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# Application of machine learning in predicting frailty syndrome in patients with heart failure

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## Abstract

Prevention and diagnosis of frailty syndrome (FS) in patients with heart failure (HF) require innovative systems to help medical personnel tailor and optimize their treatment and care. Traditional methods of diagnosing FS in patients could be more satisfactory. Healthcare personnel in clinical settings use a combination of tests and self-reporting to diagnose patients and those at risk of frailty, which is time-consuming and costly. Modern medicine uses artificial intelligence (AI) to study the physical and psychosocial domains of frailty in cardiac patients with HF. This paper aims to present the potential of using the AI approach, emphasizing machine learning (ML) in predicting frailty in patients with HF. Our team reviewed the literature on ML applications for FS and reviewed frailty measurements applied to modern clinical practice. Our approach analysis resulted in recommendations of ML algorithms for predicting frailty in patients. We also present the exemplary application of ML for FS in patients with HF based on the Tilburg Frailty Indicator (TFI) questionnaire, taking into account psychosocial variables.

**Key words:** heart failure, medical personnel, machine learning, frailty syndrome, artificial intelligence

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## Introduction

Frailty syndrome (FS) is broadly defined as the premature or abnormal aging of elderly patients, indicated by a set of symptoms associated with a higher risk of mortality, lower quality of life and increased healthcare utilization.<sup>1,2</sup> Understanding the contributions of physical, social or psychological factors in the prevalence of frailty is an important research problem in contemporary medicine. Addressing this challenge should result in novel frailty measurements that help healthcare personnel promptly identify and optimally manage patients with FS.

In clinical literature, frailty is often associated with terms such as weakness and fatigue.<sup>3</sup> Most definitions consider frailty to be a clinically recognizable condition resulting from aging that reduces the ability to cope with daily or severe stressors.<sup>4</sup> However, frailty is also linked to post-surgery complications and other consequences of stress associated with prolonged hospitalization and the risk of death.<sup>5</sup> Until recently, the frailty concept was defined as closely linked to old age, but there are indications that younger patients can also develop this syndrome.<sup>6,7</sup>

Frailty is an increasingly well-recognized clinical syndrome in cardiology that extends beyond the physiological aging process and commonly co-occurs with many cardiovascular diseases as disease-related frailty.<sup>7</sup> Frailty is more common in patients with heart failure (HF) than in the general population.<sup>8</sup> Heart failure is a clinical syndrome in which the heart is not able to pump enough blood to meet the demand of the body. The condition leads to symptoms (e.g., dyspnea, swelling in the ankles and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) The number of patients with HF is increasing due to the aging of the population and the therapeutic advancements that improve the survival of patients with heart disease.<sup>7</sup>

The prevalence of FS in patients with HF is approx. 45%.<sup>9</sup> The Cardiovascular Health Study showed that frailty is significantly associated with HF, affecting 1 in 2 adults, independent of age or the New York Heart Association (NYHA) classification.<sup>10,11</sup> A diagnosis of HF indicates the additional loss of biological reserves and increased vulnerability to several adverse clinical consequences.<sup>12</sup> Frailty increases the risk of HF and, in patients already diagnosed, contributes to increased mortality, rehospitalization and decreased quality of life.<sup>13–16</sup> The clinical identification of frailty can play an important role in developing preventive strategies against age-related conditions. Stressors that may affect a patient with frailty, and may predispose the patient to adverse health consequences, as well as lend themselves to modification or control, are divided into 4 groups: clinical, physical-functional, psychological, and social. These stressors can be clinical or non-clinical, acute or chronic, reversible or irreversible, and require supportive care.<sup>8</sup>

## Objectives

This paper presents the potential of using an artificial intelligence (AI) approach, specifically machine learning (ML), to predict frailty in patients with HF.

