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Machine learning based prediction of cognitive metrics using major biomarkers in SuperAgers

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As populations age, understanding cognitive decline and age-related diseases like dementia has become increasingly important. "SuperAgers," individuals over 65 with cognitive abilities similar to those in their 40s, provide a unique perspective on cognitive reserve. This study analyzed 55 blood biomarkers, including cellular components and metabolism/inflammation-related factors, in 39 SuperAgers and 42 typical agers. While conventional statistical analyses identified significant differences in only four biomarkers, advanced feature selection and machine learning techniques revealed a broader set of 15 key biomarkers associated with SuperAger status. A predictive model built using these biomarkers achieved an accuracy of 76% in cognitive domain prediction. To address the limitation of small sample sizes, data augmentation leveraging large language models improved the model's robustness. Shapley Additive exPlanations (SHAP) provided interpretability, revealing the impact of specific blood factors on cognitive function. These findings suggest that certain blood biomarkers are not only associated with cognitive performance but may also serve as indicators of cognitive reserve. By utilizing simple blood tests, this research presents a clinically significant method for predicting cognitive function and identifying SuperAger status in healthy elderly individuals, offering a foundation for future studies on the biological mechanisms underpinning cognitive resilience.

Keywords Super-Agers, Cognitive function, Blood biomarkers, Machine learning, Cognitive metric prediction, Recursive feature elimination (RFE), BORUTA, Cognitive decline

Abbreviations

C-ABC	Cognitive Assessment Battery
DCR	Digital Clock and Recall
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
SNSB-II	Seoul Neuropsychological Screening Battery, Second Edition
ELISA	Enzyme-Linked Immunosorbent Assay
HbA1c	Hemoglobin A1c
HDL cholesterol	High-Density Lipoprotein Cholesterol
TC	Total Cholesterol
oxLDL	Oxidized Low-Density Lipoprotein
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
ApoE	Apolipoprotein E
FABP-3	Fatty Acid Binding Protein 3
FABP-4	Fatty Acid Binding Protein 4
CD36	Cluster of Differentiation 36
EPO	Erythropoietin
Free T4	Free Thyroxine
RAGE	Receptor for Advanced Glycation End-products

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BUN	Blood Urea Nitrogen
RDW	Red Cell Distribution Width
RFE	Recursive Feature Elimination
AUC	Area Under the Curve
MCC	Matthews Correlation Coefficient
GReaT	Generation of Realistic Tabular Data
LLM	Large Language Model
CTGAN	Conditional Tabular Generative Adversarial Network
SHAP	Shapley Additive Explanation

The elderly population is rapidly expanding, heightening the significance of elderly health management as a critical societal concern. Research is ongoing regarding cognitive changes associated with brain health in older age. While age-related cognitive functions often decline or become impaired, these changes are subject to individual variations influenced by diverse factors[1].

Paper-based or computerized cognitive function tests are standard tools for identifying mild cognitive impairment and dementia. However, these tests are time-consuming and can be particularly challenging for the elderly, especially those with reading difficulties. Additionally, the inability to conduct repetitive testing complicates the systematic observation of cognitive changes over time[2]. Recent advancements have led to the development of computer-based cognitive assessments and intervention programs to address some of these challenges. For instance, a prior study introduced a new, computer-based cognitive assessment battery (C-ABC) with higher precision and faster testing time than traditional paper-based tests[2,3].

Research indicates that computer-based cognitive intervention programs are more accessible and cost-effective than traditional programs. Computer-based programs enhance cognitive functions in the elderly through the use of various software programs, while digital assessments such as the Digital Clock and Recall (DCR) test can detect impairments more effectively than traditional methods[4].

These studies collectively suggest that computer-based cognitive assessments are more time-efficient, allow for repeated testing, and are better suited for large-scale screenings than traditional paper-based methods. These tools provide a systematic way to monitor cognitive changes over time, offering timely intervention opportunities to maintain and improve cognitive health in the elderly.

However, computer-based cognitive assessments have limitations. Some patients may face difficulties due to their unfamiliarity with digital devices, additionally, some individuals may struggle to use screens due to physical or cognitive impairments, necessitating alternative methods[5]. Although the shift to computer-based assessments was intended to address the limitations of paper-based testing, these newer methods still encounter challenges, emphasizing the need for alternative assessment methods.

Past cognitive ability research has focused primarily on patients with pathological conditions including Alzheimer's disease, Parkinson's disease, diabetes, and hypertension. However, recent studies have assessed the cognitive abilities of people without specific diseases, increasingly emphasizing the concept of "SuperAgers"[6,7]. SuperAgers exhibit exceptionally high cognitive performance for their age, often matching or exceeding that of individuals several decades younger. SuperAgers are clinically significant because they provide a unique model for understanding the contributing factors of healthy cognitive aging. Identifying and studying these individuals can offer insights into protective factors against cognitive decline and dementia, potentially guiding interventions to promote cognitive health in the broader elderly population.

Research indicates that SuperAgers possess unique brain characteristics such as a thicker cortex and larger, more numerous Von Economo neurons, which are associated with social cognition and emotional processing[8]. These brain structures are believed to be important factors in cognitive ability, helping to maintain high cognitive performance despite aging. Additionally, lifestyle factors such as regular physical exercise, a healthy diet, and strong social connections are common among SuperAgers[9]. These factors are linked to better brain health and reduced cognitive decline.

SuperAgers have been identified through a combination of cognitive testing and neuroimaging techniques. Cognitive tests assess various domains such as memory, executive function, and attention; while neuroimaging studies focus on brain structure, often revealing greater cortical thickness and lower levels of brain atrophy than typical older adults[10–12]. However, these methods are resource-intensive and not always practical for large-scale screenings.

Neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans provide detailed images of brain structure and function but are expensive, time-consuming, and not always accessible. Cognitive tests, while useful, can be influenced by factors such as education level and literacy, and often require considerable time and effort from both the participant and the administrator. Questionnaires and self-reports, although easier to administer, are subjective and can be biased by the individual's perception and memory[13–16]. Currently, most SuperAger research focuses predominantly on lifestyle patterns and neuroimaging[9–11,17,18].

Our study marks the first attempt to explore blood-based biomarkers related to the cognitive abilities of SuperAgers. Recent studies have revealed that brain morphology is affected by metabolic derangements such as metabolic syndrome. Metabolic syndrome is associated with increased cortical surface area and thinning, particularly in the frontal, temporal, and sensorimotor cortex; and reduced basal ganglia volume[19]. Cognitive functions are impaired by brain damage caused by metabolic inflammation and microvascular disorders, which develop from metabolic mediators[20]. Aging is also known to affect neuronal glucose and energy metabolism[21]. Therefore, blood factors including metabolic parameters would show differences between SuperAgers and typical elderly individuals.

Instead of categorizing participants into SuperAgers and typical elderly individuals without health abnormalities, we introduce algorithms based on participants' blood factors to predict various cognitive function measurements. By focusing solely on blood biomarkers, this study aims to provide a more accessible, cost-effective, and objective method to identify SuperAgers. This approach has significant clinical implications, as it could facilitate large-scale screenings and early interventions, ultimately contributing to better cognitive health outcomes for the elderly.

In addition, this study will help identify methods to prevent or treat cognitive decline due to aging by investigating the mechanisms through which blood factors associated with SuperAgers influence cognitive function.

Method

Population

This study uses 55 features obtained from Ewha Womans University Mokdong Hospital, Seoul, Korea. The initial participant pool consisted of SuperAgers ($n=62$) and typical agers ($n=59$) with higher cognitive function, compared with a control group of 121 people with normal cognitive function. After application of inclusion criteria and data quality controls, our final analysis included 39 SuperAgers and 42 typical agers (total $n=81$). Due to limited data availability, we modified the obtained data by comparing it to individuals aged 65 and above. Consequently, SuperAgers (aged 65 and above) demonstrate cognitive abilities comparable to those in their early 40s, showcasing exceptional cognitive performance for their age (Fig. 1).

Cognitive function tests

In this study, cognitive function tests were conducted using the Seoul Neuropsychological Screening Battery 2nd Edition (SNSB-II). Cognitive function tests were categorized into distinct domains: Attention, Language Fluency, Memory, Visuospatial Ability, and Frontal (function). Each domain was evaluated through a combination of specific tests rather than a single assessment. To emphasize the importance of memory assessments in our study, the Memory domain was further divided into Verbal Memory and Visual Memory, for a total of six test domains. Notably, as our study focused on individuals without dementia, we utilized specific tests within each domain instead of calculating z-scores, allowing us to differentiate participants based on their cognitive performance relative to their age group. The tests selected as dependent variables in our study are as follows:

