Explainable machine learning framework for biomarker discovery by combining biological age and frailty prediction

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Abstract

Background: Biological age (BA) and frailty are two distinct measures of health that offer insights into aging. The existing machine learning (ML) predictors of BA or frailty from blood-based biomarkers are incapable of comparing and analyzing these biomarkers, which may deepen our understanding of these two distinct pathways toward aging.

Objective: This study aimed to develop a framework to compare and analyze biomarkers by combining BA and frailty ML predictors with eXplainable Artificial Intelligence (XAI) techniques.

Methods: We utilized data from middle-aged and older Chinese adults (?45 years) in the 2011/2012 wave (n=9702) and the 2015/2016 wave (n=9455, as external validation) of the China Health and Retirement Longitudinal Study (CHARLS). Sixteen blood-based biomarkers were used to predict BA and frailty. Four ML algorithms were employed in the training and validation, and performance metrics were compared to select the best models. Then, SHapley Additive exPlanations (SHAP) analysis was conducted on the selected models.

Results: Gradient Boosting performed the best in the BA predictor, and CatBoost performed the best in the frailty predictor. Traditional ML feature importance identified cystatin C and glycated hemoglobin as the major contributors for their respective models. However, subsequent SHAP analysis demonstrated that only cystatin C was the primary contributor in both models, suggesting that it plays an important role in both pathways.

Conclusions: Our novel framework can compare and analyze biomarkers by integrating BA and frailty predictors and XAI techniques. The present approach leverages routine blood biomarkers and can easily incorporate additional biomarkers, providing a scalable and comprehensive toolset that offers a quantitative understanding of interesting biomarkers and complex physiological traits. Clinical Trial: N/A

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Keywords: Biological age; Frailty; Machine learning; eXplainable Artificial Intelligence; Biomarker discovery

Introduction

Understanding biological aging and frailty provides valuable insights to comprehend and decipher age-related diseases, as well as to extend the lifespans and health spans of the senior population. Blood-based biomarkers are the most commonly used, explainable, and cost-effective health indicators in clinical practice [1]. Predicting BA and frailty from these biomarkers would help identify novel biomarkers related to aging, which are imperative for understanding the aging process, assessing individual health status, and developing interventions to promote healthy aging [2,3].

Machine Learning Predictors of Biological Age and Frailty and Biomarker Finding

The concept of BA has been increasingly used in ageing research in an attempt to measure the progression of biological aging as opposed to chronological age (CA). A reliable model of BA is of crucial importance in the fields of geriatrics and gerontology. BA, calculated from blood-based biomarkers across multiple physiological systems, provides a comprehensive assessment of an individual's functional status and overall health. It identifies factors contributing to accelerated ageing (where BA exceeds CA) and offers strategies to optimize health span [1,4,5]. Furthermore,

BA enables both personalized and population-level monitoring of the aging trajectory, empowering healthy aging and informing public health initiatives. The accurate quantification of BA not only facilitates screening of high-risk individuals for accelerated aging but also provides a surrogate endpoint for evaluating the effectiveness of various anti-aging interventions.

The most commonly applied approach to predicting BA is to employ ML algorithms to develop an aging clock based on these varying biomarkers. By comparing actual CA with predicted age, the age-independent part of the difference obtained is called AgeAccel or AgeDiff. The metric can be utilized to estimate the rate of biological aging [3]. Biochemical blood parameters are among the first data types used to build these aging clocks , also known as 'hematological clocks' [6–11]. These clocks, based on biochemical blood tests, aim to discover sensitive biomarkers of aging and provide a quantitative measure of aging, potential mortality and morbidity risks [12]. A range of novel blood-based biomarkers associated with aging has been identified in these studies, such as glycated hemoglobin [6], cystatin C [7–9,13].

Several serum biomarkers, such as hemoglobin and albumin, have been associated with frailty, indicating that aging blood exhibits the circulating hallmarks of frailty [14]. However, very few studies have modeled frailty using blood-based biomarkers [15–19]. Sargent et al. developed a predictive model that integrates biological and clinical frailty measures to identify robust biomarkers across datasets, finding that white blood cells and glucose are the most important blood-based biomarkers in frailty prediction [17]. Tseng et al. trained ML models using clinical, demographic, and polygenic-risk-scores, finding cystatin C, vitamin D, and creatinine the most important biomarkers contributing to frailty prediction in SHAP analysis [18]. Gomez-Cabrero et al. analyzed omic and routine laboratory variables from robust and frail or pre-frail individuals, finding three protective biomarkers (vitamin D3, lutein zeaxanthin, and miRNA125b-5p), and one risk biomarkers (cardiac troponin T) [19].

Machine Learning and Explainable AI for Biomarker Discovery

The advent of ML has been instrumental in advancing our understanding of the aging process, thus it has the potential to revolutionize how we monitor and treat age-related conditions [20]. This data-driven approach outperforms common statistical methods as it computes covariates even in complex interactions by considering a broader range of factors [21]. However, the "black box" nature of ML models hinders direct understanding, particularly in healthcare, where comprehending the underlying reasons behind a model's predictions is crucial. Increased interpretability may necessitate the simplification of a model or the sacrifice of some predictive accuracy [22]. The trade-off between interpretability and predictive accuracy poses a challenge in constructing ML models for estimating BA.

Recently, XAI has emerged as a powerful tool for interpreting the results of complex models, which provides transparency and understanding of how these models make predictions or decisions [23]. XAI methods such as Permutation Feature Importance [17,24–26] and SHAP [6,9,18,27] have been used to explain the predictions. Explainability analysis has revealed many important biomarkers of aging in the constructed BA clocks or frailty predictors. For example, Qiu et al. demonstrated that glycated hemoglobin displays a major relative weight in the BA estimation, potentially representing a novel biomarker[9]. Tseng et al. demonstrated that cystatin C the most important biomarkers contributing to frailty prediction, and it has an inverse relationship with creatinine [18]. Additionally, SHAP toolkit provides several visualization tools to depict the impact of features on the prediction model, such as the SHAP summary plot, waterfall plot, and partial dependence plot. These plots have been applied in many studies to explain the effects exerted on BA or frailty prediction models [18,23,27–29].

Blood constitutes an important part of the human body, and interacts with all systems, routine

blood-based biomarkers hold great potential to offer a comprehensive assessment of a person's health status and to construct instruments for health evaluation. As individuals age, specific biomarkers often change. Therefore, estimating BA or frailty based on a group of blood-based biomarkers has consistently been a main focus in aging research [6,7,9,10,17,18,26,30–34]. Moreover, these readily available biochemical markers are not only easily accepted by clinicians and the general public but also highly interpretable, rendering them suitable targets for application in XAI techniques.

Research Gap and Study Purpose

It is widely recognized that frailty shares a close yet intricate relationship with BA and can be considered a manifestation of accelerated biological aging [35,36]. Comparing and analyzing the biomarkers that contribute to BA and frailty prediction concurrently is highly beneficial for comprehending their complicated relationship, and it may even deepen our understanding of these two distinct pathways toward aging. Currently, although there are numerous ML predictors for BA or frailty separately, there is a noticeable absence of studies that integrate BA and frailty predictors along with XAI techniques to compare and analyze biomarkers by their feature importance and contribution to the ML models.

Therefore, we conducted the present study to develop a comprehensive analytic ML framework that combines BA and frailty predictors with SHAP analysis using routine blood-based biomarkers from the CHARLS database. The framework aimed to discover novel biomarkers in the BA and frailty ML models and identify the relative and precise quantitative weight of contributing biomarkers through subsequent SHAP analysis. Next, we compared and analyzed the most important biomarkers determined in the two ML pipelines.

Methods

Study Population and Variables

Data were extracted from the baseline survey (2011-2012) of CHARLS, an ongoing longitudinal cohort study of a nationally representative sample of community-dwelling adults from 28 provinces in China [37]. Adults aged 45 years and older were initially recruited in 2011/2012, and completed 5 waves of follow-up visits every two years until 2019/2020. In our study, only those participants who provided blood samples were included. After excluding those with severely missing data, the final sample size is 9702 out of 11847 participants enrolled in the baseline survey. Furthermore, we used the data from the third wave (2015-2016) of CHARLS as external validation dataset for the developed ML models. The dataset included 9455 participants out of 13,013 who provided blood samples.

