-PEFF score. These ML models would enable simple, easy bedside diagnosis of HFpEF even by the non-HF specialist without the need for sophisticated tests. In addition, ML models help to make a diagnosis of HFpEF in a binary way rather than the three sub-categories of HFpEF by the H2PEF and HFA-PEFF score.

The study attempts to address the challenges in the diagnosis of HFpEF through machine learning. Four aspects in the diagnosis of HFpEF in South Asian patients were studied. We developed machine learning (ML) models (logistic regression and neural networks) for the diagnosis of HFpEF. Secondly, we assessed how these ML models performed against the clinical expert's diagnosis of HFpEF. Next, we studied the extent to which the ML based models could predict the diagnosis of HFpEF in comparison with the HFA-PEFF scores. Finally, in the subset of patients, identified as "intermediate" probability of HFpEF by HFA PEFF score we studied how

the ML models could make a diagnosis of HFpEF and compared the results with the predictions from HFA-PEFF score.

Methods

Study Population and Data Collection

In a single center retrospective study conducted at a tertiary care hospital from January 2019 to December 2020, the data pertaining to 1068 consecutive admitted patients in whom HF was suspected were analyzed. Demographic data along with vital signs, medical and personal history, medication history, biochemical parameters, chest radiography and focused echocardiography evaluation for HF diagnosis was collected. The diagnosis of HF and categorisation into HFrEF and HFpEF was made by two independent physicians well experienced in the diagnosis and management of HF. The diagnosis was based on clinical, biochemical and echocardiography data. After removal of outliers data, HFpEF was diagnosed based on LVEF values of above 50% and other associated findings. This dataset consisted of 418 patients.

HFpEF is a complex disease and it could be sub classified into primary HFpEF where the cardiac disease is mainly responsible for HF or secondary HFpEF where the HF is the consequence of another disease pathology. The secondary HFpEF included underlying cardiac conditions (valvular heart disease, pericardial disease, pure right ventricular failure due to pulmonary hypertension), high-output states (anaemia, thyroid disease), sepsis and fluid overload from kidney or liver disease. Based on expert clinical diagnosis, we classified the cohort into two groups – primary and secondary HFpEF and analysed the predictive ability of our machine learning models.

Generation of the Machine Learning Model

We retrospectively analysed 27 variables in 418 patients with suspected HFpEF and classified them into two groups: 214 (51.1%) where HFpEF is the primary diagnosis and the remaining had HFpEF consequent to an underlying disease. The underlying diseases leading to secondary HFpEF were both cardiac and non-cardiac. Distinction between primary and secondary HFpEF was important because the ML model developed was generated from the primary HFpEF cohort. Baseline characteristics of both groups are shown in Table 1. Continuous variables are presented as means+/-SD, categorical variables are presented as numbers and percentages. Intergroup differences were tested using student t test for continuous variables and chi-square test for categorical variables. Of the 27 variables studied, 15 variables were identified as significant.

For this study, two ML models (Logistic Regression and Neural Networks) were developed and then compared with both expert opinion and the HFA-PEFF score.

Concordance between expert clinical opinion and ML models as well as HFA-PEFF score was calculated using the Cohen's kappa coefficients and proportion of agreement. This model testing was limited to those patients with a definitive diagnosis of HFpEF identified by the HFA-PEFF score only. h. The concordance was defined as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), and optimal (0.81–1). All tests were two tailed. Data analysis was performed using R Version 3.5.1.

Results

The entire cohort of 418 patients with HFpEF was classified into primary and secondary HFpEF. This distinction is important because we used a supervised machine learning protocol that was developed from the primary HFpEF category. Out of the 27 variables studied, 15 variables were identified to be significantly different between primary and secondary HFpEF. These variables have been used for development of the ML models.

Using clinical expert opinion as the gold standard, the predictive accuracy of the two ML models - neural networks and logistic regression - for the diagnosis of HFpEF has been shown in Table 2. Both ML models exhibited good diagnostic predictive ability of nearly 75%. Sensitivity, Specificity, Positive Predictive Values, Negative Predictive Values and Area Under the Curve (AUC) values are computed from both the ML models. These are popular and well-utilised assessments of studying a model-performance.