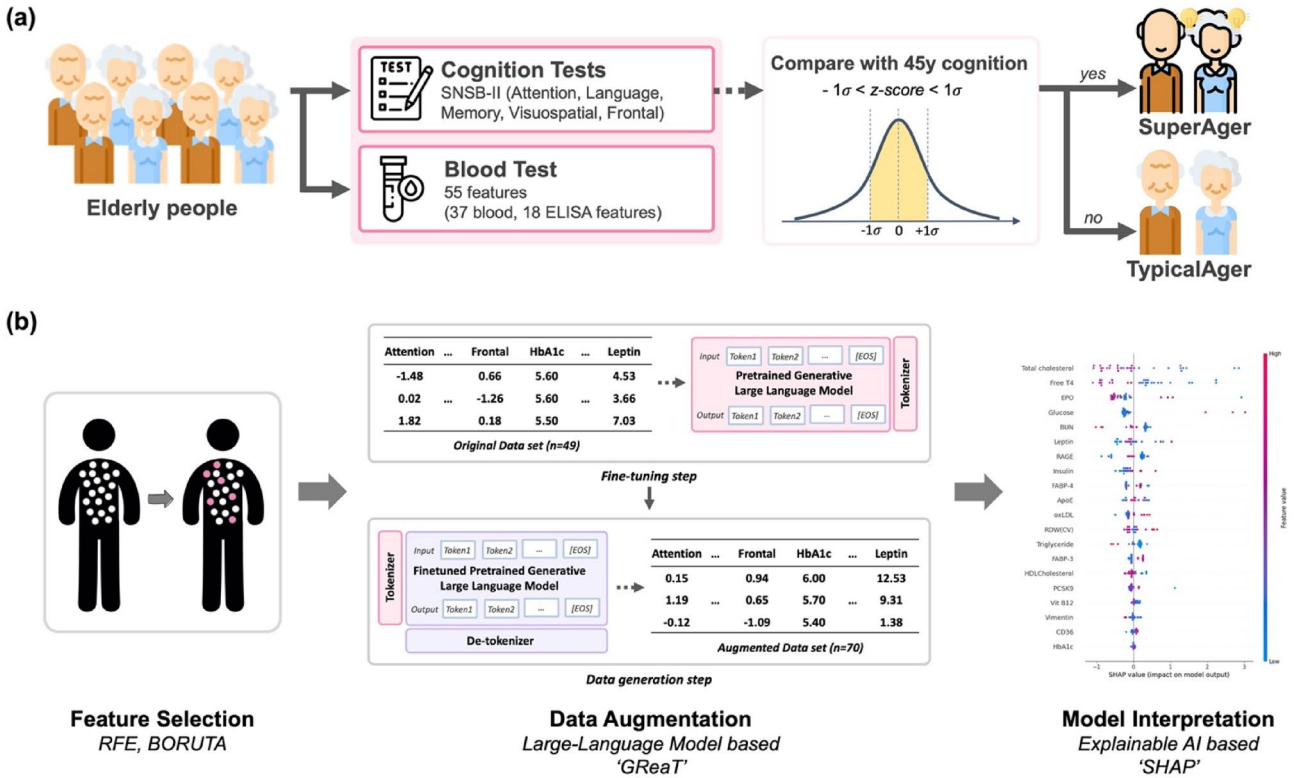

Fig. 1. Workflow of the SuperAger identification study. This figure illustrates the workflow of the study aimed at identifying SuperAgers among elderly individuals. (**a**) SuperAger classification is performed using SNSB-II cognitive tests and blood biomarkers, compared to the cognitive performance of individuals in their 40s. (**b**) The machine learning pipeline incorporates feature selection (RFE, BORUTA), data augmentation using fine-tuned large language models (GReaT), and model interpretation with SHAP to reveal key biomarkers associated with cognitive resilience.

Blood data acquisition

The participants underwent a blood test that resembled a typical routine health checkup. However, for this study, 18 additional metabolic and inflammatory factors in the blood samples were measured using Enzyme-Linked Immunosorbent Assay (ELISA).

Plasma separation method for measuring blood protein concentration

Whole blood was collected into EDTA (5.4 mg) or Heparin (75 USP units) treated tubes. Plasma was separated by centrifugation for 10 min at 4000 rpm at 4℃ and stored at -80℃. Human plasma protein levels (PCSK9, ApoE, CD36, EPO, AGE, RAGE, Vimentin, FABP-3, FABP-4, oxLDL, Adiponectin, and Leptin) were measured using ELISA kits following the manufacturer's instructions. The ELISA kits with experimental conditions are specified in Table S1.

Statistical analysis

In this study, IBM SPSS Statistics and Python were used for statistical analysis. An independent t-test was employed to analyze the differences between the SuperAger and typical ager groups. The participants were categorized based on their cognitive function assessments and blood biomarker data. This approach allowed a systematic comparison of cognitive performance between the two groups and an evaluation of the efficacy of blood-based biomarkers in identifying SuperAgers. Python code was used to validate the results obtained from SPSS and to perform additional analyses as necessary.

Feature importance

To identify SuperAger biomarkers, various feature selection methods were employed. The dataset provided by the hospital contained binary classifications for SuperAger status and continuous variables for individual cognitive scores. To ensure methodological rigor and prevent data leakage, we first divided the entire dataset of 81 subjects into completely separate training ($n = 48$) and testing ($n = 33$) sets. All feature selection procedures were performed exclusively on the training set, while the test set was kept entirely isolated until final model evaluation.

Using only the training data ($n = 48$), we implemented multiple feature selection approaches due to the challenge of detecting relevant biomarkers from 55 blood features with a limited sample size. We divided the subjects in the training set into a top quartile group, with remaining subjects grouped based on cognitive scores. Recursive Feature Elimination (RFE) was conducted using Random Forest, AdaBoost, and LightGBM classifiers, extracting overlapping factors among the top ten features obtained from each algorithm.

Additionally, the R-based Boruta algorithm was applied based on the cognitive score quartile grouping. Unlike traditional feature selection algorithms, Boruta does not allow pre-selection of the number of features to retain; it solely evaluates the relevance of features to the target variable. Given that the SuperAger group comprised healthy individuals without significant differences in blood components, and there was a lack of strong correlation between SuperAger and typical ager groups identified by Boruta, a more detailed approach was adopted.

For model training and validation, we used 49 samples from the training set for data augmentation, resulting in 77 total samples for training. The feature selection process remained entirely within the training data workflow, ensuring that the test set ($n = 33$) remained completely unseen during model development, thereby preventing any data leakage that could artificially inflate performance metrics. This strict separation between training and testing data ensures the validity and generalizability of our biomarker identification approach.

Machine learning-based assessment

For biomarker identification associated with SuperAgers, we utilized Gradient Boosting Classifier, a powerful ensemble learning technique that builds decision trees sequentially to correct errors from previous trees. This algorithm was chosen for its ability to handle complex relationships in biological data and its robustness against overfitting in small datasets.

To address potential limitations with our sample size, we implemented a 10-fold cross-validation protocol. This divided our training data into ten equal partitions, using nine for training and one for validation in each iteration, ensuring robust performance assessment across different data subsets.

For hyperparameter optimization, we utilized grid search methodology to identify the optimal model configuration. We systematically explored parameters including learning_rate, max_depth, min_samples_split, n_estimators, and subsample, selecting the combination that maximized performance while preventing overfitting.

To quantify model stability and prediction uncertainty, we implemented bootstrap evaluation with 100 iterations. This involved random sampling with replacement from our training dataset, creating multiple training sets to evaluate performance variability across different data distributions. Bootstrap analysis provided confidence intervals for all performance metrics, offering statistical assurance of model reliability.

For feature selection refinement and model interpretability, we employed Shapley Additive explanations (SHAP) analysis using the shap Python library. This technique quantifies individual feature contributions to model predictions, enabling identification of the most predictive biomarkers and their threshold values. We generated SHAP summary plots to visualize overall feature importance and dependence plots to examine the relationship between specific biomarker values and their impact on SuperAger prediction.

Performance assessment utilized multiple metrics to provide comprehensive evaluation: accuracy (overall correctness), AUC (discrimination ability), recall (sensitivity), precision (positive predictive value), F1 score (harmonic mean of precision and recall), Kappa (agreement accounting for chance), and Matthews correlation coefficient (MCC, general quality of binary classification).

Data augmentation

To enhance the robustness of our model training, we augmented the data and tested its effectiveness by comparing it to the original data. The augmented data was statistically similar to the original data, as indicated by a high p-value of 0.462, demonstrating that the augmented data was appropriate for the analysis (Table S2, Fig. S1). For data augmentation, we utilized the Generation of Realistic Tabular Data (GReaT) model[22], a large language model (LLM)-based approach. Unlike the Conditional Tabular Generative Adversarial Network (CTGAN)[23], which is typically used for table data augmentation, GReaT offers a more nuanced approach to capturing complex relationships between features. Specifically, GReaT leverages the transformer architecture to model feature dependencies and interactions, thus providing more accurate and context-aware synthetic data generation. Out of the total 81 samples, 49 were used for training and augmentation (generating 70 additional synthetic samples), while 32 samples were strictly reserved as an independent test set, ensuring no data leakage between training and evaluation phases[22–24].

Interpretation with SHAP

In clinical practice, it is vital to interpret results correctly. Therefore, based on the machine learning model assessment results, we used the SHAP method to illustrate the impact of each variable on individual predictions. SHAP assigns the influence of each feature on the prediction in an additive manner regardless of model class, providing insights beyond feature importance alone. SHAP values, derived from cooperative game theory, ensure a fair distribution of the contribution of each feature, aiding in the identification of biomarkers that significantly impact prediction[25,26].

Shapley values played a pivotal role in identifying biomarkers that significantly contributed to the prediction of each cognitive function test. Let R represent an arbitrary permutation of N features, and let S_i^R denote the set of elements in permutation R that precedes i. The formula for Shapley Value $\varnothing_i$ for subject i in this context is expressed in Eq. (1), with the inner summation signifying the contribution of i.

$$\varnothing_i = \frac{1}{|N|!}\sum\nolimits_R \left[v\left(S_i^R \cup \{i\}\right) - v(|S_i^R)\right] \tag{1}$$

Results

Original data analysis

Among the 81 individuals whose SuperAger status was determined through cognitive function tests, we observed significant differences in cognitive scores between SuperAgers and typical agers in all areas except for the Attention domain (Table 1). Furthermore, t-tests were conducted on independent samples for blood factors between the two groups. As shown in Table 2, statistically significant differences were observed in the factors HbA1c, Glucose, Cl, and Free T4 ($p < 0.05$).

While only four biomarkers showed statistically significant differences ($p < 0.05$), several others approached significance and demonstrated notable trends. HDL cholesterol was higher in SuperAgers (59.13 ± 10.76 vs. 55.55 ± 12.74, $p = 0.089$), consistent with its known neuroprotective properties[27]. EPO levels were notably lower in SuperAgers (10.56 ± 4.23 vs. 12.08 ± 4.46, $p = 0.060$). Oxidized LDL also showed lower values in SuperAgers (51.00 ± 3.88 vs. 52.37 ± 4.88, $p = 0.085$), potentially indicating reduced oxidative stress.

Cytokine factors such as TNF-α and interleukin, as well as Alzheimer's disease-related proteins such as tau protein and APP, were excluded from this study due to no difference between groups (Table S3).

Biomarker detection process

The 55 blood biomarkers analyzed in this study were selected based on their established or potential associations with cognitive function, aging processes, and metabolic health relevant to brain function. We included conventional clinical parameters (e.g., glucose, lipids, liver enzymes) that reflect general metabolic health and have been associated with cognitive performance in previous studies. Additionally, we incorporated specialized markers of metabolic inflammation (e.g., RAGE, AGE), lipid transport (e.g., ApoE, FABP-3, FABP-4), and metabolic regulation (e.g., Leptin, Adiponectin) based on their documented roles in brain aging and

Cognitive domain (specific test name)	Typical agers ($n = 42$)	SuperAgers ($n = 39$)	p
Attention (Digit_span_Forward_z)	0.08 ± 0.99	0.39 ± 1.03	0.173
Language (Naming_K_BNT_z)	− 0.06 ± 0.88	0.34 ± 0.79	0.038
VerbalMemory (SVLT_Delayed_recall_z)	0.32 ± 1.01	1.06 ± 0.73	< 0.001
VisualMemory (RCFT_delayed_recall_z)	− 0.12 ± 0.74	0.88 ± 0.91	< 0.001
Visuospatial (Rey_CFT_copy_score_z)	− 0.26 ± 0.83	0.28 ± 0.63	< 0.001
Frontal (StroopTest_Colorreading_correct_z)	0.58 ± 0.83	0.79 ± 0.64	0.210

Table 1. Comparison of cognitive function between superagers and typical agers. Each cognitive domain was assessed using specific tests. Scores for typical agers and superagers are presented as means ± standard deviations (Mean ± SD). Differences between the two groups were analyzed using independent t-tests. The p-value indicates the statistical significance of the differences between the groups, with $p < 0.05$ considered statistically significant.