The datasets used in this study were constructed by extracting and merging data from original sources across multiple Stata data files, covering demographics, blood biochemical parameters, biomarkers, and health status and functioning.

CA was derived from demographic data, and frailty status (a binary variable) was determined by a frailty index calculated from 43 scoring items in a series of physical examinations and questionnaires, which will be described in detail later.

A total of 16 blood-based biomarkers, including total cholesterol, triglyceride, glycated hemoglobin (HbA1c), urea, creatinine, high-sensitivity C-reactive protein, platelet count, white blood cell count, mean corpuscular volume, glucose, high-density lipoprotein, low-density lipoprotein, hemoglobin, cystatin C, uric acid, and hematocrit were used in the present study.

We imputed the missing data with the mean and normalized data using a min-max scalar [38,39]. It's worth noting that the data missing rate in the CHARLS database is quite low, less than

1.5%.

The characteristics of CA, frailty status and blood biochemical parameters used in the BA and frailty predictors are summarized in the Supplementary Table S1.

Biological Age Predictor Modeling

The target variable of ML is CA, and the feature variables consist of all blood-based biomarkers. The candidate models include Random Forest (RF), Gradient Boosting (GB), CatBoost, eXtreme Gradient Boosting (XGBoost). The selection of these models was based on the published literature and the requirement for interpretability [6,8,10,11,27].

The dataset was divided into a training and test set in an 80:20 proportion to train these models per se, with CA as the target value and 16 biomarkers as the feature variables [40]. Models were trained using 10-fold cross-validations to obtain the R-squared value and the mean absolute error (MAE). We then selected the best model by considering the two metric results as well as the model's interpretability. Feature importance of biomarkers was calculated and plotted. It is a powerful tool for model interpretation, helping us gain insights into which features drive the model's behavior and decision-making process.

Determination of Frailty Status and Frailty Index Construction

We followed the standard procedure of Searle et al. to construct the frailty index (FI)[41]. Variables were included in the calculation if they were associated with health status, accumulated with age, were not prematurely saturated, and covered a range of organ systems. We calculated a deficit accumulation FI using 43 health deficit items in 5 health domains that were assessed: self-rated health (1 item), chronic diseases (14 items), activities of daily living (6 items), instrumental activities of daily living(5 items), physical functional limitation（9 items） and mental health (8 items). Each item was scored between 0 and 1 point using different cut-off points listed in the Supplementary Table S2. The FI was calculated as the proportion of health deficits present. We then classified participants into 2 categories (frail and non-frail) using the FI cut-point of 0.25 [42–44] and named the binarized variable “frailty status”.

Frailty Status Predictor Modeling

The target variable of ML is frailty status. The feature variables and candidate models used are the same as those employed in the BA predictor building. The choice of models was also based on publications and later XAI analysis [28,45].

Since the original training data in frailty estimation were imbalanced (with only 14.8% being frail), we applied Synthetic Minority Over-sampling Technique (SMOTE) to generate synthetic samples of frail subjects, resulting in an equal number of two categories (n=8267). As imbalanced data may lead to biased estimates of training performance, it is necessary to apply SMOTE to balance the class distribution in the final preprocessing step [46]. SMOTE is a hybrid method that generates new samples of synthetic data based on information from the original samples, so that a balance can be achieved between categories with more and fewer observations.

We used the receiver operating characteristic (ROC) curve and area under the curve (AUC) to evaluate the models' performance. Feature importance of biomarkers was calculated and plotted.

Model Interpretation

We employed the SHAP technique to interpret the selected BA and frailty status predictors [47]. SHAP is a model-agnostic method widely used for explaining the output of a model by assigning importance scores to input features. It's based on Shapley values from cooperative game theory and provides a unified framework for interpreting black-box models. In the context of game theory, the model is considered the rules of the game while the input features are the potential players that may

either participate in the game (observed feature), or not (feature cannot be observed). Consequently, the SHAP technique calculates the Shapley values by evaluating the model under several different combinations of input features and finding the average difference in the output (prediction) when a feature is present compared to when it is absent. This difference is known as the Shapley value and represents the contribution of the feature to the prediction made by the model.

Researchers and practitioners use SHAP extensively to analyze and interpret models, identify influential features, detect biases, and improve model transparency. One of the key advantages of SHAP is its ability to provide not only feature importance rankings but also insights into how each feature affects individual predictions. We used the SHAP summary plot and waterfall plot to visualize the importance of biomarkers and their effects on the BA and frailty status prediction models. In summary plot, these effects are depicted using both a sign and magnitude, where the sign of the SHAP value indicates the direction of the association between the biomarkers and the targets. The waterfall plot visually represents each feature's contribution to a model's prediction for a specific data point, highlighting how the prediction varies with changes in feature values.

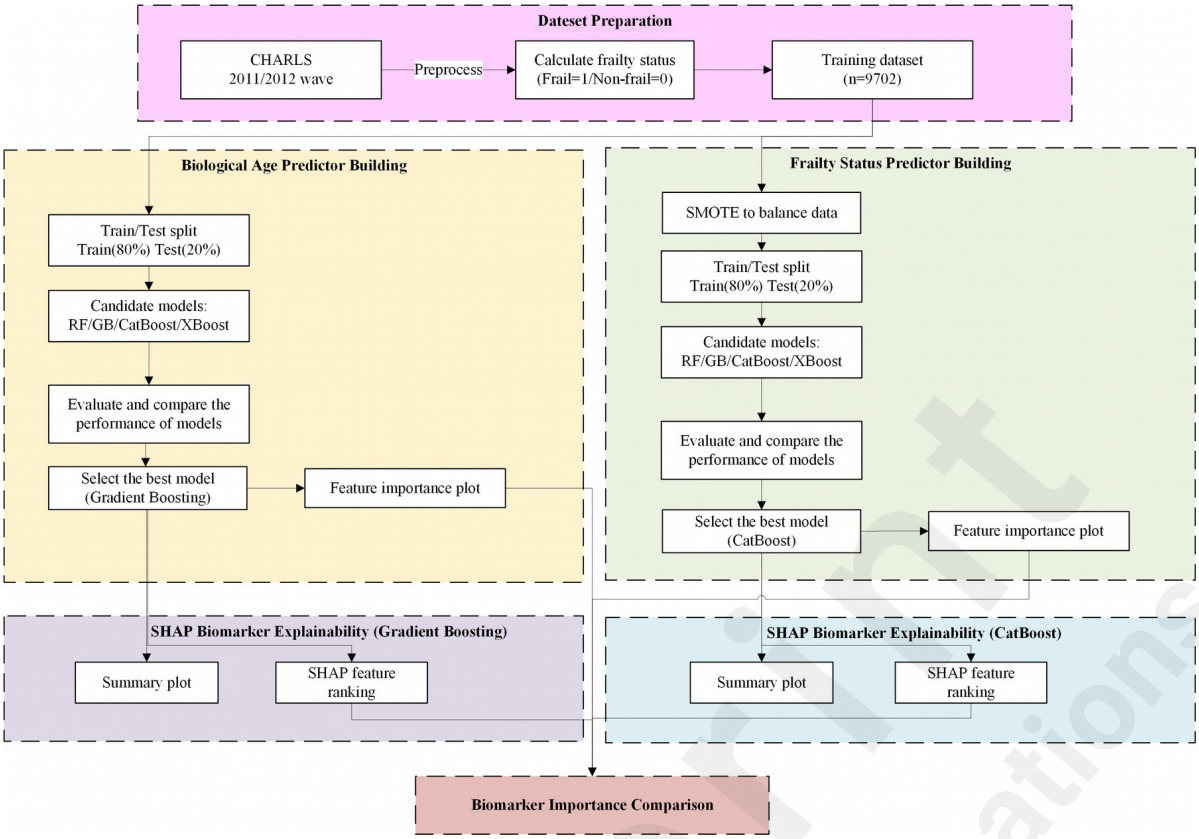
Feature ranking is a process in ML where the importance of each feature in a dataset is determined. It helps us understand which biomarkers contribute the most to the predictive performance of the BA or frailty status prediction model. In contrast to traditional ML feature importance that provides an overview of the input variables, SHAP-based feature importance reveals how the parameters contained in each variable contribute to the overall predictive ability of the model. In short, feature importance offers a broad overview of feature ranking for assessing model performance. On the other hand, SHAP-based feature importance ranking provides a more detailed understanding of how features contribute to individual predictions, including their interactions.