## Measurement instruments of frailty

There are several measures to diagnose frailty and identify the potential risk of developing FS. These measures differ in their approach to detecting frailty, which is historically consistent with the long-discussed ambiguity in effectively operationalizing the definition of FS.<sup>17</sup> The operationalization of FS focuses on the accumulation of deficits or embraces multidimensionality of the FS. The first approach assumes that more health deficits indicate higher frailty.<sup>18,19</sup> On the contrary, the multidimensional approach describes frailty as a dynamic state affecting an individual who experiences losses in 1 or more domains of human functioning (physical, psychological, social).<sup>19</sup> Here, we present selected frailty measures based on either deficit's accumulation or multidimensional approaches<sup>19</sup>:

- The Tilburg Frailty Indicator (TFI) is a self-report questionnaire that consists of 15 questions related to physical, psychological and social deficits to identify frailty.<sup>20</sup> The TFI measures losses caused by the influence of a range of variables, and losses which increase the risk of adverse outcomes.
- The Electronic Frailty Index (eFI) includes the diagnosis of 36 deficits (symptoms, diseases, disabilities, and abnormal laboratory results) to classify patients into 4 groups: no frailty, low frailty, moderate frailty, and high frailty.<sup>21</sup>
- The FI-CD index (Frailty Index based on Clinical Deficits, or Frailty Index of Cumulative Deficits) is based on clinical deficits, including at least 30 comorbidities, symptoms, diseases, and disabilities.<sup>18</sup>
- The frailty phenotype developed by Fried et al. includes the assessment of unintentional weight loss of over 5 kg in the past year, fatigue, lower grip strength, slower walking gait, and lower physical activity to classify older people.<sup>22</sup>
- The frailty Index based on Biomarkers (FI-B) is innovative but time-consuming and costly compared to the questionnaire-based approaches.<sup>18</sup>
- The Frailty Trait Scale (FTS) consists of 12 elements covering 7 dimensions: energy balance and nutrition, activity, nervous system, circulatory system, weakness, endurance, and slowing down.<sup>23</sup>
- A simplified FTS5 (based on 5 elements) was developed from the full FTS.<sup>24</sup>

The Heart Failure Association (HFA) of the European Society of Cardiology advocated that a holistic, multidimensional approach was more reliable than a physical approach only in identifying those patients with HF who have coexisting FS.<sup>8</sup> According to these assumptions, frailty in patients with HF should be defined as a multidimensional and dynamic condition independent of age, making

a person diagnosed with HF more vulnerable to stressors. As frailty in HF is viewed as a dynamic and partially reversible condition, recognizing those modifiable components is important to guide management and improve HF outcomes. Focusing on the reversible components of frailty in HF may reduce the risk of adverse clinical effects, such as increased morbidity, increased healthcare needs (hospitalization, prolonged recovery and institutionalization) and increased dependency and higher mortality risk.<sup>8</sup> Early recognition of frailty in older adults with HF is needed to target interventions to slow functional decline and improve patient-centered outcomes.

## Artificial intelligence in clinical decision-making

Artificial intelligence is gaining popularity and recognition as a feasible tool to support clinical decisions. There is a noticeable trend in the number of publications on AI in biomedicine, including topics such as living assistance, information processing, research, and the most urgent need in medicine: disease diagnostics and prediction.<sup>25</sup> Currently, the most popular AI method is ML, which is a particular subclass of AI methods. In short, ML is a data-driven approach which uses algorithms to learn, instead of using explicit programming, complex patterns from existing data and uses these patterns to make predictions on unseen data to make increasingly better decisions.<sup>26</sup> Support-vector machines (SVM) are one of the most popular options in the broadly understood medical applications,<sup>27</sup> whereas convolutional neural networks (CNN) are the most popular in the case of disease diagnosis.<sup>28</sup> Most cases of disease detection methods using AI are based on data in the form of diagnostic imaging,<sup>27,29</sup> and the 3 most common disorders detected are cardiovascular disease, sensory system disease and cancer.<sup>29</sup>

As noted, cardiology is at the forefront of AI applications in medicine. Machine learning is used in various parts of this field, and this connection is gaining popularity, which can be observed in the number of papers published on this subject.<sup>30</sup> Usage of AI includes echocardiography, nuclear cardiology, electrophysiology-enhanced diagnosis, prediction of treatment, and prognosis of disease development.<sup>31</sup> There is a great need to improve the algorithms for detecting patients at risk of hospital admission, apart from the possibility of analyzing patient data from devices such as pacemakers or smartwatches.<sup>31</sup> AI-based models for cardiology can also be divided by the type of task they are designed to perform, respectively: diagnosis, classification and prediction. Although the classification was presented as more challenging than the diagnosis, better results were obtained for this purpose. In contrast, the prediction task proved to be the most difficult and produced the worst outcomes, which may be due to the variety of factors that influence disease development and mortality.<sup>32</sup> The most frequently used models were neural networks (including deep and