Variable	Typical agers ($n=42$)	SuperAgers ($n=39$)	t	P (one-tailed)
HbA1c	6.00 ± 0.75	5.75 ± 0.57	1.732	0.044
Total calcium	9.33 ± 0.32	0.31 ± 0.38	0.332	0.370
Phosphorus	3.64 ± 0.34	3.69 ± 0.46	− 0.580	0.282
Glucose	106.10 ± 3.55	98.38 ± 12.92	1.844	0.035
BUN	15.71 ± 3.79	17.00 ± 4.83	− 1.337	0.092
Creatinine	0.76 ± 0.20	0.75 ± 0.17	0.408	0.342
eGFRMDRD	84.60 ± 18.64	85.79 ± 19.89	− 0.280	0.390
eGFRCKDEPI	82.00 ± 13.10	81.82 ± 12.24	0.064	0.475
Triglyceride	106.33 ± 44.62	106.97 ± 46.28	− 0.063	0.475
Total Cholesterol	169.10 ± 40.25	173.23 ± 40.25	− 0.462	0.323
Total Protein	7.13 ± 0.34	7.02 ± 0.39	1.358	0.089
Albumin	4.51 ± 0.20	4.51 ± 0.23	0.190	0.425
AST	25.98 ± 14.97	24.28 ± 7.55	0.636	0.263
ALT	21.24 ± 11.73	19.51 ± 7.39	0.137	0.217
ALP	70.86 ± 22.39	70.33 ± 19.90	0.111	0.456
Total Bilirubin	0.62 ± 0.22	0.63 ± 0.26	− 0.215	0.415
HDL Cholesterol	55.55 ± 12.74	59.13 ± 10.76	− 1.361	0.089
LDL Cholesterol	98.74 ± 34.50	99.54 ± 36.49	− 0.101	0.460
Na	141.21 ± 2.24	141.49 ± 1.59	− 0.629	0.266
K	4.40 ± 0.36	4.48 ± 0.45	− 0.960	0.170
Cl	104.90 ± 2.44	105.85 ± 2.19	− 1.822	0.036
CRP	0.12 ± 0.14	0.12 ± 0.14	0.002	0.499
TSH	2.37 ± 1.86	2.24 ± 1.48	0.345	0.366
Free T4	1.30 ± 0.38	1.17 ± 1.18	1.850	0.034
Insulin	9.06 ± 6.23	7.71 ± 5.24	1.1051	0.148
C-peptide	2.11 ± 0.89	2.03 ± 1.00	0.409	0.342
Folic acid	14.59 ± 8.47	15.42 ± 8.22	− 0.448	0.328
Vit B12	928.76 ± 540.90	797.46 ± 290.13	1.346	0.091
WBC	5.15 ± 1.00	5.49 ± 1.35	− 1.284	0.102
RBC	4.32 ± 0.44	4.31 ± 0.49	0.114	0.455
Hb	13.28 ± 1.34	13.18 ± 1.15	0.343	0.366
Hct	38.98 ± 3.74	38.87 ± 3.57	0.137	0.446
MCV	90.26 ± 2.54	90.41 ± 3.67	− 0.209	0.417
MCH	30.73 ± 1.06	30.67 ± 1.34	0.227	0.411
MCHC	34.04 ± 0.80	33.93 ± 0.89	0.604	0.274
RDW	12.60 ± 0.55	12.75 ± 0.56	− 1.208	0.115
Platelet	210.32 ± 48.77	220.17 ± 3.55	− 0.956	0.171
PCSK9 (ng/ml)	109.91 ± 42.60	106.06 ± 37.03	0.433	0.333
ApoE (ug/ml)	110.79 ± 67.71	99.68 ± 56.74	0.797	0.214
CD36 (ng/ml)	123.20 ± 141.49	135.49 ± 144.07	− 0.387	0.350
EPO (mIU/ml)	12.08 ± 4.46	10.56 ± 4.23	1.568	0.060
AGE (ng/ml)	13.56 ± 7.12	12.23 ± 5.08	0.911	0.183
RAGE (pg/ml)	85.54 ± 32.37	80.95 ± 20.81	0.765	0.224
Vimentin (pg/ml)	167.10 ± 102.07	168.41 ± 157.25	− 0.045	0.482
FABP-3 (pg/ml)	1235.89 ± 657.41	1197.39 ± 724.67	0.251	0.401
FABP-4 (ng/ml)	30.45 ± 14.38	28.66 ± 13.13	0.582	0.281
oxLDL (ng/ml)	52.37 ± 4.88	51.00 ± 3.88	1.388	0.085
Adiponectin (ug/ml)	35.85 ± 27.86	44.24 ± 39.87	0.060	0.136
Leptin (ng/ml)	8.27 ± 5.30	7.93 ± 6.32	0.258	0.398

Table 2. Independent samples *t*-test results for blood features by superager status. This table presents the 'mean ± standard deviation' of various blood features for typical agers ($n=42$) and superagers ($n=39$). Independent samples *t*-tests were conducted to compare the two groups. The *t*-value and one-tailed p-value are provided for each variable.

neuroprotection[28]. This comprehensive panel enabled us to explore both established and novel connections between peripheral blood factors and cognitive resilience in aging.

Feature selection was performed in three stages to identify the most predictive biomarkers from this extensive panel. The first and second methods involved using RFE with Random Forest, AdaBoost, and LGBM classifier algorithms. Each algorithm extracted the top 10 features, and the common features were identified. In the first approach, based on SuperAger status, RFE extracted EPO, BUN and Vit B12. In the second approach, based on the top quartile of cognitive scores, RFE identified WBC, oxLDL, HDL Cholesterol, AGE, Vimentin, Leptin, Cl, CD36, RAGE, Phosphorus, ALT, RDW(CV), LDLCholesterol, TSH, K, and Glucose. Finally, using R-based Boruta for the top 25% group in each cognitive domain, the selected features were LDL Cholesterol, WBC, MCHC, Phosphorus, Cl, Insulin, Leptin, MCV, and TSH. These complementary approaches allowed us to identify key biomarkers associated with SuperAger status through multiple analytical perspectives.

Subsequently, we combined the extracted features in several ways to predict SuperAger status, as shown in Table 3. The machine learning algorithms used for each method are as follows: All features, AdaBoost Classifier; RFE_{SA}, SVM with Linear Kernel; RFE_{Cog}, AdaBoost Classifier; $Boruta_{Cog}$, Gradient Boosting Classifier; RFE_{SA} and $Boruta_{Cog}$, Decision Tree Classifier; RFE_{Cog} and $Boruta_{Cog}$, AdaBoost Classifier; RFE_{Cog}^$Boruta_{Cog}$, Random Forest Classifier.

The highest accuracy rate of 66.67% was achieved when predicting SuperAger status using features identified by both RFE based on cognitive scores and Boruta algorithm (RFE_{Cog} & $Boruta_{Cog}$), with an impressive AUC of 0.7684. This combination yielded a total of 19 biomarkers: Phosphorus, Glucose, ALT, HDL cholesterol, LDL cholesterol, K, Cl, TSH, Insulin, WBC, MCV, MCHC, RDW(CV), CD36, AGE, RAGE, Vimentin, oxLDL, and Leptin. Therefore, these features were selected as SuperAger biomarkers. Among these, Glucose and Cl were the factors that showed significant differences in the initial independent sample t-test, while the others demonstrated predictive value through their complex interactions in the multivariate model rather than as individual markers.

Data augmentation for quantitative problem resolution in clinical data

Limited sample size is a common challenge in clinical studies, especially those involving specialized populations such as SuperAgers. To address this limitation while maintaining data integrity, we implemented a Large Language Model-based data augmentation approach using the GReaT model. Before proceeding with analyses using augmented data, we conducted comprehensive validation to ensure the augmented dataset faithfully represented the original data characteristics.

Figure 2 presents a multi-faceted visual comparison between original and augmented data distributions. The kernel density estimation (KDE) plots (Fig. 2a) demonstrate substantial overlap between real (blue) and augmented (orange) distributions across all key biomarkers. Particularly noteworthy is the preservation of complex distributional features such as the bimodal pattern observed in the SuperAger classification. This similarity indicates that the augmentation process captured not only simple summary statistics but also the underlying distributional nuances of the original data.

To evaluate the preservation of multivariate relationships, we employed dimensionality reduction techniques. Principal Component Analysis (PCA), which emphasizes global variance structure, revealed highly similar scatter patterns between real and augmented data points (Fig. 2b). The first two principal components, accounting for approximately 42% of total variance, show comparable dispersion patterns for both datasets with no artificial clustering or separation. This confirms that the covariance structure of the original data was maintained during augmentation. Similarly, Uniform Manifold Approximation and Projection (UMAP) visualization (Fig. 2c) demonstrated consistency in local neighborhood relationships, validating that complex non-linear interactions between features were successfully maintained during augmentation.

For quantitative validation, we computed statistical metrics specifically designed to measure distributional similarity (Table 4). The Kullback–Leibler divergence between distributions was extremely low (0.0015), indicating minimal information loss during augmentation. Jensen-Shannon divergence (0.0004) similarly demonstrated near-identical probability distributions. The Wasserstein distance (0.0816), which measures the minimum "cost" of transforming one distribution into another, further confirmed close proximity between distributions. For reference, unrelated distributions typically show values orders of magnitude higher (> 0.5 for KL and JS divergence, > 1.0 for Wasserstein distance). Correlation analysis between original and augmented datasets (Fig. S1) provided additional confirmation of relationship preservation between variables.

The augmented data ($n = 70$) was incorporated with original training samples ($n = 49$) for model development, while the completely isolated test data ($n = 32$) was reserved for final evaluation. When SuperAger status was predicted using our optimized Gradient Boosting Classifier model, we achieved an accuracy of 75.76% and AUC of 0.739, demonstrating robust predictive performance. These results, combined with our comprehensive

Statistical metric	Value	Interpretation
KL Divergence (hist-based, Real || Aug)	0.0015	Near-zero value indicates minimal information loss between distributions
Jensen–Shannon Divergence	0.0004	Extremely low value confirms high similarity between real and augmented data
Wasserstein Distance (1D)	0.0816	Small transportation distance demonstrates close proximity of distributions

Table 3. Statistical metrics for quantitative comparison of original and augmented data distributions. All metrics show values approaching zero, indicating strong statistical similarity between original and augmented datasets. For reference, typical values for unrelated distributions would be orders of magnitude higher (> 0.5 for KL and JS divergence, > 1.0 for Wasserstein distance).