Results

Analytical Framework Overview

To develop an analytical framework unraveling BA and frailty from blood-based biomarkers, we first extracted, merged, cleaned, and imputed data from the CHARLS database to obtain a robust and usable dataset for subsequent ML (the baseline wave 2011-2012) and external validation (the third wave 2015-2016). Then, we trained the BA and frailty predictors through preprocessing, train/test splitting, optimization and cross-validation. The best models were selected from candidate models by comparing evaluation metrics. Next, we developed a SHAP explainability pipeline to compare and analyze the most important contributing biomarkers identified in the two models. We believe that the analytical framework combining BA and frailty predictors and SHAP analysis proposes a novel paradigm for biomarker discovery (Figure 1).

Figure 1 Analytical framework overview is present here.



Evaluation Metrics and Feature Importance of the BA and Frailty Status Predictors

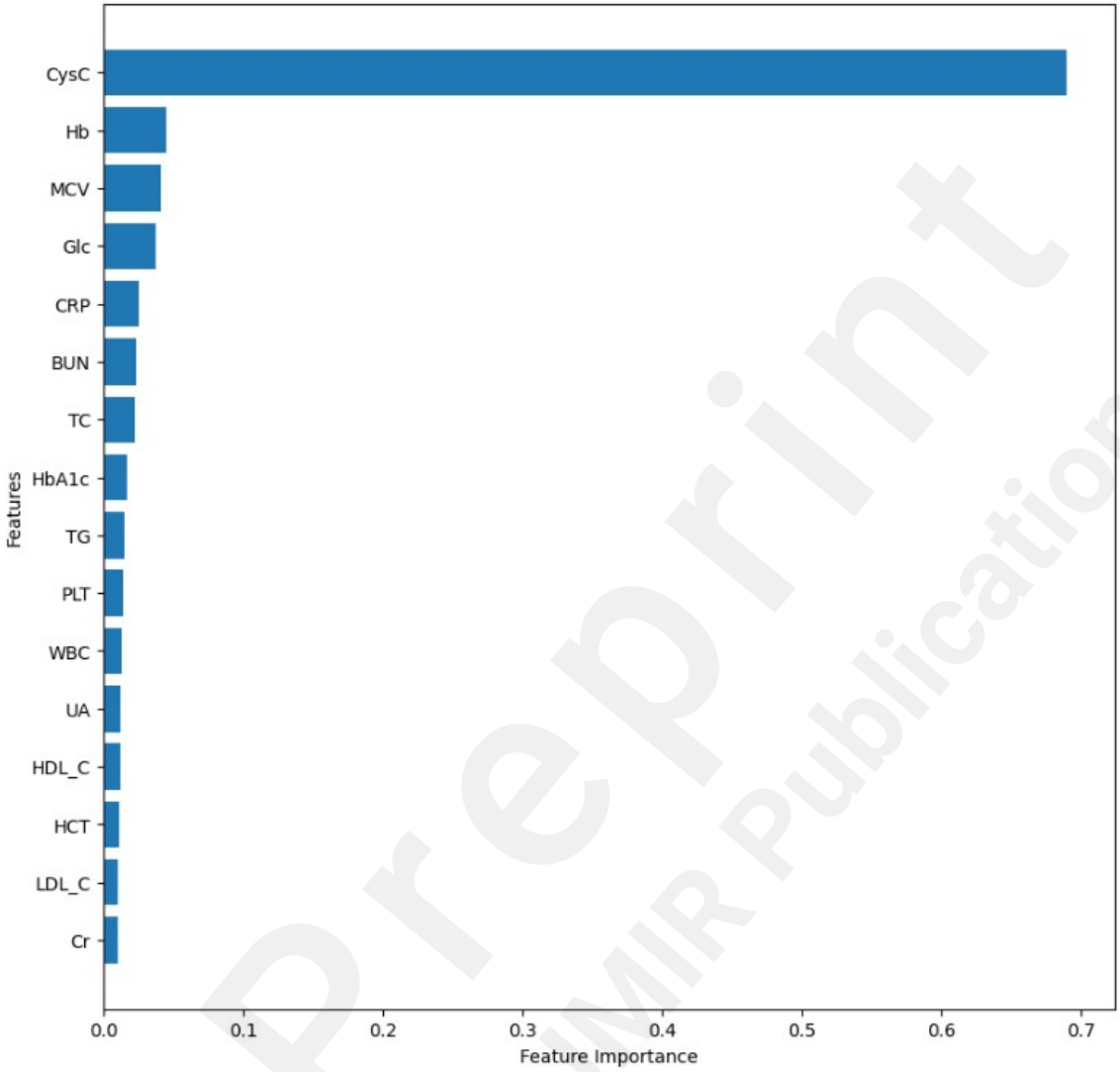
For the BA predictor, We listed the candidate models and their performance metrics in Table 1. The performance of candidate models for predicting BA was evaluated using MAE and R-squared. The best-performing model selected was Gradient Boosting. The external validation metrics of this selected model are presented in the last row of the table.

Table 1. Performance metrics of candidate models of BA predictor are listed here.

Model	MAE	MSE	RMSE	R-squared value
Random Forest	6.409	62.029	7.874	0.252
Gradient Boosting	6.371	61.159	7.819	0.262
CatBoost	6.371	61.787	7.859	0.254
XGBoost	6.689	68.612	8.281	0.172
Gradient Boosting (External Validation)	6.289	60.386	7.771	0.187

The feature importance plot of biomarkers in the BA prediction model (Gradient Boosting) is presented in Figure 2. The top five important biomarkers in the model are cystatin C, hemoglobin, mean corpuscular volume, glucose, and C-reactive protein.

Figure 2. Feature importance plot of BA prediction model (Gradient Boosting) is presented here.