convolutional networks), obtaining the most accurate results. Among other valuable algorithms, we can distinguish Random Forest, Naïve Bayes, Support Vector Machines, k-Nearest Neighbors, and Gradient Boosting Machines.<sup>32</sup> It is also worth mentioning that during the COVID-19 pandemic, AI-supported cardiological research methods were developed that allowed for better medical examination, especially for patients infected with the coronavirus.<sup>33</sup>

Since frailty is an interdisciplinary issue, there is a need for multidisciplinary frailty definitions and their corresponding measures. Recent technological advances allow for much more extensive data to be collected, integrated and processed in a more complex way, resulting in a significant understanding of frailty. A recent approach to predict frailty is the application of ML. Machine learning algorithms are designed to apply ML to extract knowledge from available data.<sup>34</sup>

The explainable AI (XAI) approach could be considered a suitable method for dealing with frailty problems and evaluating the relations between different syndromes, which cannot be seen directly from separate questionnaires. The XAI facilitates the diagnosis and treatment of frailty as we can determine the importance of input features, enabling interpretation of the results obtained, dependencies between inputs and their values, and identification of data and concept drift. An example of such methods is tree-based algorithms applied in healthcare due to their property of explainability. Among all possibilities, XGBoost implementation can be considered a reasonable choice as it naturally deals with continuous, binary/discrete and missing data consistently.

## Benefits of applying ML in managing frail patients with HF

From a medical perspective, ML brings potential advantages in predicting FS. These potential benefits are following<sup>35,36</sup>:

- Employing an explainable ML model may help clinicians to gain new insight into the possible determinants of frailty. While some features are non-modifiable, e.g., age and height, other factors may be directly modifiable through lifestyle changes, physical exercise or cognitive stimulation (e.g., weight, smoking and mobility). As a result, it may be possible to ensure that a patient avoids reaching critical threshold values associated with frailty for some features. Conversely, those threshold values may be set as the targets to achieve a more stable state if engaging in rehabilitation.
- Facilitating a patient's diagnosis in the event of incomplete data about the patient (e.g., for a patient from another country or a patient who has not previously used medical services).
- Possibility of indicating significant relations between the frailty variables. Many frailty measures are based on highly correlated variables (e.g., see the Frailty Index (FI) of FI-CD measure). As indicated above, frailty includes dozens of measures, e.g., physical health, behavioral risks,

cognitive function, and mental health, which are also highly correlated (e.g., age and marital status). In practice, these measures do not provide new information important from the standpoint of frailty diagnosis. Machine learning algorithms can effectively identify the most representative associations between frailty variables. Here are the most prominent benefits for managing frail HF patients with a machine-learning approach:

- Developing a semi-open system with sufficient data, where AI system is screening patients based on specific diagnostic taxonomy with confidence intervals (frail status, pre-frail condition/endangered/healthy).
- Determination of diagnostic importance of frailty components and their contribution to the FS and other comorbid diseases (e.g., assessing the importance of frailty measures for frail patients with HF). For instance, one can target those who suffer from multiple diseases, e.g., frailty and hypertension. There may be synergy effects where co-existing diseases can be linked to an increased risk of the condition under study. This will probably be more specific for this subgroup than for both diseases separately (nonlinearity, in addition to the nonlinearity concerning age groups and gender). Subgroup-specific “diagnostic importance of variables” could be used to diagnose patients, for example, in precision and holistic medicine.
- Identification of the FS and its importance (see below) based on incomplete data. Healthcare professionals can benefit from this functionality when facing extensive historical data, as well as a shortage of resources.
- Panel data mining from long-term observation. Possibility to have a more advanced predictive model for prophyllaxis (preventive care).
- Updating and expanding the AI systems by including existing clinical data and demographics of a given region and country.
- Possibility of screening pre-frail patients (non-binary output).
- Limiting human error caused by tiredness, subjectivity, abundance of data, or other factors.
- The AI system supports the selection of therapeutic strategies, i.e., personalization of multidisciplinary care in HF, building health literacy and patient empowerment, and personalization of educational recommendations for patients with HF and FS.
- The AI system provides support for multimorbid patients with FS in a modern, holistic manner. This allows patients to gain greater insight into their disease and improve their self-care.