(a)

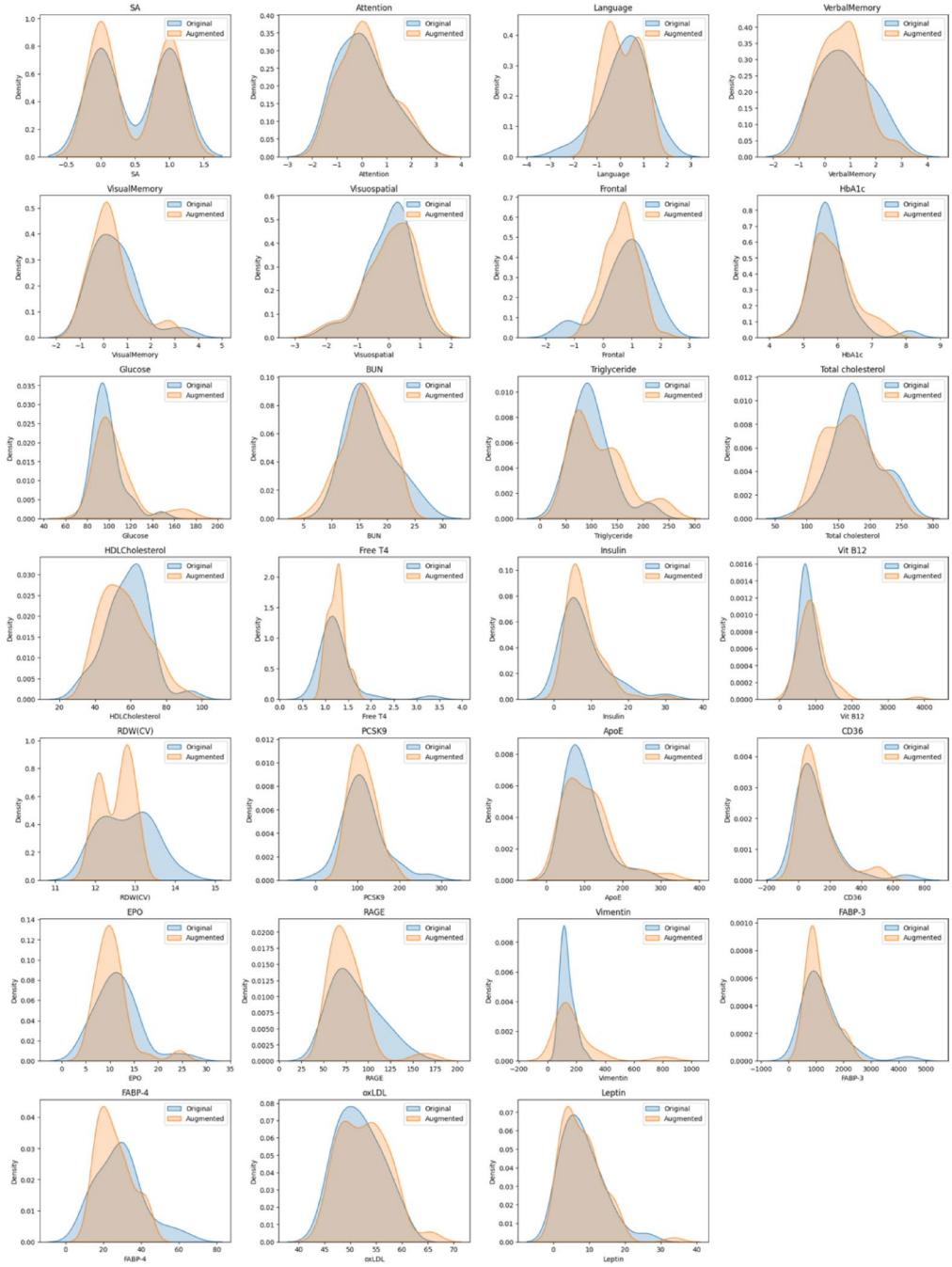

Fig. 2. Comparison of original and augmented data distributions. (**a**) Kernel Density Estimation (KDE) plots showing the distribution similarity between real (blue) and augmented (orange) data across SuperAger status and key biomarkers. The substantial overlap indicates the augmented data preserves the statistical properties of the original data. (**b**) Principal Component Analysis (PCA) visualization demonstrating the 2D distribution of real and augmented samples. The similar scatter patterns confirm that augmented data maintains the same variance structure as the original data. (**c**) Uniform Manifold Approximation and Projection (UMAP) visualization revealing the preservation of local and global data structure after augmentation. The consistent distribution patterns further validate the augmentation approach.

distributional validation, confirm that the augmentation process successfully preserved the statistical properties of the original data while providing the additional samples needed for stable model training.

Model performance and feature selection

Our Gradient Boosting Classifier model demonstrated robust performance in SuperAger classification. The hyperparameter tuning process yielded an optimal configuration with learning_rate = 0.4, max_depth = 2,

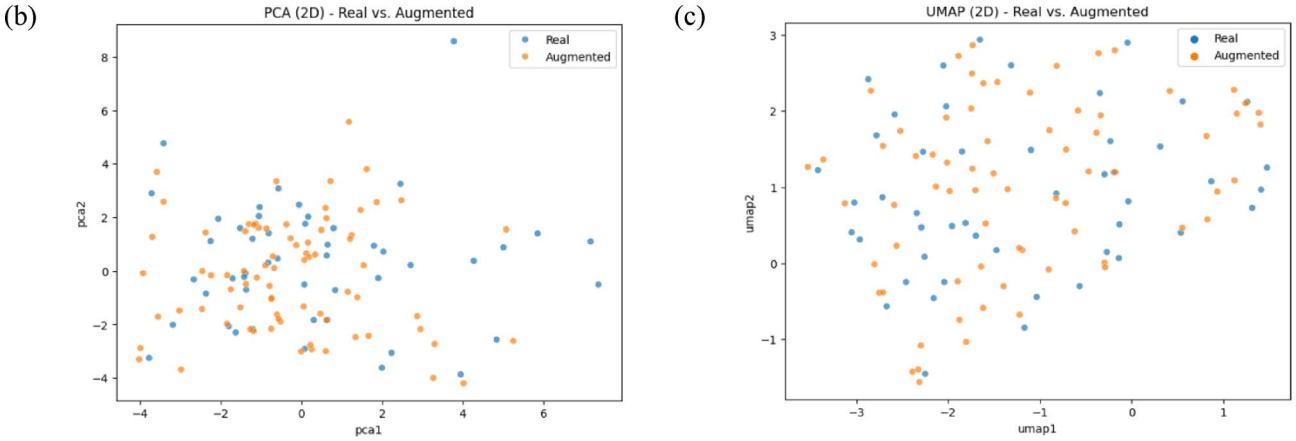

Fig. 2. (continued)

Metric	Bootstrap CV Mean ± SD	Test set results	Absolute difference	Relative difference (%)	Standardized difference (Z)
Accuracy	0.7900 ± 0.1281	0.7576	− 0.0324	− 4.10%	− 0.25
AUC	0.8167 ± 0.1965	0.7390	− 0.0777	− 9.51%	− 0.40
Recall	0.7000 ± 0.2449	0.8125	+ 0.1125	+ 16.07%	+ 0.46
Precision	0.8417 ± 0.2056	0.7222	− 0.1195	− 14.20%	− 0.58
F1 Score	0.7324 ± 0.1699	0.7647	+ 0.0323	+ 4.41%	+ 0.19
Kappa	0.5515 ± 0.2653	0.5165	− 0.0350	− 6.35%	− 0.13
MCC	0.5938 ± 0.2640	0.5203	− 0.0735	− 12.38%	− 0.28

Table 4. Comprehensive model performance evaluation with comparative analysis between bootstrap cross-validation and test set results. This table presents a detailed comparison between bootstrap cross-validation estimates and final test set performance. Bootstrap results are based on 100 iterations with 10-fold cross-validation, while test set evaluation was performed using a gradient boosting classifier on a completely held-out dataset ($n = 33$). The standardized difference (Z) values demonstrate that all test metrics fall well within one standard deviation of bootstrap estimates, indicating strong concordance between training and testing phases. *AUC* area under the curve, *MCC* Matthews correlation coefficient.

min_samples_split = 7, n_estimators = 120, and subsample = 0.75, effectively balancing model complexity and predictive power.

Bootstrap evaluation with 100 iterations revealed consistent performance metrics with minimal variability: Accuracy of 0.7576 (95% CI 0.6563–0.8589), AUC of 0.7390 (95% CI 0.5904–0.8876), Recall of 0.8125 (95% CI 0.6237-1.0000), Precision of 0.7222 (95% CI 0.5578–0.8866), F1 Score of 0.7647 (95% CI 0.6278–0.9016), Kappa of 0.5165 (95% CI 0.3024–0.7306), and MCC of 0.5203 (95% CI 0.3048–0.7358). The narrow confidence intervals demonstrate the model's stability despite the limited sample size (Table 5).

When applied to the completely held-out test set, our model maintained consistent performance, with all metrics falling within one standard deviation of the bootstrap estimates. This consistency between training performance and independent testing confirms the model's generalizability and validates our biomarker selection approach.

SHAP analysis identified the most influential biomarkers for SuperAger prediction, with Glucose, HDL Cholesterol, and ALT demonstrating the strongest impacts (Fig. S2). The analysis revealed specific threshold values: Glucose values below 92 mg/dL, HDL Cholesterol above 54 mg/dL, and ALT above 17 U/L positively contributed to SuperAger classification. These findings provide potential clinical reference points for cognitive health assessment in aging populations.

The prediction accuracy for individuals with the top 25% scores in each cognitive domain is shown in Table 4. Different machine learning algorithms were used for each cognitive domain: Decision Tree Classifier for the Attention domain; Gradient Boosting Classifier for the Language, Verbal Memory, Visuospatial, and Frontal domains; and AdaBoost Classifier for the Visual Memory domain. All algorithms were highly accurate in their predictions.