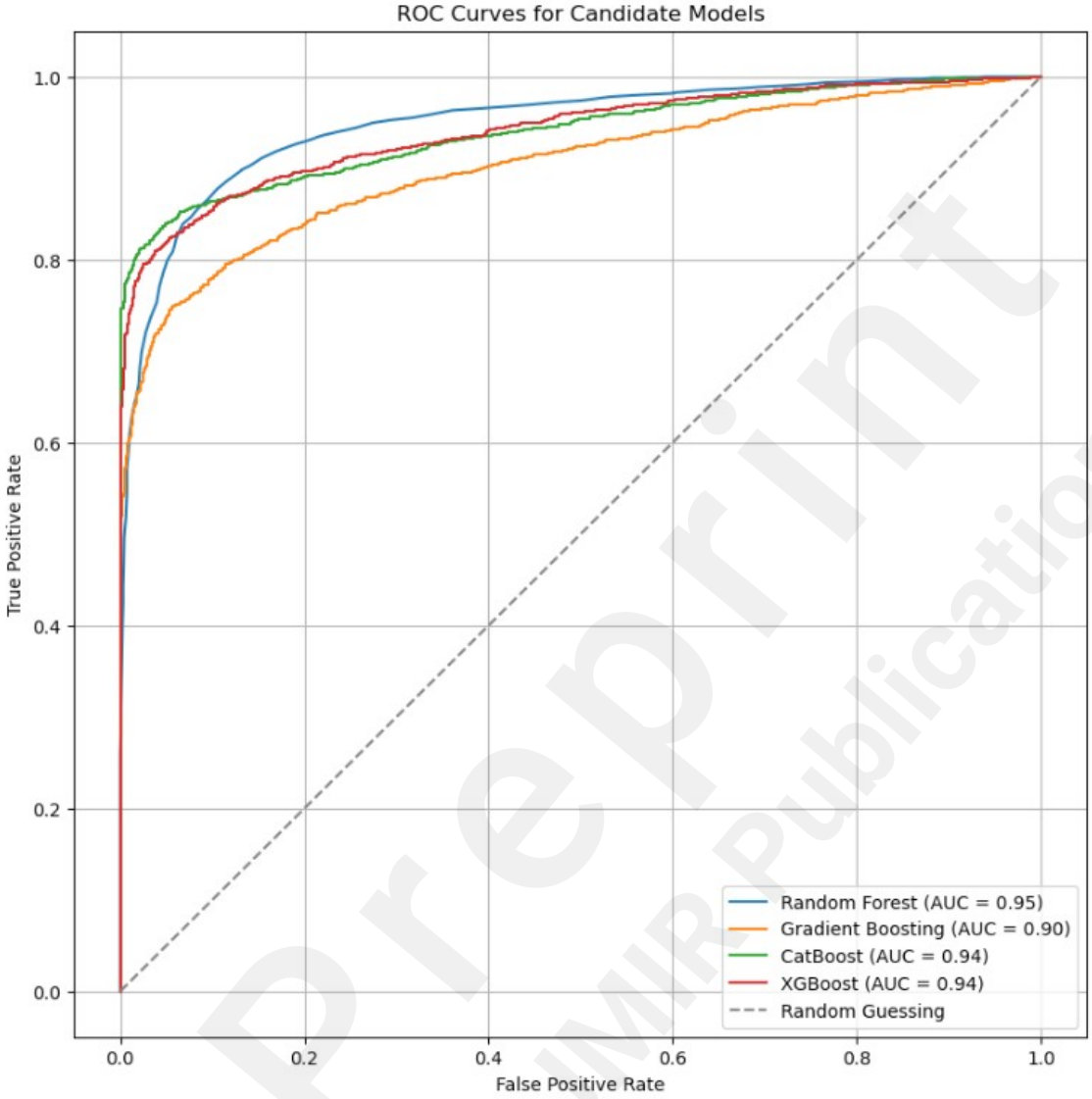
For the frailty status predictor, we listed the candidate models and their performance metrics in Table 2. The best model selected for this predictor was CatBoost. The external validation metrics of the selected model are presented in the last row of the table.

Table 2. Performance metrics of candidate models of frailty status predictor are listed here.

Model	**Accuracy**	**Precision**	**Recall**	**F1 Score**
Random Forest	0.885	0.872	0.895	0.883
Gradient Boosting	0.841	0.868	0.794	0.829
CatBoost	0.896	0.957	0.823	0.885
XGBoost	0.883	0.921	0.831	0.874
CatBoost(External Validation)	0.797	0.873	0.695	0.774

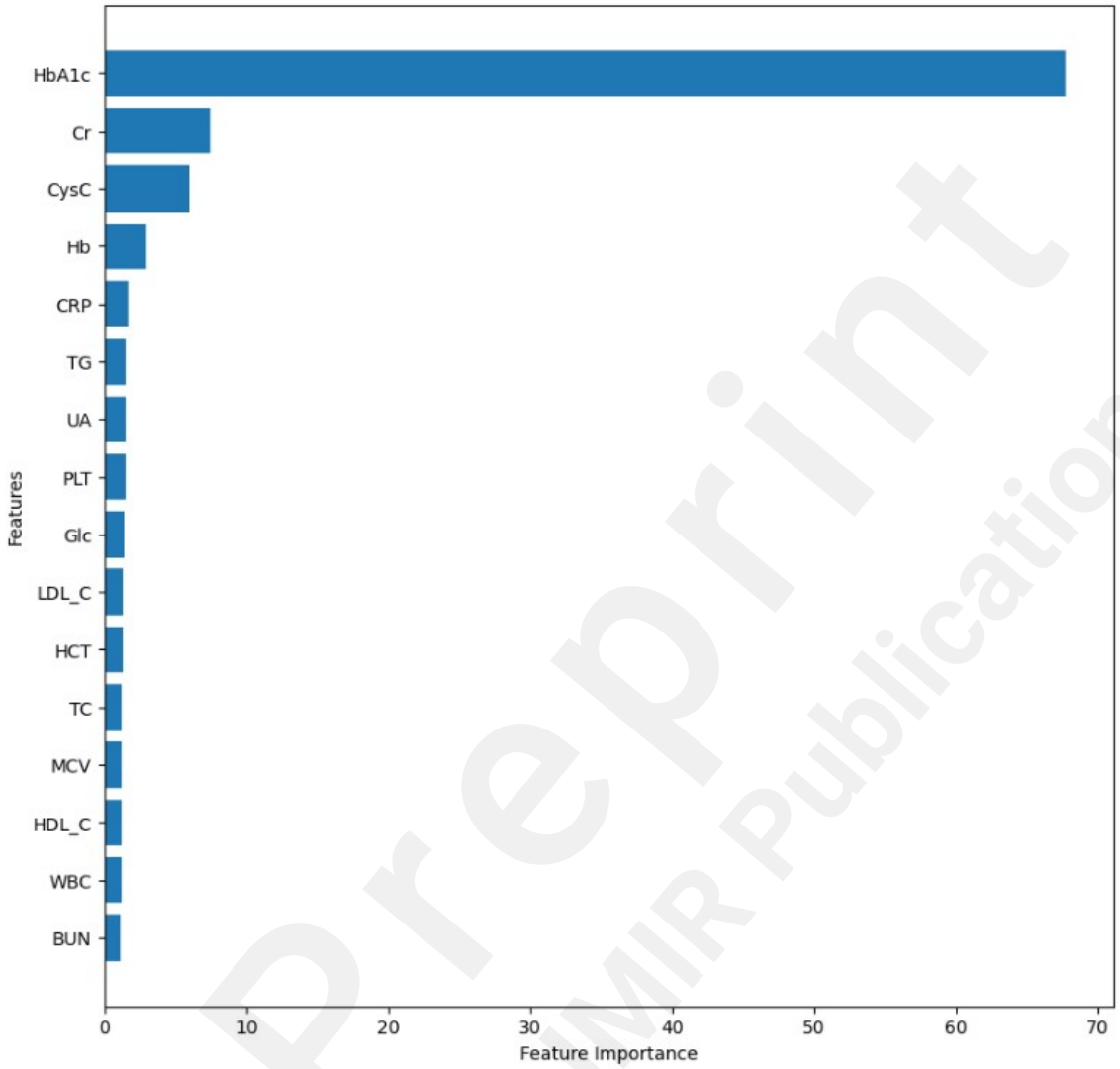
The performance of candidate models for predicting frailty status was assessed based on receiver operating characteristic (ROC) curves and the evaluation of the area under receiver operating characteristic curves (AUCs). The ROC curves of candidate models are shown in Figure 3.

Figure 3. ROC curves of the candidate models in the frailty status predictor are presented here.



The feature importance plot of biomarkers in the frailty status prediction model (CatBoost) is presented in Figure 4. The top five important biomarkers in the model are glycated hemoglobin, creatine, cystatin C, hemoglobin, C-reactive protein.

