Application of Machine Learning in Predicting Frailty Syndrome in Patients with Heart Failure

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Research Article

Keywords: Frailty Syndrome (FS), Heart Failure (HF), Artificial Intelligence (AI), Machine Learning, Medical Personnel

Posted Date: February 15th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2139591/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Advances in Clinical and Experimental Medicine on March 26th, 2024. See the published version at https://doi.org/10.17219/acem/184040.
Abstract

Background

Prevention and diagnosis of frailty syndrome (FS) in patients with heart failure (HF) requires innovative systems supporting medical personnel to tailor and optimize their treatment and care. Classical methods of diagnosing the FS in patients are not entirely satisfactory. Healthcare personnel in clinical setting use a combination of test and self-reports 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.

Methods

This paper aimed to present the potential of using the AI approach, emphasizing machine learning in predicting frailty in patients with HF. Our team critically scrutinized the literature on machine learning applications for FS syndrome, as well as reviewed frailty measurements applied to modern clinical practice.

Results

Our approach analysis resulted in recommendations of machine learning algorithms for predicting frailty in patients. We also presented the exemplary application of machine learning for frailty syndrome in HF patients based on TFI questionnaire measurements, taking into account psychosocial variables.

Conclusions

We recommend AI and machine learning for the holistic and personalized care of patients at risk of the consequences of FS, improve diagnostic tools examining this syndrome, and effective collaboration between psychologists and health care professionals.

Background

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 the increased healthcare utilization [1, 2]. Understanding the contributions of physical, social, or psychological factors in the prevalence of frailty is an important research problem in contemporary medicine. Addressing such a challenge should result in novel frailty measurements that help healthcare personnel to promptly identify, prevent, and optimally manage patients with FS.
In the clinical literature, terms such as weakness and fatigue are often associated with frailty [3]. Most definitions consider frailty as a clinically recognizable condition resulting from aging that reduces the ability to deal with daily or severe stressors [4]. However, frailty is also linked to post-surgery complications and other consequences of stress associated with prolonged hospitalization and the risk of death [5]. 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 [6, 7].

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 [7]. Frailty is more common in patients with HF than in the general population [8]. HF 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., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) The number of patients with HF is increasing due to the aging of the population and the therapeutic advancements which improve survival of patients with heart disease [7].

The prevalence of FS in patients with HF is approximately 45%. [9]. The Cardiovascular Health Study showed that frailty is significantly associated with HF, affecting one in two adults, independent of age or New York Heart Association (NYHA) class [10, 11]. A diagnosis of HF indicated the additional loss of biological reserves and increased vulnerability to several adverse clinical consequences [12]. Frailty increases the risk of HF and, in patients already diagnosed, contributes to increased mortality, rehospitalization, and decreased quality of life [13–16]. 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 that, on the one hand, may predispose the patient to adverse health consequences and, on the other hand, may lend themselves to modification or control are divided into four groups: clinical, physical-functional, psychological, and social. They can be clinical, non-clinical, acute, chronic, reversible, treatable, and irreversible and require supportive care [8].

**Measurement Instruments Of Fs**

There are several measurements to diagnose frailty and identify the potential risk of developing this syndrome. These measures are diverse in their approach to detecting frailty. The operationalization of FS focuses on accumulation-of-deficits or embraces multidimensional dimensions of the FS. The first approach assumes that more health deficits indicate higher frailty [17, 18]. On the contrary, the multidimensional approach describes frailty as a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social) [18]. Here, we present selected frailty measures based on either deficit’s accumulation or multidimensional approaches [18]:

- 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 [19]. The TFI measures losses caused
by the influence of a range of variables, and losses which increases the risk of adverse outcomes

- The Electronic Frailty Index (eFI) includes the diagnosis of 36 deficits, ranging from symptoms, diseases, disabilities, and abnormal laboratory results to classify patients into four groups – no frailty, low frailty, moderate frailty, and high frailty [20].

- The FI-CD index (Frailty index based on clinical deficits, alternatively, Frailty index of accumulative deficits) is based on clinical deficits, including at least 30 comorbidities, symptoms, diseases, and disabilities [17].

- The frailty phenotype developed by Fried et al. includes the assessment of unintentional weight loss of over 5 kgs in the past year, fatigue, lower grip strength, slower walking gait, and lower physical activity to classify older people [21].

- The FI-B (Frailty Index based on Biomarkers) is innovative but time-consuming and costly compared to the questionnaire-based approaches [17].

- The FTS (Frailty Trait Scale) consists of 12 elements covering seven dimensions: energy balance and nutrition, activity, nervous system, circulatory system, weakness, endurance, and slowing down [22].

- A simplified FTS5 (based on five elements) was developed from the full FTS [23].

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) advocated a holistic, multidimensional approach was more reliable than a physical approach only, in identifying those patients with HF who have coexisting FS [8]. 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 heart failure 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 health care needs: hospitalization, prolonged recovery, institutionalization, and increased dependency and higher mortality risk [8]. Early recognition of frailty in older adults with HF is needed to target interventions to slow functional decline and improve patient-centred outcomes.

**Ai In Medical/application/cardiology**

Artificial intelligence (AI) 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 [24]. In terms of AI methods, Support-vector machines (SVM) are one of the most popular options in the broadly understood medical applications [21], whereas convolutional neural networks (CNN) are the most popular in the case of disease diagnosis [26]. Most cases of disease detection methods using AI are based on data in the form of diagnostic imaging [25, 27], and the three most common disorders detected are cardiovascular disease, sensory system disease, and cancer [27].
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 [28]. Use cases include echocardiography, nuclear cardiology, electrophysiology enhanced diagnosis, prediction of treatment, and prognosis of disease development [29]. There is a great need to improve the algorithms for detecting patients at risk of hospital admission. Despite access to patient data from devices such as pacemakers or smart watches [29]. Al-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 (over 83.70% accuracy). 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 [30]. 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, Naive Bayes, Support Vector Machines, k-Nearest Neighbours, and Gradient Boosting Machines [30]. It is also worth mentioning that during the Covid19 pandemic, Al-supported cardiological research methods were developed that allowed for better medical examination, especially for patients infected with the coronavirus [31].