## Applying ML algorithms to predict frailty

There are recent reports on applying ML algorithms to facilitate the integration of existing, traditional frailty diagnosis tools. For instance, one group used ML algorithms to develop predictive models for hospitalization, fracture occurrence, disability, and mortality as proxies for

frailty.<sup>37</sup> In another work, different combinations of indicator variables were used to predict frailty with the results compared to eFI diagnoses.<sup>38</sup> Their results hinted that the support vector machines (SVM) outperformed k-nearest neighbors and the decision tree algorithms. The results of these studies were promising, but the number of explanatory variables used in the most effective SVM model was 70. The accuracy of this model was 93.5%, with a very promising Cohen’s kappa index of 87%. At the same time, the models containing 10 and 11 explanatory variables turned out to be better than some of the more numerous explanatory variables of the models, which suggests significant possibilities of using various combinations of variables. However, this work only concerned patients over 75 years of age and did not focus on any specific disease.

In the context of frailty prediction, research on biomarkers has also been used to identify and classify patients with no frailty, risk of frailty and suffering from frailty.<sup>39</sup> These works highlight the effectiveness of ML methods to extract relevant information. The AI-based framework applies both supervised and non-supervised learning methods. Non-supervised learning is involved in the classification or grouping methods using, for example, k-means, k-nearest neighbors, decision tree algorithms, or other such as the stochastic gradient descent (SGD) or naïve Bayes classifiers applied depending on the size of data. Supervised learning uses the following methods: SVM, neural networks (NN), convolution neural networks (CNN), or other deep learning methods.

Our review also highlights several recent studies where AI, particularly ML algorithms like XGBoost and SVM, have shown effectiveness in frailty prediction using electronic medical records (EMRs), with evidence of high sensitivity and specificity.<sup>38,40</sup> These studies demonstrate the potential of AI to enhance the accuracy and efficiency of frailty screening compared to traditional methods.<sup>38</sup> Additionally, AI has been shown to improve the predictive performance of frailty indices in patients with HF, outperforming conventional models.<sup>41,42</sup>

Several recent studies have demonstrated the effectiveness of ML techniques in cardiovascular and ageing domains. A study utilized a gradient-boosting decision-tree method, showing the robustness of ML models in analyzing vascular function, cardiac motion and myocardial fibrosis, as well as conduction traits for cardiovascular ageing prediction.<sup>43</sup> Another research on ML algorithms for heart disease prediction highlighted how feature selection in ML models can enhance prediction accuracy, indicating that these models are capable of identifying and utilizing redundant information effectively.<sup>44</sup> Furthermore, a study using ML model demonstrated how ML techniques, including random forest models, can be employed to impute missing values in datasets.<sup>45</sup> This work identified a set of pre-frail indicators in middle-aged, community-dwelling adults. A recent work using SVM for identifying frailty in elderly individuals concluded that it is feasible



to use incomplete and imbalanced medical data for developing predictive models for FS. This not only reinforces the adaptability of ML models to diverse data conditions but also underscores their ability to discover potential predictive factors that are clinically relevant.<sup>46</sup> In summary, the application of ML in healthcare holds significant promise, particularly in understanding and addressing frailty conditions in aged individuals.

One of the main problems in ML methods application is appropriate data preparation and feature extraction. Data that will be used to feed AI-based FS prediction system can be divided into 2 main categories:

- Data that are possible to be joined, i.e., standard identifiers, are available => these are the data on which the analysis will be performed.
- Data that feed the model irrespective of patients => there are the data that will help create models and validate hypotheses.