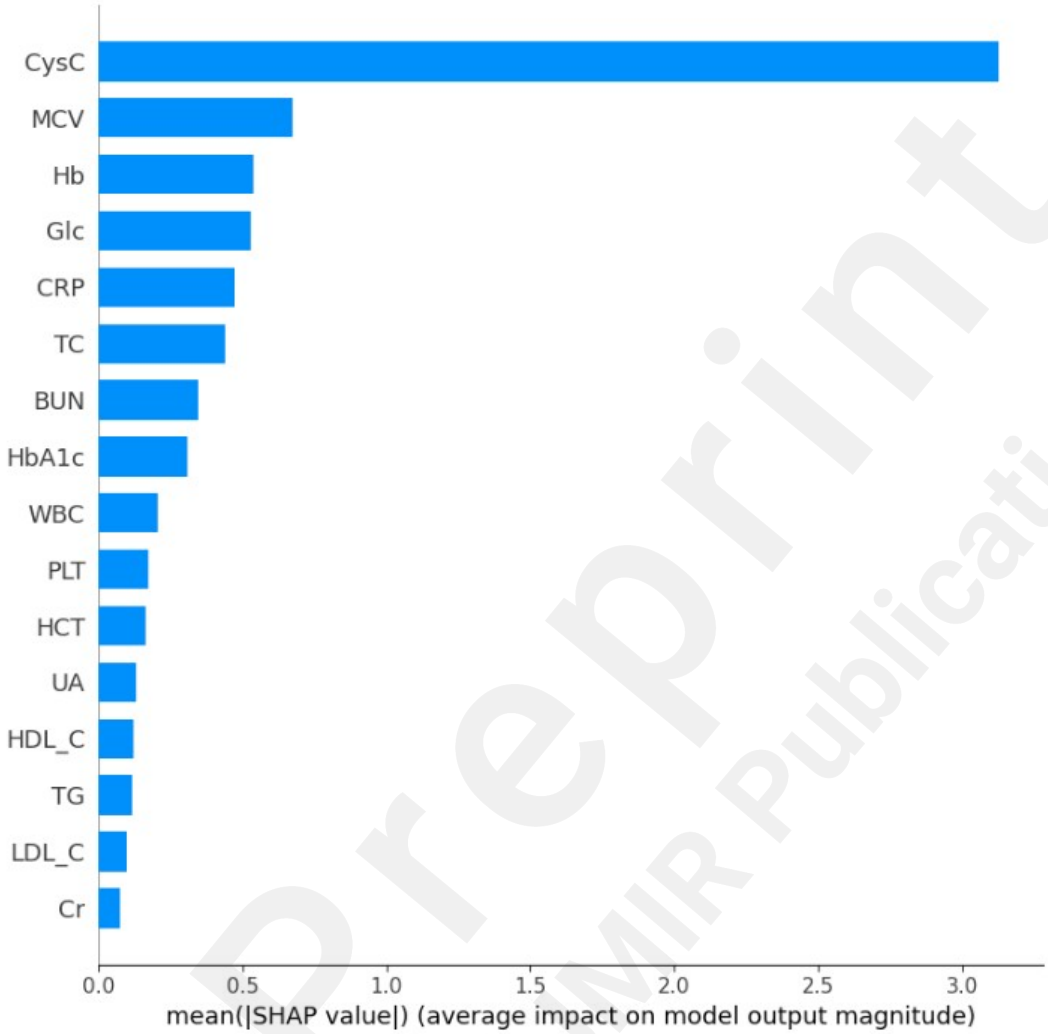
Figure 4. Feature importance plot of frailty status prediction model (CatBoost) is presented here.



SHAP Plots and Analysis

The SHAP feature ranking of biomarkers in the BA prediction model is presented in Figure 5. Cystatin C, mean corpuscular volume, hemoglobin, glucose, and C-reactive protein are the top five important biomarkers in the predictor.

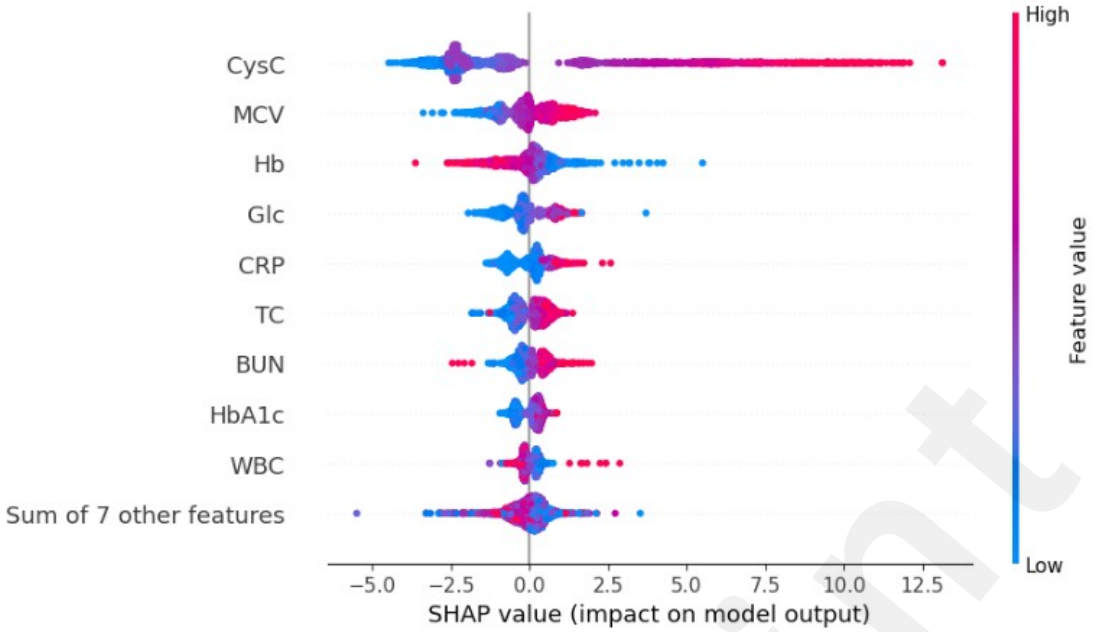
Figure 5. SHAP feature ranking of BA prediction model is presented here.



The summary plot and waterfall plot of the BA prediction model are presented in Figure 6 and Figure 7, respectively.

Figure 6 displays the SHAP summary plot for the top blood-based biomarkers used in BA prediction. This plot showcases the SHAP values for the most important biomarkers derived from the Gradient boosting model trained on the data. On the y-axis of the summary plot, features are ordered based on their mean absolute SHAP values, indicating their importance in driving BA prediction on the x-axis. Each participant's feature values are color-coded to show their relative value, with red indicating high values and blue indicating low values. Positive SHAP values suggest an increased risk for BA acceleration, while negative values suggest protective effects or BA deceleration.

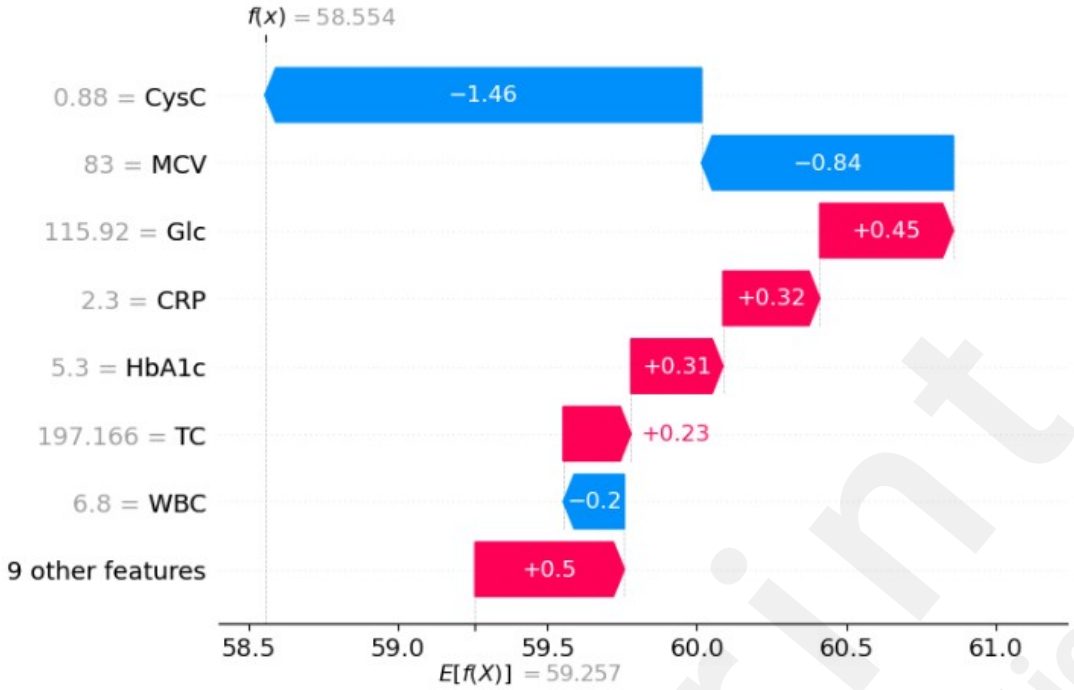
Figure 6. Summary Plot of SHAP values of BA prediction model is presented here.