Diagnostic accuracy of these models is also determined by calculating the AUC of the receiver operating characteristic (ROC) curve are shown in Figure 1 and Figure 2. These figures show ROC curves for the tested models and the corresponding convex hull for cases with secondary HFpEF and primary HFpEF. The ROC curve is plotted with Total Positive Rate (TPR) (sensitivity) on the y-axis against the False Positive Rate (FPR) (1-Specificity) on the x-axis. It serves as a mean of comparison between the models. AUC represents the degree or measure of separability. Higher the AUC, the better the model is at distinguishing between patients with the disease and no disease.

The performance of ML was then compared with HFA-PEFF score. The HFA-PEFF score has classified the possibility of HFpEF into three groups; but for the purposes of this analysis we divided them into 2 groups - definitive diagnosis group (both rule-in and rule-out) and borderline or HFpEF not excludable group. ML models exhibited good sensitivity when they analysed the definitive group which are shown in Table 3. The major limitation of the HFA-PEFF score was that it categorised nearly 291 of the 418 (70%) as borderline and 127 (30%) as definite HFpEF.

We further analysed the ML models' diagnostic ability in the group of 291 out of 418 patients categorised as borderline by the HFA-PEFF score. Even in this group, both ML models

displayed a good sensitivity, specificity, PPA and NPA for the diagnosis of HFpEF. This data is shown in Table 4.

The concordance between the models has been studied using the Cohen's kappa coefficient statistic. Comparing ML with HFA-PEFF score, the concordance for those diagnosed as definite was 0.46 indicating a reasonable correlation. The ML models exhibited a much better concordance of 0.56 when compared with expert clinical opinion. The kappa coefficient diagram is represented for ML comparison with expert opinion and ML comparison with HFA-PEFF score in Figure 3 and 4 respectively.

Discussion

Diagnosis of HFpEF remains challenging because the traditional parameters for the diagnosis - echocardiography parameters and natriuretic peptides have low sensitivity, low awareness about HFpEF amongst physicians, phenotypic heterogeneity of HFpEF, concomitant organ system involvement and considerable variation of HFpEF presentation based on the stage of disease as well as hospitalisation status.[10] The recent scoring systems proposed to improve the diagnosis of HFpEF had important limitations - low sensitivity and majority of patients being classified as borderline or not excludable HFpEF.[3,10]

The current study attempts to resolve the diagnostic challenge of HFpEF by developing ML models for easy diagnosis. ML models – LR and NN were found to have a good sensitivity, specificity, positive and negative predictive accuracy for the diagnosis of HFpEF with clinical diagnosis considered as the gold standard. The HFA-PEFF score by the ESC had a lower sensitivity for diagnosis of HFpEF and majority of patients categorised as borderline HFpEF. The ML models had better diagnostic sensitivity even in those identified as borderline by HFA-PEFF score.

Of the 418 patients with HFpEF, 218 (51%) were primary HFpEF and the rest were secondary HFpEF. This classification of HFpEF is gaining momentum in recent studies because many patients with HFpEF have extra-cardiac manifestations and co-morbidities.[10,11] In these patients, the non-cardiovascular outcomes outweigh the cardiovascular disease end points.[11,12] Primary HFpEF, as a clinical entity, should be reserved for those cases in which there is a primary diastolic dysfunction leading to HF, as result of interaction of multiple risk factors such as hypertension, ageing, systemic inflammatory status or metabolic disorders, but without any specific underlying cause.[11] This distinction is important because the therapeutic approach to manage a heterogeneous entity such as HFpEF needs to be based on the pathophysiology of the underlying disorder. In this study, we sought to improve the HFpEF diagnosis through the development of ML based models based on primary HFpEF for which we needed to distinguish primary HFpEF from the secondary entity.