We do not require a standard model for all patient-specific data on the level of data lakes. However, joining data from different sources should be feasible using known identifiers. While many AI methods have proven to be efficient, deep NN have shown remarkable improvements in big data marts and offer the best efficiency in many application areas. Most neural models, such as networks of simple non-linear, enable exchanging information via fixed connections, adapting simple parameters to learn vector mappings. However, complex neurons, microcircuits and small neural cortical ensembles with structural connections (fixed or slowly changing) can also be applied to model complex network states, which contain rich internal knowledge in modules interacting flexibly. The most straightforward model suitable for a given data and easy to handle should be used, as simpler models generalize better and are easier to interpret. A proper hybrid cloud approach should be considered to carry out efficient AI calculations. Some personal data points are susceptible and should not leave local infrastructure. Anonymization techniques should be utilized here, or maybe only data summaries should be processed in the cloud.<sup>47</sup>

## Predicting importance of frailty components in heart failure: Analysis of TFI measure

Our research team analyzed the diagnostic importance of individual psychosocial and physical criteria in the diagnosis of FS in elderly patients with HF.<sup>48</sup> Based on the AI approach and the TFI questionnaire, including physical, psychological and social components, ML models were constructed using a decision tree, random decision forest and AdaBoost classifier. These models were trained, validated and tested on 3 separated subsets of the full dataset.

To find the feature importance of the explanatory variables in ML classifying models, it was necessary to choose an appropriate method of evaluating these

variables. The permutation method compares the accuracy of the model with its accuracy when we shuffle the values of specific variables. The procedure was performed separately for each of the 15 TFI explanatory variables, with many permutations. The calculations were made for 10,000 permutations and a single variable in our case. The greater the number of respondents (and their answers to a given TFI question) in the sample's subsets, the more permutations should be made to obtain more accurate results. Machine learning models were built and verified in a sample of patients with HF. To determine the diagnostic validity and verify the hypotheses, selected components of the physical domain were compared with all the psychological and social domain components within the TFI questionnaire.

The models with the highest classification accuracy were selected from the 3 ML algorithms, i.e., the random decision forest and the AdaBoost classifier (Table 1). The conducted ML analysis showed that none of the variables within the social domain was more diagnostically important than the physical variables (i.e., experiencing difficulties due to difficulties in walking, lack of strength in the hands and physical fatigue). In the case of psychological criteria for the diagnosis of FS, the variable related to irritability (i.e., feeling excited or nervous in the last month) was diagnostically more important than all considered physical variables, while the variable related to depressive mood (i.e., a decrease in mood in the previous month) was diagnostically more important than the physical variables: lack of strength in the hands and physical fatigue.

Table 1. Results from testing phase for selected machine learning (ML) – true positives and true negatives

ML model	True positives	True negatives
Decision tree	79.07	87.50
Random forest	93.02	100.00
AdaBoost	100.00	93.75

## Limitations

Our review has some limitations. First, from the perspective of model development, it is essential to generalize the frailty ML model to different healthcare settings and patient populations. Because the models were validated in a few studies and available datasets, the model's real-world applicability in clinical conditions may be limited. Second, our paper discusses some general aspects of feature selection and interpretability related to the ML approach. However, this review does not elaborate on the specific features, their combinations or how they relate to the frailty concept. Therefore, the interpretability of the chosen features and their clinical relevance may be a limitation. Additionally, whereas particular ML models of frailty show promising results in accuracy, it would be essential to examine their performance on independent datasets to validate practical claims rigorously. We also know

that the ML model's generalizability to a broader age range should be considered. The present work focuses on elderly patients, and the findings may not apply to younger patients with HF. Finally, the work suggests the potential benefits of using AI-based approaches in predicting frailty and the possibility of integrating these predictions into clinical practice. In fact, the real-world implementation of the frailty ML model and its acceptance by healthcare staff might be challenging.

## Conclusions

Identifying, interpreting and managing patients with both FS and HF requires a significant amount of information, resulting in a time-consuming and costly process. Artificial intelligence, specifically ML, can aid in parsing this data. Machine learning can be used to develop new diagnostic measurements of frailty and support research on improving classic measures, as well as addressing the theoretical issue of the operational definition of this clinical syndrome. These ML computations can aid in providing personalized care for patients at risk of the consequences of FS, improving diagnostic tools for examining this syndrome and facilitating effective collaboration between psychologists and healthcare professionals. This approach is applicable in holistic and patient-centered medicine, which requires knowledge from various disciplines to enable causal and symptomatic treatment while considering the patient's different domains of life and behavior. Future development should include a discussion on the compatibility of clinical patient data sources and privacy.

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