SHAP values greater than 0 (on the right half) contribute to predicting increase of BA, while values less than 0 contribute to predicting decrease of BA. Red dots indicate presence, while blue dots indicate absence of the condition.

A SHAP waterfall plot is used to visualize and interpret the contributions of individual features to the prediction made by a ML model. The impact of blood-based biomarkers on the BA predictor is shown using a SHAP waterfall plot in Figure 7. The starting point of the waterfall plot (58.554 years) represents the baseline BA value, with each feature's contribution shown as either positive (red bar, BA increase) or negative (blue bar, BA decrease). The plot demonstrates an increase in cystatin C leads to an BA decrease, while an increase in glucose results in an BA increase.

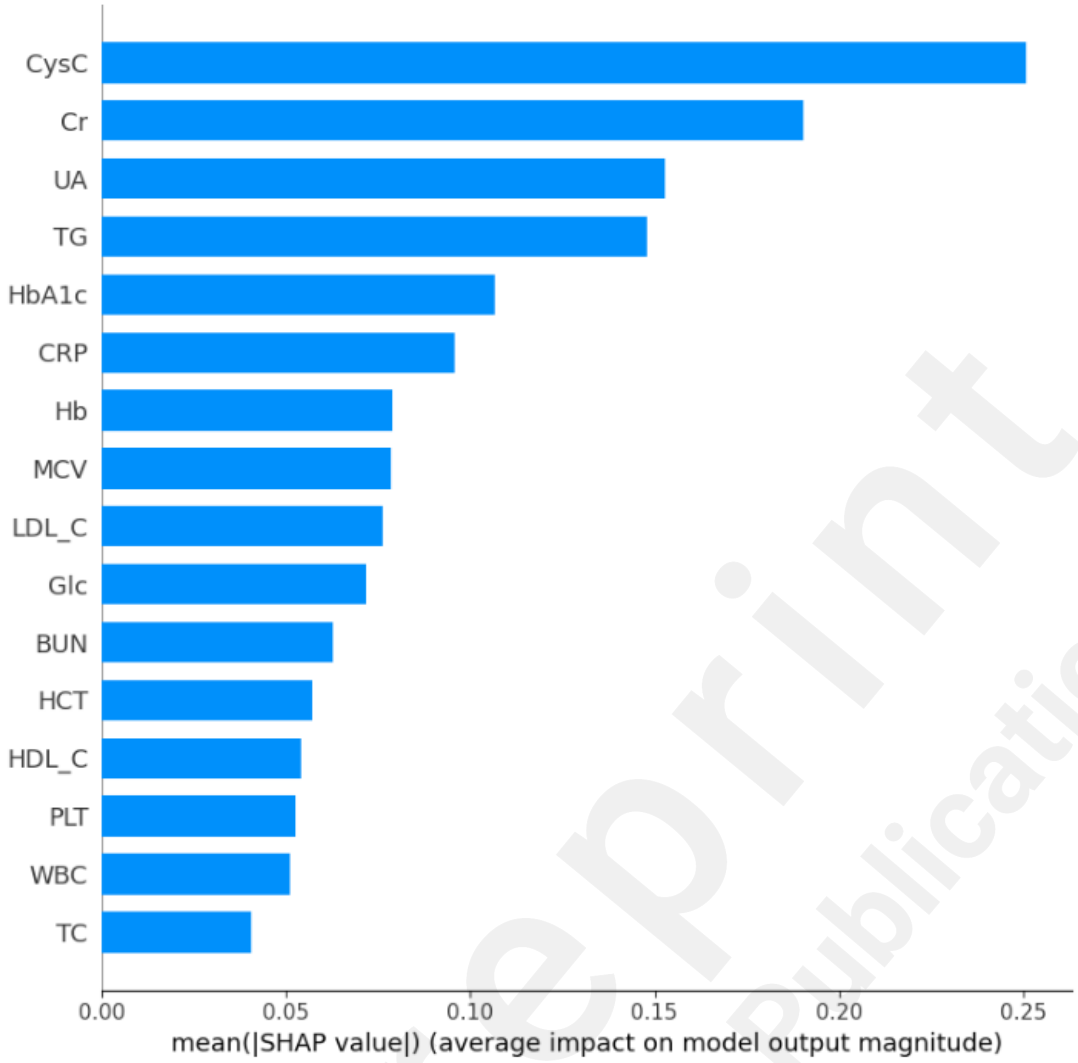
Figure 7. Waterfall Plot of BA prediction model



The SHAP partial dependence plots for the five top features in the BA predictor (cystatin C, mean corpuscular volume, hemoglobin, glucose, and C-reactive protein) are shown in the Supplementary Figure S1.

The SHAP feature importance plot of biomarkers in the frailty status prediction model is presented in Figure 8. Cystatin C, creatine, uric acid, triglycerides and glycated hemoglobin are the top five important biomarkers in the frailty status predictor.

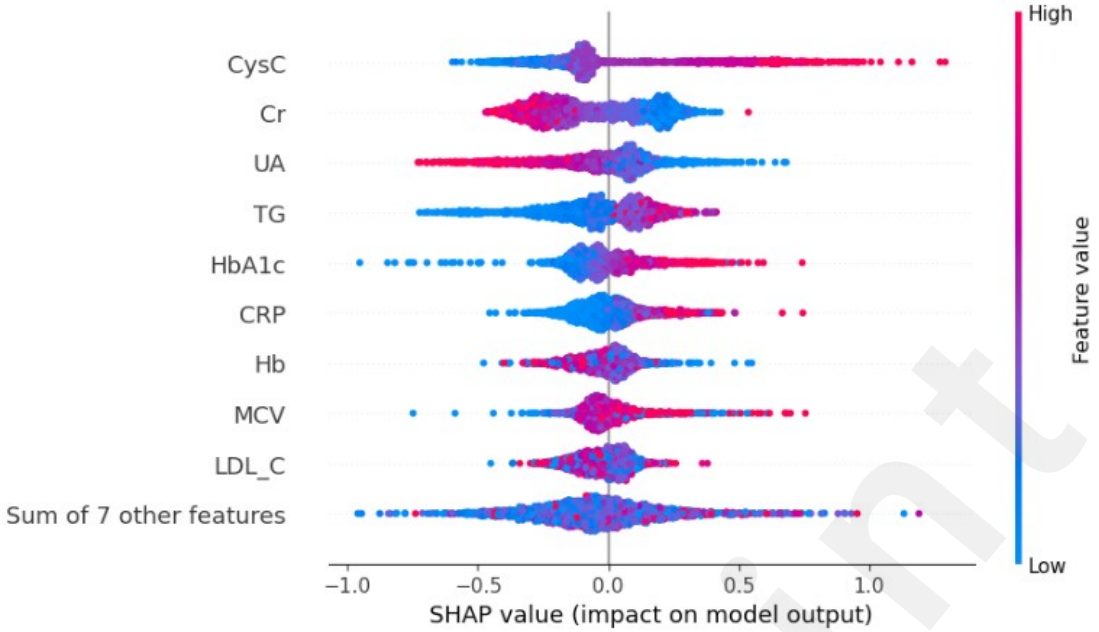
Figure 8. SHAP feature ranking of the frailty status prediction model is presented here.



The summary plot and waterfall plot of the frailty status prediction model are presented in Figure 9 and Figure 10, respectively.

Figure 9 displays the SHAP summary plot for the top blood-based biomarkers utilized in frailty status prediction. This plot illustrates the SHAP values for the most significant biomarkers derived from the CatBoost model trained on the data. The y-axis of the summary plot organizes features based on their mean absolute SHAP values, indicating their importance in influencing frailty status prediction along the x-axis. Each participant's feature values are color-coded to indicate their relative value, with red denoting high values and blue denoting low values. Positive SHAP values imply an increased risk for frailty, while negative values suggest protective effects or non-frailty.