Despite the rising incidence and prevalence of HFpEF relative to HFrEF, in the EURObservational Research Programme Heart Failure Long-Term Registry using the 2016 ESC criteria for diagnosis, HFpEF could be diagnosed in only 25% of patients and could be confirmed in only 50% of them.[12,13] In two recent studies, the HFA-PEFF score did not show a good sensitivity for the diagnosis of HFpEF. In two cohorts of previously confirmed HFpEF from Europe (Maastricht) and USA (North Western University) applying the HFA-PEFF score it was found that approximately 60% could be identified as definite HFpEF and around 36% were categorised as borderline HFpEF. For the minority with a low HFA-PEFF score the negative predictive accuracy was nearly 99%.[14] In a community based study for the diagnosis of HFpEF using three different algorithms, both HFA-PEFF and H2PEFF showed much lower sensitivity with poor concordance between them. This study also questioned the specificity of HFA-PEFF

score as it identified 3.7% of general population without unexplained dyspnea as HFpEF. In addition, natriuretic peptides and various echocardiographic parameters showed extensive variability in the HFpEF patients. Various scores identified different, discordant sub populations of HFpEF with each having a propensity to identify a specific phenotype.[3]

The 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2022 version of the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure admit that the diagnosis of HFpEF is challenging because the LVEF cut-off points for HFpEF diagnosis are not uniform amongst various studies, LVEF number is dynamic that could either improve or worsen and LVEF measurements have intra/inter-observer variability.[1,15]

The major limitation of the diagnostic performance of both HFA-PEFF and H_2PEFF scores is to assign a substantial proportion of suspected HFpEF patients as intermediate likelihood, wherein additional diagnostics are proposed.[16] In addition, subsequent workup depends on the algorithm used for initial algorithm and different patients will be referred for different additional testing. The ESC 2021 guidelines also acknowledge the fact that physicians may not have access to all the specialised tests recommended by the specific diagnostic algorithms limiting the broad clinical applicability of the scores and demonstrates the ongoing diagnostic uncertainty in HFpEF.[1,16]

Three central points are established by these developments – diagnosis of HFpEF remains difficult despite advances in the diagnosis and novel scoring systems, physicians still look for simpler tools for integration into daily practice and the diagnosis of HFpEF is not based on a single parameter but instead is based on multiple factors - clinical, echocardiography, biochemical, exercise testing, invasive hemodynamics and other imaging modalities. This provides an excellent

setting for using other novel modalities such as ML based approach for the diagnosis of a complex entity such as HFpEF.[17]

ML based models for the diagnosis of HF have been studied using a hybrid approach of artificial intelligence based clinical decision support system (AI- CDSS) in combination with expert clinical diagnosis which yielded a diagnostic accuracy of 100%. More specifically, for the diagnosis of HFpEF, a non HF specialist could diagnose HFpEF in only 55% of cases whilst the hybrid approach had a concordance rate of 99.6%. This study amplified the limitation of clinical skills as well as the superiority of a hybrid approach involving ML and clinical skills in the diagnosis of HF.[18] ML based diagnostic algorithms have not been studied in the subset of HFpEF in the past. ML based algorithms in the realm of HFpEF till date have been studied for phenotype differentiation and their discriminatory ability in prognostication.[19] In addition, using the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist [TOPCAT] database, ML based approaches found different parameters that could predict mortality and hospitalization in HFpEF patients.[20]

In our study, expert clinical diagnosis of HFpEF was taken as the gold standard and ML models were developed using the database of 418 patients with suspected HFpEF. Of the ML-based diagnostic models tested we found the LR and NN models had a better discriminatory ability. Both the ML models - LR and NN exhibited better predictive accuracy with sensitivity of 0.76 and 0.81, specificity of 0.73 and 0.73, positive predictive accuracy of 0.74 and 0.76 and negative predictive accuracy of 0.74 and 0.78 respectively.

The HFA-PEFF score categorised nearly 291 (70%) of 418 patients in the borderline group, 127 (30%) as definite HFpEF. Compared to HF PEFF score, ML based models in this study showed superior discriminatory ability for the definite diagnosis group (both rule-in and rule out)

of the diagnosis of HFpEF. In the group with primary HFpEF, LR model had a sensitivity of 0.97 and positive predictive accuracy of 0.85; the NN model also similarly showed high sensitivity of 0.90 and positive predictive accuracy of 0.93.