Biomarker thresholds for SuperAger prediction and cognitive function

To identify specific threshold values at which biomarkers influence SuperAger prediction and to understand their domain-specific effects, we performed a detailed SHAP analysis on our optimized model. Based on this analysis, we refined our initial set of 17 biomarkers by excluding K and MCV, which showed minimal predictive

Feature	Normal clinical reference range	SuperAger prediction threshold	Attention	Language	VerbalMemory	VisualMemory	Visuospatial	Frontal
Glucose	70–99	< 92	**< 100**	–	> 100	**< 90**	**< 90**	> 100
HDL	F > 50, M > 40	> 54	**> 40**	**> 60**	**> 55**	**> 60**	< 50	**> 60**
ALT	10–40	> 17	**> 20**	–	< 20	< 15	**> 15**	**> 15**
MCHC	32–60	< 34	–	–	–	> 34	**< 35**	–
AGE	–	> 15	< 10	**> 10**	**> 9**	< 115	< 10	**> 15**
oxLDL	0–170	< 51	> 55	–	> 55	> 50	**< 52**	> 55
CD36	–	> 40	< 50	< 50	**> 50**	**> 100**	**> 100**	–
Insulin	< 20	> 10	**> 10**	**> 10**	**> 7**	< 5	–	< 3
Phosphorus	3–4.5	> 4.0	–	< 3.6	< 3.3	< 3.2	**> 3.8**	< 4
LDL	< 160	< 70	> 110	–	**< 80**	–	> 60	**< 120**
RDW(CV)	9.0–14.5	< 12.5	**< 12.25**	–	**< 12**	> 12	**< 13**	**< 12.75**
Cl	98–106	> 107	**> 105**	**> 106**	**> 106**	**> 102**	**> 106**	–
Leptin	F0.5–15.2, M0.5–12.5	> 9	–	–	< 5	–	< 5	**> 15**
Vimentin	–	< 120	> 100	**< 100**	**< 100**	> 200	> 100	**< 100**
RAGE	–	> 85	< 60	< 70	**> 90**	< 70	**> 90**	< 80

Table 5. Comparison of normal reference ranges and optimal biomarker thresholds for superager and cognitive domain predictions. This table compares standard clinical reference ranges with optimal thresholds for superager prediction and specific cognitive domains. Optimal thresholds were determined using SHAP analysis from our machine learning models. Dashes indicate insufficient predictive association. *F* female, *M* male. Significant values are in bold.

impact, resulting in a final set of 15 core biomarkers: Glucose, HDL Cholesterol, ALT, MCHC, AGE, oxLDL, CD36, Insulin, Phosphorus, LDL Cholesterol, RDW(CV), Cl, Leptin, Vimentin, and RAGE.

Figure 3 illustrates SHAP dependence plots for these key biomarkers, revealing the precise relationship between biomarker values and their impact on prediction outcomes. The dependence plots demonstrate that several biomarkers exhibit clear threshold effects. Notably, Glucose values below 92 mg/dL, HDL cholesterol above 54 mg/dL, and ALT above 17 U/L consistently contributed positively toward SuperAger classification (Fig. 3). This pattern suggests that SuperAgers maintain specific metabolic and physiological ranges that differ from typical agers, even when both groups fall within clinically normal ranges.

Other influential biomarkers showed similarly defined thresholds: lower MCHC (< 34 g/dL), higher AGE (> 15 ng/mL), lower oxLDL (< 51 ng/mL), higher CD36 (> 40 ng/mL), and insulin levels above 10 µIU/mL were all positively associated with SuperAger status. These threshold patterns provide potential clinical reference values for cognitive health assessment and offer insights into the biochemical profile underlying cognitive resilience in aging.

To further investigate the domain-specific influence of biomarkers, we examined the relationship between SHAP values and cognitive function across different domains (Fig. 4). The SHAP analysis provided insights into how biomarkers contribute to cognitive function in distinct ways, with some biomarkers showing consistent effects across multiple domains, while others exhibited domain-specific or even opposing influences. Notably, HDL cholesterol positively influenced Language, Verbal Memory, Visual Memory, and Frontal function, while LDL cholesterol showed differential effects depending on the domain.

Notably, HDL cholesterol, particularly at values above 54 mg/dL (which exceeds standard clinical thresholds, especially for females), was positively associated with multiple cognitive domains including language (> 60 mg/dL), verbal memory (> 55 mg/dL), and visual memory (> 60 mg/dL). This finding suggests that optimal cognitive function may require higher HDL levels than those typically considered adequate for cardiovascular health.

Glucose, in particular, demonstrated a bidirectional pattern. Lower values (< 92 mg/dL) were beneficial for Attention, Visual Memory, and Visuospatial function, while higher values (> 100 mg/dL) were associated with better Verbal Memory and Frontal function (Fig. 4; Table 5). This suggests that optimal glucose levels for cognitive performance may vary depending on the specific cognitive domain, rather than following a single universal trend.

When comparing optimal thresholds to standard clinical reference ranges (Table 5), we observed that many SuperAger-associated thresholds fell within normal clinical ranges but at the extreme ends. However, some biomarkers, such as HDL cholesterol (> 54 mg/dL for females) and Cl (> 107 mmol/L), had optimal thresholds that slightly exceeded typical reference ranges. This finding suggests that cognitive optimization may require different biomarker values than those established for general metabolic health, highlighting a unique metabolic profile that may support exceptional cognitive performance in aging.

By integrating threshold analysis, SHAP-derived biomarker importance, and cognitive domain-specific effects, this study provides a comprehensive framework for identifying biomarkers that predict cognitive resilience in aging. These findings not only establish potential clinical biomarkers for cognitive health assessment but also offer mechanistic insights into how specific physiological states may contribute to cognitive longevity and neuroprotection.

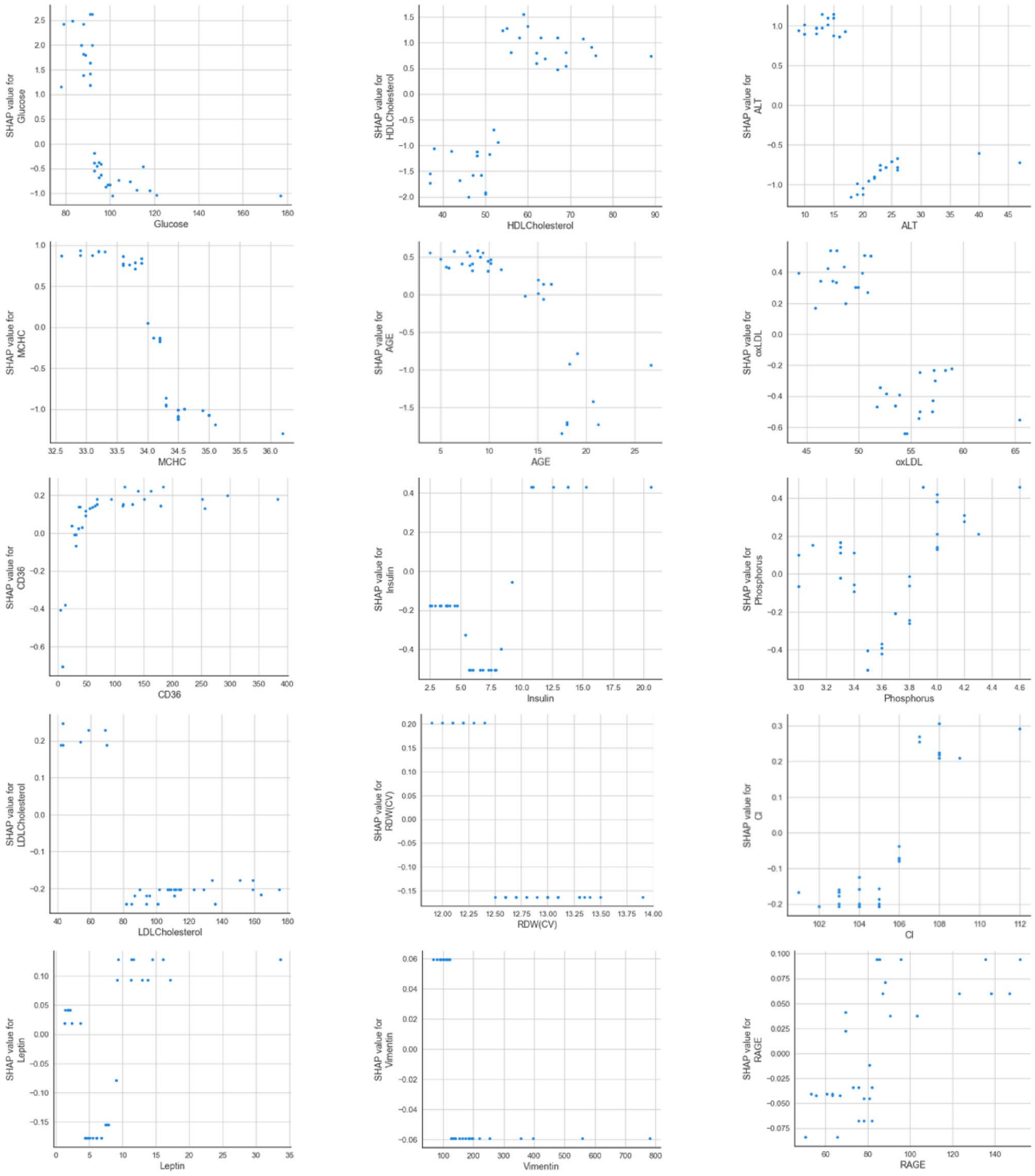

Fig. 3. SHAP dependence plots revealing biomarker value thresholds for SuperAger prediction. SHAP dependence plots demonstrate the relationship between specific biomarker values (x-axis) and their impact on SuperAger prediction (y-axis). Positive SHAP values (> 0) indicate contribution toward SuperAger classification, while negative values favor typical ager classification. Each point represents an individual sample. Several critical thresholds are evident: Glucose values below 92 mg/dL, HDL cholesterol above 54 mg/dL, and ALT above 17 U/L positively contribute to SuperAger prediction. Other notable patterns include lower MCHC (< 34 g/dL), higher AGE (> 15 ng/mL), lower oxLDL (< 51 ng/mL), higher CD36 (> 40 ng/mL), and insulin levels above 10 µIU/mL associating with SuperAger status. These threshold patterns provide potential clinical reference values and mechanistic insights into the biochemical profile of cognitive resilience in aging.