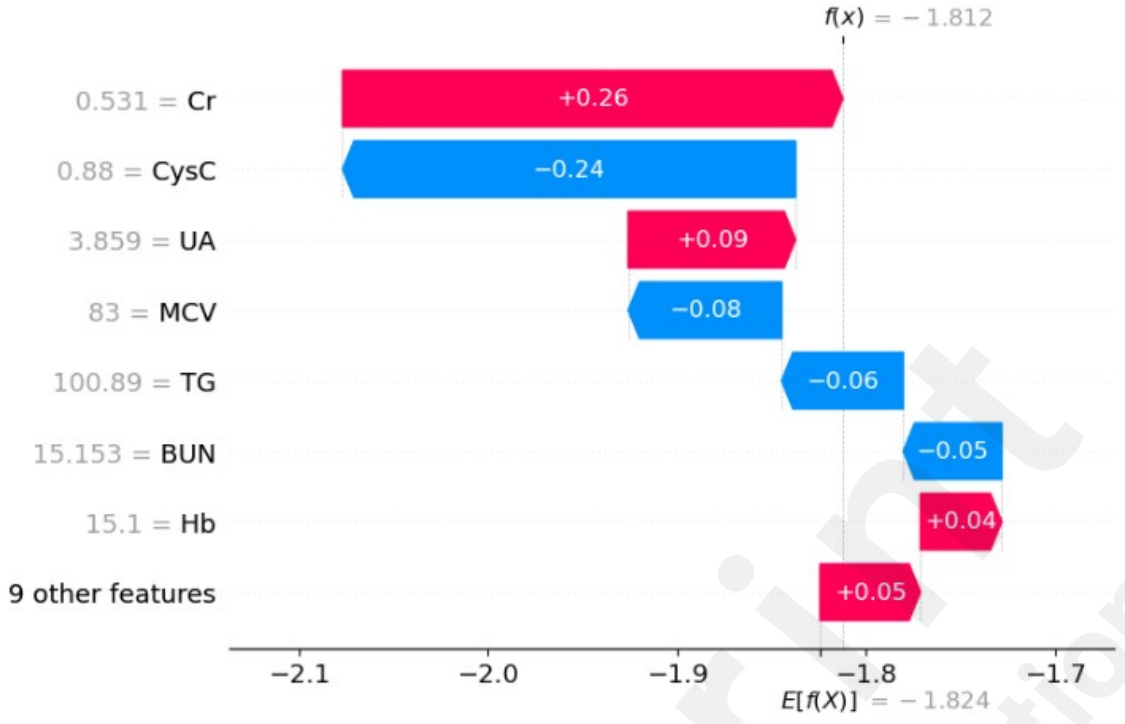
Figure 9. Summary Plot of SHAP values of the frailty status prediction model is presented here.



SHAP values greater than 0 (on the right half) contribute to predicting frailty, while values less than 0 contribute to predicting non-frailty. Red dots indicate presence, while blue dots indicate absence of the condition.

Similar to Figure 7, The impact of blood-based biomarkers on frailty status predictor is shown using SHAP waterfall plot in Figure 10. The starting point of the waterfall plot (-1.812) represents the baseline frailty status value, with each feature's contribution shown as either positive (red bar, frailty) or negative (blue bar, non-frailty). The plot demonstrates an increase in creatinine leads to an increase in frailty status value, while an increase in cystatin C results in an decrease in frailty status value.

Figure 10. SHAP Waterfall Plot of the frailty status prediction model is presented here.



The SHAP partial dependence plots for the five top features in the frailty status predictor (cystatin C, creatine, uric acid, triglycerides, and glycated hemoglobin) are shown in the Supplementary Figure S2.

Biomarker comparison

The feature importance plot of the BA predictor (Figure 2), reveals that the relative importance of cystatin C significantly surpasses that of other biomarkers. Consequently, cystatin C emerges as a paramount contributor in BA prediction, underscoring its merit for further in-depth research. Similarly, the feature importance plot of the frailty status predictor (Figure 4), illustrates that the relative importance of glycated hemoglobin markedly exceeds that of other biomarkers. This underscores glycated hemoglobin as a pivotal contributor in frailty status prediction, warranting thorough investigation and analysis.

The SHAP feature importance plots for the selected models are depicted in Figure 5 and Figure 8. Notably, cystatin C emerges as the most important biomarker in both the SHAP BA predictor (Figure 5) and the SHAP frailty status predictor (Figure 8). These findings align with the earlier result seen in Figure 2, where cystatin C also demonstrated significant importance in BA prediction. However, it is worth noting that the most important biomarker identified by the SHAP predictors differs from the one identified by the frailty status predictor. In Figure 8, cystatin C takes the lead, contrasting with the prominence of glycated hemoglobin in Figure 5.

The traditional ML feature importance is often calculated based on metrics such as Gini impurity (for decision trees), coefficients (for linear models), or permutation importance (for ensemble models). While traditional machine learning (ML) feature importance methods offer a broad understanding of feature importance across the dataset, SHAP analysis provides a more nuanced and interpretable perspective. By assessing the impact of features on individual predictions, SHAP analysis becomes a potent tool for model interpretation and explanation.

Considering the limitations inherent in traditional feature importance methods, we place higher priority on the results derived from SHAP analysis when addressing inconsistencies. This approach

ensures a more robust and accurate interpretation of the models' behavior and feature importance.

Discussion

The present study introduced a novel approach that combines BA and frailty prediction ML modeling and XAI methods to identify, compare and analysize potential aging-related blood-based biomarkers by cross-model investigation.

Unraveling the association between BA or frailty and biomarkers may provide a gateway to understanding aging processes, thereby developing targeted interventions, promoting healthy aging trajectories and extending lifespan and health span of older people. It provides insights into the mechanistic pathways linking aging with systemic alterations, such as chronic inflammation, hormonal dysregulation, oxidative stress, and immune dysfunction.

The relationship between frailty and BA is complex. Frailty is a multidimensional indicator of the deteriorating physiological processes of aging that reflects the accumulation of deficits across multiple physiological systems. Biological factors and pathways associated with the frailty also differ from those associated with CA, indicating that biological aging is not a simple linear process but rather a complex interplay of various factors [35]. A productive method for comprehending the diverse aging processes involves establishing a reliable measure for BA and frailty, then studying the associated biological factors across models.

While BA clocks are primarily designed to detect the rate of aging, another important goal is to explore aging-related biomarkers [48]. As blood-based biomarkers offer a non-invasive and readily accessible means to assess physiological processes associated with biological aging and frailty, our proposed framework represents a practical and cost-effective way to quantify the relevance of new biomarkers. In addition to hematological clocks, researchers have utilized various kinds of biomarkers to build clocks. Our framework can be easily extended to multiple biological markers other than blood-based ones. This involves testing a set of biomarkers within the same cohort, using them for both BA and frailty estimation, and then comparing the feature importance after ML and conducting an explainability analysis.

Advantages of Machine Learning and BA and Frailty Status Prediction

Estimating BA is a challenging task that involves systematically measuring key aging biomarkers, mortality modeling, health status, and disease risk evaluation. BA for an individual is typically estimated by comparing a set of variables from referent population. These strategies have traditionally been hypothesis-driven and involved using a limited number of pre-selected variables, such as socio-economic, clinical, and/or biological variables [49,50]. However, this approach implies the risk of overlooking important variables in biological aging. The advent of ML have dramatically transformed the realm of BA estimation. ML has the capability to handle a multitude of covariates and capture complex interactions between variables, potentially outperforming traditional statistical methods.

Multiple linear regression, principal component analysis (PCA) have traditionally been widely used to construct aging clocks, but rapidly emerged new techniques such as deep learning (DL) and tree-based models have provided relatively reliable BA estimates with prediction accuracy [4,6,8,10,12]. DL has introduced powerful techniques that are compatible with tabular data, including biochemical data that inherently follows this format. However, DL models often lack interpretability, which is a crucial aspect for gaining acceptance and usage among clinicians and for generating potential pathophysiological hypotheses [51].

Therefore, researchers generally tend to use tree-based models for machine learning modeling that requires interpretability. Tree-based models, such as decision trees and random forests, provide clear decision paths that can be easily visualized and comprehended. Moreover, tree-based models

allow researchers to identify important features and their contributions to the model's predictions, facilitating the extraction of meaningful insights and domain knowledge [23,52]. In this study, we chose the same 4 tree-based models RF, GB, CatBoost, and XGBoost as candidates for the two ML pipelines, then selected the best models by evaluating performance metrics specific to the respective tasks (see Table 1 and Table 2) . Our next research step involves incorporating a broader range of models and state-of-the-art data preprocessing and feature selection techniques. We hope that these efforts will identify the most suitable model and achieve optimal predictive power.