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 Al. Al algorithms are designed to apply machine learning to extract knowledge from available data [32].

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. 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 Application Machine Learning in Management Frail Patients with Heart failure From a medical perspective, machine learning brings advantages potential in predicting FS. These potential benefits are following [33, 34]:

- Employing an explainable machine learning model may help clinicians to gain new insights 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, 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 (for instance, see the Frailty Index (FI) of Accumulative Deficits (FI-CD) measure). As indicated above, frailty includes dozens of measures, e.g., physical health, behavioural risks, cognitive function, and mental health being also highly correlated (e.g., age and marital status). In practice, these measures do not bring new information important from the standpoint of frailty diagnosis. ML algorithms can effectively identify the most representative associations between frailty variables. ML algorithms can capture correlations without duplicating the same information multiple times.

- Developing a semi-open system with sufficient data, where AI 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 (non-linearity, in addition to the non-linearity 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. Health care 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 prophylaxis (preventive care).

- Updating and expanding the AI systems by the inclusion of 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, the abundance of data, or other factors.

- AI supports the selection of therapeutic strategies, i.e., personalization of multidisciplinary care in HF, building health literacy and patient empowerment, and personalization educational recommendations for patients with HF and FS.

- AI support for multimorbid patients with FS in a modern holistic way; patients can gain more insight into their disease to further enhance self-care.
Application Of AI Algorithms For Predicting Frailty

There are recent reports on applying AI algorithms to facilitate the integration of existing, classic frailty diagnosis tools. For instance, one group used AI algorithms to develop predictive models for hospitalization, fracture occurrence, disability, and mortality as proxies for frailty [35]. In another work, different combinations of indicator variables were used to predict frailty with the results compared to eFI diagnoses [36]. Their results hinted that the 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 [37]. These works highlight the effectiveness of AI 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 SGD classifier or naive Bayes applied depending on the size of data. Supervised learning uses the following methods: SVM, neural networks (NN), CNN, or other deep learning methods.

One of the main problems in AI 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 two 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. However, many other AI methods have proved to provide very efficient results; however, in the case of big data marts, deep neural networks have made great improvements and are offering 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 [38]. However, we may also apply complex neurons, microcircuits, small neural cortical ensembles with structural connections (fixed or slowly changing) that enable us to model complex network states: rich internal knowledge in modules interacting flexibly. In general, we should find the most straightforward model suitable for a given data
and easy to handle: simpler models generalize better, interpretation [39]. A proper hybrid cloud approach should be considered to carry out efficient AI calculations – some personal data points are susceptible and shouldn't leave local infrastructure. Some anonymization techniques should be utilized here – or maybe only data summaries should be processed in the cloud.

**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 suffering from HF [37]. Based on the AI approach and the TFI questionnaire, including physical, psychological, and social components, machine learning models were constructed using decision tree, random decision forest, and AdaBoost classifier. These models were trained, validated and tested on three separated subsets of the full dataset.

To find the feature importance of the explanatory variables in machine learning 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 fifteen TFI explanatory variables, with many permutations. The calculations were made for ten thousand 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.

**Simulation Results**

Machine learning models were built and verified in a sample of patients with HF treated at the University Teaching Hospital in Wrocław in 2016–2019. The sample included 666 patients, most of them had been diagnosed with FS. 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 three machine learning algorithms, i.e., the random decision forest and the AdaBoost classifier (Table 1).
Table 1

Results from testing phase for selected machine learning – true positives and true negatives

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>True positives</th>
<th>True negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision Tree</td>
<td>79.07</td>
<td>87.50</td>
</tr>
<tr>
<td>Random Forest</td>
<td>93.02</td>
<td>100.00</td>
</tr>
<tr>
<td>AdaBoost</td>
<td>100.00</td>
<td>93.75</td>
</tr>
</tbody>
</table>

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.

**Conclusions**

The amount of information that is required to correctly identify, interpret and successfully manage a patient with FS and HF is significant, resulting in a time-consuming and costly process. AI, using machine learning can help to parse the data. Machine learning can serve to develop new diagnostic measurements of frailty and support research on improving classic measures and addressing the theoretical issue of the operational definition of this clinical syndrome. These machine learning computations can be used to apply AI in the holistic and personalized care of patients at risk of the consequences of FS, improve diagnostic tools examining this syndrome, and effective collaboration between psychologists and health care professionals. This is applicable in holistic and patient centered medicine, which requires knowledge from all kind of disciplines, allowing for the causal and symptomatic treatment while considering the patient's various domains of life and behavior. Future development should include discussion on the compatibly of clinical patient data sources and privacy.

**Abbreviations**

Al: artificial intelligence; CNN: convolutional neural networks; eFI: Electronic Frailty Index; ESC: European Society of Cardiology; FI-B: Frailty Index based on Biomarkers; FI-CD: Frailty index based on clinical deficits; FI: Frailty Index; FS: frailty syndrome; FTS: Frailty Trait Scale; HF: heart failure; HFA: Heart Failure Association; NN: neural networks; NYHA: New York Heart Association; SVM: support-vector machines; TFI: Tilburg Frailty Indicator.

**Declarations**
Ethics approval and consent to participate

Not applicable. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding sources are associated with this article.

Author contributions


Acknowledgements

The authors would like to thank to all experts who cooperated in preparing this paper.

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