In our study the HFA-PEFF score identified nearly 70% of cases as intermediate group. Studying further the diagnostic performance of ML models in the HFA-PEFF borderline group we found that the ML models performed better. The major limitation of the HFA-PEFF score is the categorisation of a vast majority under the non-excludable or borderline HFpEF category. They recommend further testing to arrive at a conclusive diagnosis of HFpEF. HFA-PEFF score has a low sensitivity which seriously limits the utility of this score in general HF practice.

Analysing the performance of ML models against HFA-PEFF for the 291 identified as borderline, the ML models identified 211 (72%) as definitive HFpEF and 28% as not HFpEF. This establishes the superior sensitivity of ML models compared to HFA-PEFF score.

Kappa coefficient of agreement of 0.46 shows that there is a reasonable agreement between ML and HFA-PEFF models in those with definitive diagnosis. ML models showed a superior kappa coefficient of 0.56 compared with expert clinical diagnosis. Using this statistical model, the graphs plotted in Figure 3 and 4 shows that the ML models have better "rule-in" and the HFA-PEFF score better "rule-out" capability.

Just like the other models, ML models also employed a multi-parametric approach for the diagnosis of HFpEF and exhibited much higher sensitivity and positive predictive accuracy. Unlike the HFA-PEFF score, our ML model has been validated against expert clinician diagnosis and had a shown a good sensitivity and predictive accuracy. The limitations of the HFA-PEFF and H_2PEFF scores has been acknowledged in the ESC 2021 guidelines on HF. In the ACC 2022 guidelines, both the new scores have been described but not recommended for the daily diagnosis of HF.

Instead the ESC and ACC recommend further testing by stress echocardiography or invasive exercise hemodynamics to confirm the diagnosis of borderline cases. This further workup adds complexity and is a major hindrance for their routine adaption. A common disease with a complex pathogenesis, divergent phenotypes and diagnostic challenges ideally requires a simple bedside algorithm. ML algorithm generated in this study is a first step in that direction.

The ML algorithm from our study has been translated into a web application that has been hosted on (www.theHFpEF.com) and is available for translation into clinical practice. The robustness of this application could further be studied through analysing already existing databases of HFpEF patients enrolled in various clinical trials.

The strengths of our study include development of ML based diagnostic algorithm for HFpEF that could be used in daily practice even by a non-HF clinician. This leads to potentially enhanced treatment opportunities and outcomes. We could also categorise in a binary way the diagnosis of HFpEF – as very likely and unlikely - instead of the three categories as proposed by the HFA-PEFF algorithm. This algorithm could be used in various settings – emergency room, out-patient clinic etc – for the clinical diagnosis of HFpEF leading to appropriate utilisation of resources. In resource limited settings, where skilled echocardiography technicians, sophisticated machines, stress echocardiography and invasive cardiac catheterisation are not readily available, ML models would be immensely useful. mobile application would further translate this into daily practice. The ML models had a good predictive ability in both sub groups of HFpEF – primary and secondary. Currently, the classification of HFpEF into primary and secondary is not popular but with the identification of phenotypes in HFpEF and variable prognosis between different sub groups of HFpEF we feel that this distinction would be acknowledged in clinical practice.

Diagnosis of HFpEF remains challenging and we propose ML based diagnosis models are the way forward.

The limitations of this study include – single-centre, retrospective chart analysis; small patient dataset and lack of invasive tests to confirm the diagnosis of HFpEF. Multi-parametric expert clinical diagnosis though useful cannot be a gold standard alternative to cardiac catheterisation for the diagnosis of HFpEF.

Conclusion:

Diagnosis of HFpEF remains challenging owing to the complexity of pathophysiology, multiple phenotypes, normal LVEF in echocardiography and lack of awareness about this clinical entity amongst non HF specialists. Recent scoring systems proposed by experts in the HF field could not be translated into clinical practice as they are too complex to be used by the majority of physicians involved in HF management. ML based algorithms proposed in this study have a true potential to be used by a non HF specialist. The mobile application incorporating the ML algorithm can help translate the diagnosis of HFpEF into a simple bed side exercise.

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