Dozens of ML models predicting frailty have been developed, but few studies addressed blood-based biomarkers or considered explainability [17,18,53,54]. While previous studies have shown that certain blood-based biomarkers are associated with the risk of frailty, most studies have examined markers independently of each other[55–58]. However, the information provided by this piecemeal approach is rather limited. Hence, high-throughput techniques may provide more information on their association with the risk of frailty and their clustering tendency, and this happens to be the approach where ML or AI excels [59].

The biomarkers associated with inflammation, oxidative stress, skeletal/cardiac muscle function, and platelet function represent the most promising markers of frailty due to their pathophysiological association with this syndrome [60]. Considering all these biomarkers collectively, the ML approach shows promise in enhancing the capability to detect frailty with improved sensitivity and specificity, especially since frailty involves multiple biological systems. The feature importance of the BA and frailty predictors revealed that cystatin C, glycated hemoglobin, creatinine, hemoglobin and C-reative protein are among the most important features, which is consistent with many previous findings [6,8,9,18,28,61].

Frailty Measures and the Insight from FI-lab

In this study, we adopted the method proposed by Searl et al. for FI scoring, primarily to avoid potential correlation with blood-based biomarkers. As a measurable, clinically suggestive proxy estimate of biological aging, FI is measured by counting deficits in health (symptoms, disabilities, diseases, and laboratory, radiographic or electrocardiographic abnormalities) and expressed as a ratio of deficits present to the total number of deficits considered. The index based on the accumulation of deficits theory exhibits a principle that the more deficits a person has, the more likely that person is to be frail [41,62].

Subsequently, the concept was extended to laboratory test data, resulting in the construction of the FI-Lab index [63]. Late studies confirmed the FI-Lab correlates well with frailty phenotype and other FIs, which are often constructed from a comprehensive geriatric assessment, and associates with mortality and with a variety of adverse health outcomes [63–65]. The findings have indirectly verified the association between frailty and blood-based biomarkers. Some researchers suggested that the FI-lab construction algorithm is similar to PCA [66]. We calculated FI-lab index in the experiment and found a strong correlation with blood-based biomarkers (not shown). Nonetheless, FI-lab imposes equal weightings on all biomarkers, making it impossible to evaluate their relative importance for biomarker discovery. Through the approach proposed in this study, we are able to discover biomarkers closely related to aging, thereby identifying accelerated aging before it becomes clinically evident.

SHAP Analysis and Biomarker Discovery

For BA and frailty model interpretation, we applied the state-of-the-art explainable technique, the SHAP algorithm, to compute global and local explanations. This approach integrates not only the effects of the feature variable itself but also the effects of interactions between variables [67].

In both BA and frailty status SHAP models, cystatin C holds the most important biomarker, which may indicate its unique role in both biological aging and frailty syndrome. The finding that

cystatin C in particular, has been identified as a prominent feature of biological aging or frailty is consistent with previous studies [7–9,13,18]. Cystatin C is a sensitive renal marker of the endogenous glomerular filtration rate, which has been proven more suitable for BA models than creatinine and blood urea nitrogen. Besides cystatin C, other routine blood-based biomarkers, such as creatinine, glycated hemoglobin, red-blood-cell distribution width, C-reactive protein, have also been recognized as key features in previous studies, further substantiating their importance in the ageing process [6–8,10,27]. For example, glycated hemoglobin has been highlighted the major contributor to BA explainability [6]. Interestingly, glycated hemoglobin has been identified the most important biomarker of the frailty status predictor in our study. Furthermore, the authors also proposed using this marker in complement to the first 10–15 variables that contribute significantly to BA, not only for monitoring diseases but also as a signal for subclinical events as shown by localized SHAP. We agree with this proposal, which involves establishing an evaluation score in which each biomarker is assigned a weight based on its SHAP value.

Strengths and Limitations

After summarizing the literature on BA and frailty ML prediction, and considering model explainability, we have reached a conclusion that, to the best of our knowledge, there are currently no published papers addressing BA, frailty ML prediction, and model interpretability simultaneously.

The CHARLS study aims to detect an increase in morbidity and frailty in an aging population. It provided a detailed battery of examinations and questionnaires, enabling us to conduct the present study combining BA and frailty estimation [68].

Furthermore, the large sample size of this nationwide prospective cohort study offered us the opportunity to develop and validate a robust framework that combines aging and frailty measures and to conduct biomarker explanations among middle-aged and older Chinese adults.

Despite these advancements, certain limitations should be acknowledged. First, our study primarily focused on the dataset from middle-aged and older Chinese individuals. Although we have validated the models with data from the 2015/2016 wave of CHARLS, findings from this study may not be directly generalizable to other cohorts or populations. Nevertheless, future research can still benefit from the methodology proposed in this study.

Second, only 16 blood-based biomarkers were tested in the CHARLS cohort, all of which were routine blood indicators, without specifically testing biomarkers closely related to aging or frailty. For instance, it is generally believed that there is a series of biomarkers related to frailty, such as interleukin-6, isoprostanes, and NT-proBNP [60,69]. Therefore, in future research, it would be beneficial to include some highly relevant biomarkers, which would be more conducive to deciphering biomarkers related to aging and frailty.

Third, the construction of FI and subsequent dichotomization cannot rule out potential misclassification, as FI was calculated, and the cut point was chosen manually. An alternative approach is to treat FI as a continuous variable. However, since frailty is a multidimensional health indicator, encompassing influences including physiological, psychological, social, nutritional, and various other aspects, it is challenging to estimate FI from laboratory results. Transforming the prediction into a classification task may be the only viable solution.

Conclusions

In summary, we have developed and validated a novel framework that combines BA and frailty prediction through ML and explainable XAI techniques. This approach leverages routine blood biomarkers and can easily incorporate additional biomarkers, providing a scalable and comprehensive toolset that offers a quantitative understanding of interesting biomarkers and complex physiological traits.

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Conflicts of Interest

The authors have declared no conflicts of interest.

Abbreviations

BA: Biological Age
CA: Chronological Age
FI: Frailty Index
FI-lab: Frailty Index of laboratory test parameters
CHARLS: China Health and Retirement Longitudinal Study

Biomarkers

WBC: White Blood Cell
MCV: Mean Corpuscular Volume
PLT: Platelets
BUN: Blood Urea Nitrogen
Glc: Glucose
Cr: Creatinine
TC: Total Cholesterol
TG: Triglycerides
HDL_C: High-Density Lipoprotein Cholesterol
LDL_C: Low-Density Lipoprotein Cholesterol
CRP: C-Reactive Protein
HbA1c: Glycated Hemoglobin
UA: Uric Acid
HCT: Hematocrit
Hb: Hemoglobin
CysC: Cystatin C

Machine learning related

AI: Artificial Intelligence
XAI: eXplainable Artificial Intelligence
ML: Machine Learning
SHAP: SHapley Additive exPlanations
RF: Random Forest
GB: Gradient Boosting
XGBoost: eXtreme Gradient Boosting
MAE: Mean Absolute Error
SMOTE: Synthetic Minority Over-sampling Technique
ROC: Receiver Operating Characteristic
AUC: Area Under the Curve
PCA: Principal Component Analysis
DL: Deep Learning

Multimedia Appendix 1

The following supplementary materials are provided in a word document file named "SupplementaryFile.docx".

1. Table S1: Characteristics of chronological age, frailty status and blood biochemical variables
2. Table S2: Health deficits and their cut-off points in the construction of frailty index
3. Figure S1: SHAP partial dependence Plots of the 5 top features in the BA predictor (Gradient Boosting)
4. Figure S2: SHAP partial dependence plot of top 5 features in the frailty status predictor (CatBoost)

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Supplementary Files

Multimedia Appendixes

Supplementary Materials are presented here.
URL: http://asset.jmir.pub/assets/832362019e33228e05a0d8fcd92781ad.docx