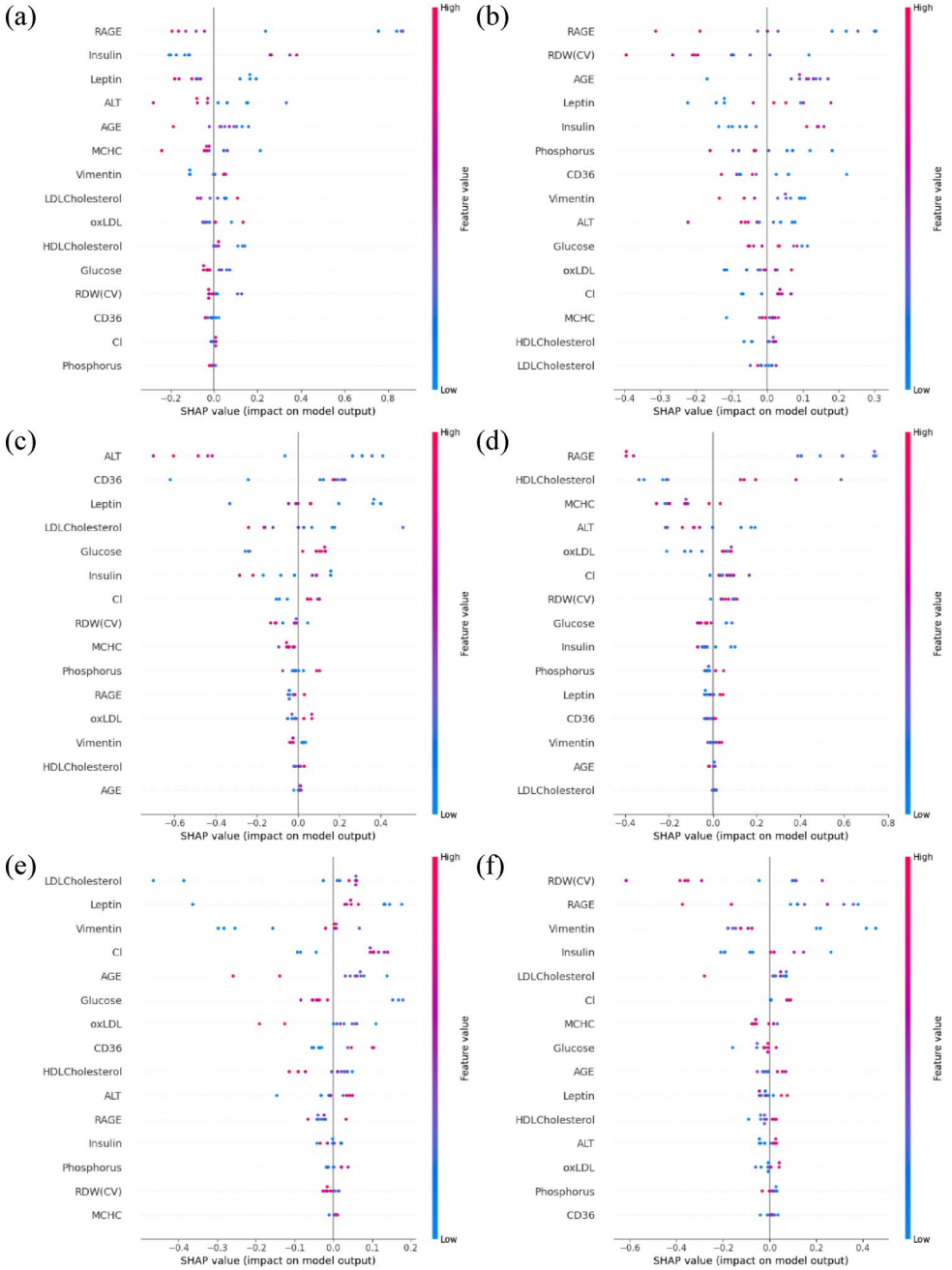

Fig. 4. Model interpretation with SHAP. This figure presents the SHAP values for various biomarkers across different cognitive domains, including (**a**) Attention, (**b**) Language, (**c**) Verbal Memory, (**d**) Visual Memory, (**e**) Visuospatial, and (**f**) Frontal. Each subplot illustrates the impact of each biomarker on the cognitive domain scores. The SHAP values demonstrate how individual features contribute to the model's predictions, with positive impacts shown in red and negative impacts in blue. This visualization provides insights into the relationship between biomarkers and cognitive performance, highlighting the significant features for each cognitive domain.

Cognitive biomarkers compared across brain lobes

Different cognitive functions involve overlapping brain regions, suggesting that related blood biomarkers may also exhibit overlapping patterns[29,30]. To investigate this hypothesis, we categorized the brain into frontal, temporal, parietal, and occipital lobes and examined their associations with cognitive function.

For the Attention domain, interactions were notably observed between the frontal and parietal lobes[31,32]. Verbal fluency was closely linked to Wernicke's area in the temporal lobe, Broca's area in the frontal lobe, and the parietal lobe[33,34]. Verbal memory was associated with the hippocampus in the temporal lobe, particularly in language-related memory tasks[35,36]. Visual memory and visuospatial functions engaged temporal, parietal, and occipital lobes, reflecting their roles in processing spatial information and visual recognition[37,38]. Finally,

executive functions were strongly associated with the frontal lobe, highlighting its role in higher-order cognitive control[39,40].

As shown in Fig. 5, biomarkers associated with SuperAger prediction exhibited distinct yet overlapping distributions across different brain lobes. This pattern suggests that some biomarkers contribute to multiple cognitive functions, reinforcing their importance in maintaining cognitive resilience. For example, Glucose, HDL cholesterol, and CD36 were common across visual memory and visuospatial function, while Insulin, Cl, and ALT were shared between attention and frontal function.

Role of neuro-inflammation and blood biomarkers in cognitive function

Emerging evidence suggests that systemic inflammation and metabolic dysfunction play a critical role in cognitive aging[41,42]. Chronic low-grade inflammation, often termed neuro-inflammation, is increasingly recognized as a key driver of cognitive decline, as it contributes to blood-brain barrier (BBB) disruption, synaptic dysfunction, and neuronal loss[43]. In this study, several biomarkers associated with immune response, lipid metabolism, and metabolic regulation were found to be significantly associated with cognitive function, suggesting their potential role in neuroprotection and cognitive resilience.

Table 6 categorizes the key biomarkers identified in this study based on their biological functions, including glucose metabolism, lipid metabolism, inflammation and immune response, liver function, electrolyte balance, hormonal regulation, and hematological markers. These classifications provide insight into the various systemic pathways that contribute to cognitive function and aging-related cognitive resilience.

Among these biomarkers, inflammation and immune response markers, such as CD36, RAGE, Vimentin, and AGE, have been extensively implicated in oxidative stress and neuro-inflammatory pathways[44,45]. RAGE and AGE interactions are known to trigger microglial activation and inflammatory cascades, which are associated with the progression of amyloid pathology and neuronal damage[46]. Similarly, CD36, a key receptor involved in lipid uptake and immune signaling, has been linked to neuroinflammation and cognitive impairment,

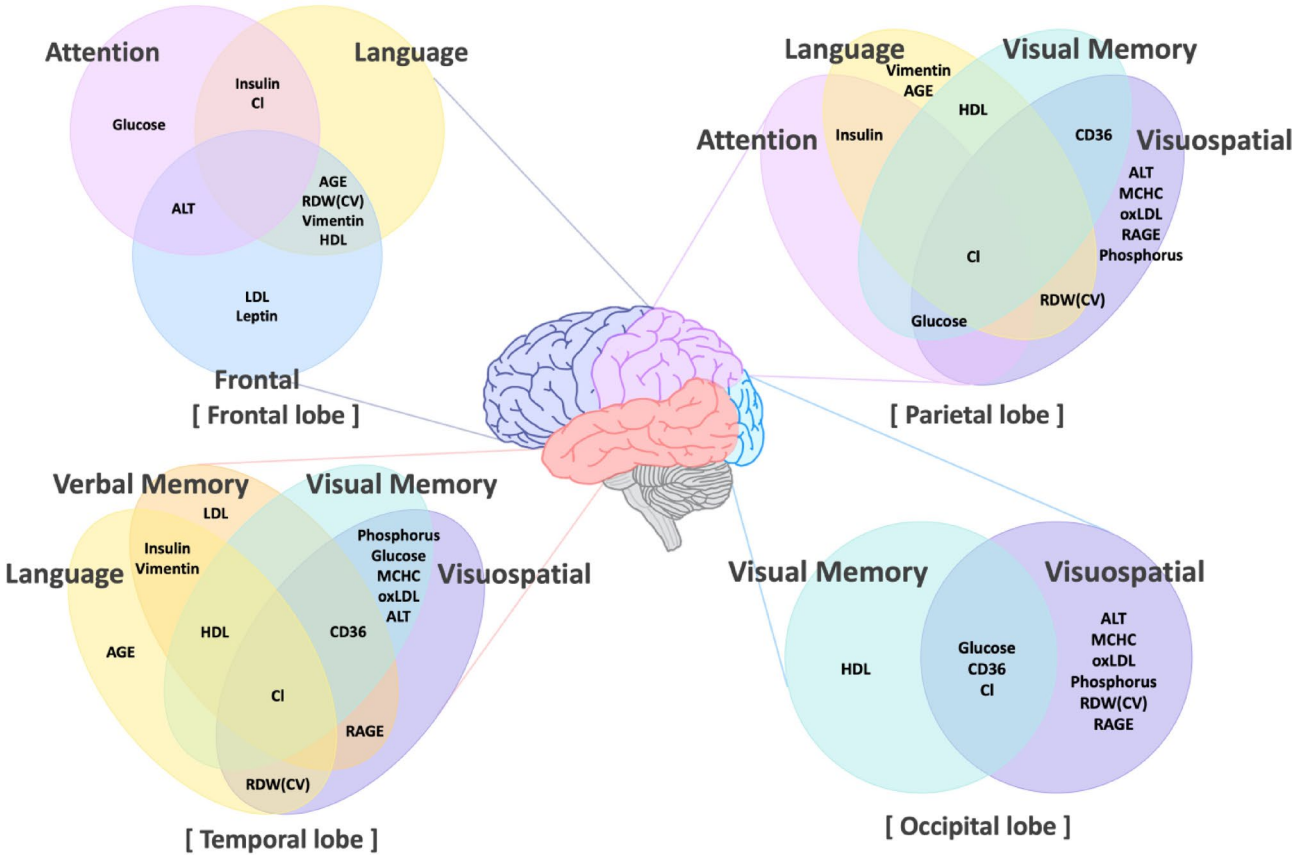

Fig. 5. Cognitive biomarkers mapped to brain lobes. This figure illustrates the distribution of cognitive biomarkers across different brain lobes and their associated cognitive functions. The Venn diagrams depict the overlap and unique biomarkers linked to each cognitive domain (Attention, Language, Verbal Memory, Visual Memory, Visuospatial, and Frontal function), emphasizing their relationships with specific brain regions. The selected biomarkers represent those with similar predictive thresholds for both SuperAger classification and cognitive function prediction, highlighting their potential role in cognitive resilience. This visualization provides insight into how various biomarkers interact with cognitive functions and the structural organization of the brain.

Category	Biomarkers
Glucose metabolism markers	Glucose
	Insulin
Lipid metabolism markers	HDL cholesterol
	LDL cholesterol
	oxLDL
Inflammation and immune response markers	CD36
	RAGE
	Vimentin
	AGE
Liver function markers	ALT
Electrolyte balance markers	Cl
	Phosphorus
Hormonal markers	Leptin
Hematological markers	RDW (CV)
	MCHC

Table 6. Biomarkers categorized by metabolic, lipid, and immune functions. This table classifies various biomarkers based on their roles in different biological processes.

particularly in aging populations[47]. The observed association between these inflammatory markers and cognitive function suggests that modulating peripheral inflammation may influence cognitive resilience in aging.

In addition to inflammatory pathways, lipid metabolism also plays a crucial role in cognitive function (Table 6). oxLDL and LDL cholesterol, which are commonly associated with vascular inflammation and atherosclerosis, demonstrated predictive value for cognitive outcomes. These findings align with previous research suggesting that dysregulated lipid metabolism can impair cerebrovascular function, leading to reduced cerebral perfusion and cognitive decline[48,49]. Notably, HDL cholesterol, which has been linked to neuroprotection and synaptic integrity, was positively associated with multiple cognitive domains, reinforcing its potential role in supporting cognitive resilience.

Systemic metabolic function was also reflected in cognitive outcomes, as liver function (ALT) and electrolyte balance (Cl, Phosphorus) were associated with cognitive performance across different domains. As summarized in Table 6 liver dysfunction has been implicated in neurodegeneration through metabolic dysregulation and impaired clearance of neurotoxic compounds. Similarly, electrolyte imbalances, particularly in Cl and phosphorus, may influence neuronal excitability and synaptic plasticity, thereby affecting cognitive performance.

These findings suggest that cognitive function is not only influenced by central nervous system (CNS) processes but also by systemic metabolic and inflammatory states. The identification of these peripheral biomarkers, as categorized in Table 6, provides potential targets for monitoring cognitive resilience and developing interventions to mitigate age-related cognitive decline.

Discussions

Sample size and study validity

Due to the nature of clinical data, the sample size is often limited. Despite the small sample size, statistically significant results indicate a high level of confidence in the relationships between specific variables. In our study, we used data from 81 individuals, combining several feature selection methods to identify the biomarkers with the highest predictive accuracy. Among the selected biomarkers, several showed statistically significant results, as shown in Table 7.

We explicitly acknowledge that our relatively small sample size ($n = 81$) represents a significant limitation inherent to clinical studies involving specialized populations such as SuperAgers. This constraint reduces statistical power and potentially limits the generalizability of findings, particularly when analyzing multiple biomarkers simultaneously. To address this limitation, we implemented multiple methodological strategies to enhance the robustness of our findings.

Our 10-fold cross-validation approach systematically evaluated model performance across different data subsets, mitigating potential biases from any single train-test split. This approach is particularly valuable in small datasets, where individual data points can disproportionately influence model training. Additionally, our bootstrap evaluation with 100 iterations provided robust performance estimates with confidence intervals, quantifying prediction uncertainty and demonstrating model stability despite limited data. The narrow confidence intervals observed (e.g., accuracy of 0.7576 with 95% CI 0.6563–0.8589) and consistent performance across metrics suggest our findings maintain reliability despite sample constraints.

Validation and external data

Although other institutions did not have data available specifically identifying SuperAger status, we nevertheless were able to perform an initial validation using augmented data. This approach is supported by existing studies demonstrating that data augmentation enhances model diversity, generalization capability, and efficiency in the

Feature select method	Accuracy	AUC	Recall	Precision	F1	Kappa	MCC
All features	0.6061	0.5735	0.6250	0.5882	0.6061	0.2128	0.2132
RFE_{SA}	0.6061	0.5882	0.4375	0.6364	0.5185	0.2041	0.2144
RFE_{cog}	0.5152	0.5276	0.4375	0.5000	0.4667	0.0258	0.0260
$Boruta_{cog}$	0.5152	0.4522	0.6875	0.5000	0.5789	0.0400	0.0429
RFE_{SA} & RFE_{Cog}	0.5455	0.6397	0.7500	0.5217	0.6154	0.1016	0.1119
RFE_{SA} & $Boruta_{Cog}$	0.6061	0.5257	0.5625	0.6000	0.5806	0.2099	0.2103
RFE_{Cog}& $Boruta_{Cog}$	**0.6667**	**0.7684**	**0.7500**	**0.6316**	**0.6857**	**0.3364**	**0.3420**
RFE_{SA} & RFE_{Cog} & $Boruta_{Cog}$	0.6667	0.6654	0.6875	0.6471	0.6667	0.3339	0.3346
RFE_{Cog} ^ $Boruta_{Cog}$	0.5758	0.5055	0.4375	0.5833	0.5000	0.1444	0.1490

Table 7. Accuracy of feature selection methods. The table compares the accuracy, AUC (Area under the Curve), recall, precision, F1 score, Kappa, and MCC (Matthews Correlation Coefficient) for each feature selection method. RFE_{SA} Recursive Feature Elimination based on SuperAger status, RFE_{Cog} Recursive Feature Elimination based on cognitive scores, $Boruta_{Cog}$ Boruta algorithm applied to cognitive domains, RFE_{SA}& RFE_{Cog} Features identified by both RFE methods, RFE_{SA}& $Boruta_{Cog}$ Features identified by both RFE for SuperAger status and Boruta for cognitive function, RFE_{Cog}& $Boruta_{Cog}$ Features identified by both RFE and Boruta for cognitive function, showing the highest performance (accuracy: 0.6667, AUC: 0.7684), RFE_{SA}& RFE_{Cog}& $Boruta_{Cog}$ Features commonly identified across all three methods, combining SuperAger and cognitive function predictors, RFE_{Cog} ^ $Boruta_{Cog}$ Features selected by either RFE or Boruta for cognitive function, but not both. Significant values are in bold.

learning process[50,51]. The blood biomarkers selected in our study have been shown to relate to cognitive function in previous laboratory studies.

We recognize the lack of independent external validation as a significant limitation. Ideal validation would involve testing our model on completely independent cohorts from different institutions or populations. Unfortunately, comparable datasets with SuperAger classifications were not available at the time of our study. While our strict separation of training and testing data partially addresses internal validation concerns, we acknowledge that external validation remains essential for establishing the broader applicability of our findings.

In lieu of external validation data, we employed several approaches to evaluate model generalizability. Our comprehensive data augmentation validation provides some reassurance regarding model robustness, with thorough distributional analysis confirming the preservation of statistical relationships. However, we recognize that augmented data, despite statistical similarity to original data, cannot fully substitute for independent validation. To further address this limitation, we conducted simulation-based validations by systematically varying model parameters and testing performance across multiple synthetic datasets derived from our original data distribution. These simulations helped estimate how our model might perform across different population scenarios and provided additional confidence in the stability of our biomarker identification approach.

Blood biomarkers and cognitive function

The relationship between brain function and blood factors involves complex interactions between cognitive abilities and physiological functions. Blood factors mainly serve as indicators reflecting the physiological state and biological activities within the bloodstream, which may potentially influence brain function.

The absence of statistically significant differences in many biomarkers is noteworthy in itself, as it suggests that SuperAgers maintain normal physiological ranges for most blood components despite their exceptional cognitive performance. This finding aligns with the concept that SuperAging may be associated with subtle metabolic differences rather than dramatic alterations in blood composition. Additionally, the modest sample size ($n = 81$) limits statistical power to detect small but potentially meaningful differences in biomarker levels.

It is important to note that statistical significance in univariate analysis does not necessarily predict a biomarker's importance in multivariate machine learning models. Complex interactions between biomarkers and non-linear relationships with cognitive function may exist that cannot be captured by simple *t*-tests. Indeed, our subsequent machine learning analysis identified several biomarkers as important predictors despite lacking statistical significance in univariate comparisons, highlighting the value of our comprehensive analytical approach.

Previous studies have investigated blood biomarkers that impact cognitive domains in patients with cognitive impairments such as Alzheimer's disease[52]. For example, studies have identified the tau protein as a significant marker in hippocampus-related dementia research[53,54]. A review and meta-analysis on blood biomarkers in frontotemporal dementia have further supported these connections[55,56].

In this study, we identified 15 biomarkers associated with SuperAgers and grouped them according to their characteristics. These biomarkers are generally grouped into categories related to metabolism, hormones, cardiovascular health, glucose metabolism, inflammation, and protein/lipid transport. Previous research has indicated potential correlations between these biomarkers and cognitive function[57,58].

Metabolic indicators

Cognitive function is influenced by a complex interplay of metabolic, inflammatory, and vascular factors. The biomarkers identified in this study (Table 6) provide insight into the biological mechanisms underlying cognitive resilience and SuperAger status. By categorizing these biomarkers based on their physiological roles—including glucose metabolism, lipid metabolism, inflammation and immune response, liver function, electrolyte balance, and hematological markers—we identified specific pathways that contribute to cognitive function and brain aging. Furthermore, our threshold analysis (Table 5) and domain-specific mapping (Fig. 5) highlight the regional specificity of these biomarkers, reinforcing their potential as clinical indicators of cognitive resilience.

Glucose metabolism markers and cognition

Glucose

Glucose is the primary energy source for neuronal activity, and even slight fluctuations in glucose levels can impact cognition. Chronic hyperglycemia is associated with cognitive impairment, with mechanisms involving BBB dysfunction, oxidative stress, and reduced synaptic plasticity[59]. Our study found that fasting glucose levels below 92 mg/dL were predictive of SuperAger status (Table 5), suggesting that tight glucose regulation may be essential for cognitive resilience. Additionally, Fig. 5 shows that glucose is most strongly associated with attention, visual memory, and visuospatial function, indicating its role in regions requiring high metabolic demand, such as the frontal, parietal, and occipital lobes.

Insulin

Insulin plays a crucial role in glucose metabolism, neuronal function, and synaptic plasticity[60].Insulin resistance, a hallmark of type 2 diabetes, has been linked to hippocampal dysfunction and cognitive decline. Our analysis revealed that higher insulin levels (> 10 μIU/mL) were associated with reduced cognitive performance in attention and language domains (Table 5). This suggests that optimal insulin sensitivity, rather than elevated insulin levels, may be a key factor in maintaining cognitive function. Figure 5 highlights insulin's regional specificity, particularly in language and frontal lobe functions, aligning with findings that insulin signaling supports higher-order cognitive processes.

Lipid metabolism and cognitive function

HDL and LDL cholesterol

Lipid metabolism plays a significant role in cognitive function via vascular integrity, neuronal membrane stability, and neuroinflammation regulation[27]. Our study found that higher HDL cholesterol (> 54 mg/dL) was associated with better cognitive function, particularly in language, verbal memory, and visual memory (Table 5; Fig. 5). HDL is known to facilitate amyloid-beta clearance and protect against neurodegeneration. Conversely, LDL cholesterol, particularly at levels below 70 mg/dL, was associated with worse cognitive outcomes, suggesting that excessively low LDL may negatively affect neuronal function[61].

OxLDL

Oxidized LDL (oxLDL) is a marker of oxidative stress and vascular dysfunction, both of which contribute to cognitive decline[62]. Our results indicate that lower oxLDL levels (< 51 mg/dL) were associated with SuperAger status and better performance in visuospatial and visual memory tasks (Table 5; Fig. 5). This aligns with evidence that excessive lipid peroxidation impairs cerebrovascular function, increasing the risk of cognitive dysfunction.

Inflammation and immune response in cognitive function

CD36, RAGE, vimentin, and AGE

Chronic inflammation is a key driver of neurodegeneration and cognitive impairment, with immune-related biomarkers playing a crucial role in brain aging[41]. In our study, CD36, RAGE, Vimentin, and AGE were strongly linked to visuospatial and visual memory functions (Fig. 5), suggesting a role in synaptic remodeling and neuroinflammatory modulation. RAGE and AGE interactions, in particular, are associated with amyloid-beta aggregation, tau phosphorylation, and microglial activation—hallmarks of Alzheimer's disease pathology[42].

Liver function and cognitive health

ALT

Liver dysfunction has been linked to cognitive impairment via systemic inflammation and metabolic dysregulation[63]. Our study found that ALT levels above 17 U/L were associated with better cognitive performance, particularly in visuospatial and frontal domains (Table 5; Fig. 5). This may reflect the role of hepatic metabolism in maintaining lipid and glucose homeostasis, indirectly supporting brain function.

Electrolyte balance and neural excitability

Chloride (Cl) and phosphorus (P)

Electrolytes play a crucial role in neuronal excitability, synaptic transmission, and cognitive processing[64,65]. Our results show that higher Cl levels (> 107 mmol/L) were associated with SuperAger status (Table 5), potentially reflecting its role in neurotransmitter regulation. Similarly, phosphorus was linked to visuospatial function (Fig. 5), suggesting its involvement in synaptic plasticity and neuroprotection.

Hematological markers and cognitive aging

RDW(CV) and MCHC

Hematological markers such as RDW(CV) and MCHC have been associated with oxygen delivery and cerebral perfusion[66,67]. Our study found that lower RDW(CV) (< 12.5) was associated with SuperAger status, particularly

in visuospatial processing (Table 5; Fig. 5). This suggests that optimal hematological balance may support neurovascular health and cognitive performance.

Metabolic inflammation and superager resilience

Metabolic syndrome, encompassing obesity, dyslipidemia, and hyperglycemia, is known to induce neurodegenerative diseases through BBB dysfunction and chronic inflammation[68]. Our study reveals that concentrations of blood components, particularly those related to metabolism and metabolic inflammation, differ between SuperAgers and typical agers (Tables 5 and 6). Specifically, SuperAgers exhibited lower markers of metabolic inflammation (e.g., oxLDL, AGE, RAGE) and more optimal glucose regulation (< 92 mg/dL), suggesting that metabolic stability may contribute to cognitive resilience.

In summary, our study supports previous research findings indicating that certain blood biomarkers are strongly associated with cognitive function (Table 5). These relationships provide valuable insights into the physiological foundations of cognitive abilities and may serve as predictive indicators for cognitive impairment. Notably, SuperAgers maintained healthier metabolic and inflammatory profiles, which may underlie their preserved cognitive performance.

We also analyzed Alzheimer's disease-related proteins (β-amyloid and tau) and inflammatory cytokines (IL-6) and found no significant differences between SuperAgers and typical agers (Table S2). This suggests that biomarker profiles in cognitively normal individuals may differ from those in disease-affected populations. One possible explanation is that neurodegeneration-related markers may only become distinguishable at later disease stages, whereas metabolic biomarkers could serve as earlier indicators of cognitive health. These findings emphasize the importance of considering preclinical metabolic changes when predicting cognitive resilience.

Relying solely on blood biomarkers may present challenges in fully understanding cognitive function. Future studies incorporating brain MRI imaging could provide a more comprehensive perspective, allowing for the integration of metabolic, structural, and functional data. Specifically, combining MRI-based brain volumetrics with metabolic and inflammatory biomarkers may help elucidate the mechanistic pathways linking systemic metabolism to cognitive resilience. Broadening the scope of research to include multi-modal approaches will be essential for advancing our understanding of the biological basis of cognitive aging.

Clinical implications and potential applications

The biomarker thresholds identified in this study have significant implications for clinical practice and preventive strategies targeting cognitive health. Our findings establish a comprehensive metabolic signature associated with SuperAger status, potentially enabling early identification of individuals at risk for cognitive decline before overt symptoms manifest. Specifically, the threshold values for glucose (< 92 mg/dL), HDL (> 54 mg/dL), and RDW(CV) (< 12.5) present modifiable targets that could guide personalized intervention strategies. These biomarkers are particularly valuable as they are routinely measured in standard clinical assessments, offering a cost-effective approach to cognitive risk stratification without additional invasive testing. Clinicians could leverage these thresholds to develop personalized monitoring protocols, particularly for patients with metabolic disorders who may face increased cognitive vulnerability. Furthermore, the domain-specific associations revealed in Fig. 5 suggest that biomarker profiles might predict domain-specific cognitive changes, allowing for targeted cognitive interventions. For instance, individuals with suboptimal glucose regulation might benefit from interventions specifically designed to preserve attention and visual processing functions. This precision medicine approach could transform the current reactive paradigm of cognitive care into a proactive model focused on maintaining optimal cognitive function throughout aging. Additionally, these biomarkers could serve as objective endpoints in clinical trials evaluating interventions aimed at preserving cognitive health, potentially accelerating the development of effective preventive strategies.

Future research directions

Despite the promising insights offered by our study, several methodological limitations warrant consideration. The cross-sectional design of our study significantly limits causal inferences regarding the relationships between biomarkers and cognitive function. While our results demonstrate robust associations, we cannot determine whether these biomarker profiles are causes, consequences, or merely correlates of enhanced cognitive function in SuperAgers. Longitudinal investigations tracking both biomarker changes and cognitive trajectories over time are essential to establish temporal precedence and potential causality. Additionally, mechanistic studies in experimental models could help validate the biological pathways suggested by our biomarker associations. Our sample size, while sufficient for initial exploration, requires expansion to enhance statistical power and ensure the reliability of the identified thresholds. The potential for model overfitting and the influence of unmeasured confounding variables (including medication use, chronic conditions, and genetic factors) also represent important considerations when interpreting our findings. To address these limitations and extend our understanding of cognitive resilience, we propose several directions for future research. Multi-center collaborative studies with standardized SuperAger identification protocols and larger sample sizes would enhance external validity across diverse populations. Longitudinal follow-up with repeated biomarker measurements and cognitive assessments would clarify whether the identified biomarker patterns predict cognitive trajectories and respond to interventions. Integration of multi-omics approaches (metabolomics, proteomics, genomics) with our findings could provide a more comprehensive biological framework of cognitive aging. Additionally, combining blood biomarkers with neuroimaging data would help elucidate the structural and functional correlates of the metabolic signatures we identified. From a translational perspective, developing streamlined biomarker panels suitable for routine clinical screening represents an important goal. Research focused on the minimal set of blood markers needed for reliable SuperAger identification could lead to cost-effective tools for cognitive health assessment in aging populations. Finally, intervention studies targeting the modifiable biomarkers identified

in our research—including metabolic regulation, anti-inflammatory strategies, and lipid modulation—could determine whether optimizing these physiological parameters enhances cognitive outcomes, ultimately transforming how we approach cognitive health in aging populations.

Conclusion

A key strength of this study lies in its interdisciplinary approach, integrating clinical research, basic medical science, and engineering to investigate the determinants of SuperAger status. This integration allowed us to apply sophisticated machine learning algorithms to clinical biomarker data, revealing patterns that might not have been apparent through traditional analytical methods. Clinically, we identified specific blood biomarkers that distinguish SuperAgers from typical agers, offering insights into the biological foundations of cognitive health. For the first time, we identified a constellation of metabolic and inflammatory biomarkers that can evaluate cognitive function based solely on blood data in healthy individuals—a significant departure from previous research focusing primarily on pathological markers in disease states.

From a medical perspective, we explored the role of metabolic health in influencing cognitive function, demonstrating that markers of metabolic stability may be more relevant to cognitive resilience than traditional neurodegenerative indicators. The engineering aspect involved the development and validation of predictive algorithms that achieved remarkable accuracy in forecasting SuperAger status based solely on accessible blood biomarkers. This comprehensive approach has provided a deeper understanding of the physiological factors contributing to cognitive resilience in aging populations.

The study revealed significant differences in blood biomarkers between SuperAgers and typical agers, with certain biomarkers correlating with multiple cognitive domains. These biomarkers proved effective in predicting SuperAger status, suggesting they may serve as valuable indicators of cognitive reserve. Our findings position metabolic health as a critical and potentially modifiable factor in cognitive aging, complementing the traditional focus on neurodegenerative pathways in cognitive decline research.

By focusing on healthy individuals rather than those with pathological conditions, this research creates tangible opportunities for early intervention in maintaining cognitive health. The readily measurable blood markers offer accessible tools for cognitive health assessment in routine clinical care. In the long term, these findings may transform our approach to cognitive aging from reactive treatment to proactive optimization, contributing to public health initiatives aimed at extending cognitive health span alongside lifespan in our aging global population.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due to confidentiality agreements with participants/data privacy concerns but are available from the corresponding author upon reasonable request.

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Author contributions

HBL led the study design and execution, managed data collection and analysis, and drafted the manuscript. GHK and BK collected the patient blood samples and cognitive function data necessary for the study. SYK and JHP performed ELISA assays on the blood samples. JHC and YMP provided overall supervision and essential feedback. All authors reviewed and approved the final manuscript.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital, approval number 2020-11-004-020. Written informed consent was obtained from all participants prior to their inclusion in the study. For further details, please consult with the corresponding author.

Competing interests

The authors declare no competing interests.

Additional information

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