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Research Article

Developing an Artificial Intelligence Framework for Identifying Fusion Blood-Based Biomarkers in Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is an irreversible neurological disorder, a major cause of disability among the elderly, with no effective therapeutic options currently available. It is an asymptomatic disease in the prodromal stages and begins many years before clinical appearances. Early diagnosis of AD allows patients to obtain appropriate healthcare assistance, accelerating the development of new medications. A biomarker that evaluates the alterations in the brain cells produced by AD in its preliminary periods might be significant for its early identification. Blood-based biomarkers (BBBMs) facilitate the early detection of AD. The BBBMs detection procedure is cost-efficient and minimally invasive. The aim of this study is to identify the best BBBMs, and machine learning (ML) algorithms play a significant role in identifying people at the high-risk of AD. A total of 146 BBBMs from a database by ADNI, and 12-ML algorithms were investigated. The results show that linear discriminant analysis, Naive Bayes, and support vector machine are the promising ML algorithms for AD detection that integrated into the novel ensemble voting detection model. Furthermore, the four BBBMs i.e., Immunoglobulin M (IGM), Placenta Growth Factor (PLGF), Serum Glutamic Oxaloacetic Transaminase (SGOT), and Alpha-1-Microglobulin (A1Micro) are the significant biomarkers to detect AD in its early stages with performance of 92.86% for sensitivity and 82.35% for specificity. Consequently, BBBMs are the preferred option in clinical practice. In addition, integrating artificial intelligence such as ML into healthcare might help with early detection of AD.

Keywords: Early detection of AD, Artificial Intelligence Framework, Database and Machine learning (ML), Ensemble voting classifier, Healthcare, Blood-based biomarkers.

1. Introduction

Alzheimer's disease (AD) is an irreversible, mortal, progressive and neurodegenerative disorder of the brain cells. It is marked by loss of memory, gradual cognitive impairments accompanied by abnormal behaviour, and personality changes (Sethi et al., 2024). There are no effective therapeutic options currently available (Bajaj & Mahesh, 2024). AD begins many years before clinical appearances (Tahami Monfared, Byrnes, White, & Zhang, 2022). Early diagnosis of AD allows patients to obtain appropriate healthcare assistance, accelerating the development of new medications. Early identification of AD would benefit from a biomarker that quantifies the alterations in the brain brought on by the disease in the early stages (A H Al-Nuaimi, Jammeh, Sun, & Ifeachor, 2017)(Ali H Husseen Al-Nuaimi, Al-Juboori, Jammeh, Sun, & Ifeachor, 2019).

As the world's population ages, the growing number of people suffering from Alzheimer's disease (AD) and other types of dementia pose considerable challenges for global social and healthcare systems (Kerwin et al., 2022).

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Globally, there are currently 46.8 million dementia sufferers, with an estimated $818 billion in care costs per year. By 2030, this amount is predicted to rise to 74.7 million, with an estimated $2 trillion in care costs(Bhattacharyya, 2021). By 2050, it is anticipated that there will be more than 153 million dementia sufferers worldwide (Livingston et al., 2024), resulting in a significant economic impact. However, many people with dementia do not receive an early diagnosis.

The development of high-sensitivity and novel tests allowed for the use of blood-based biomarkers (BBBMs) for AD diagnosis (AlMansoori, Jemimah, Abuhantash, & AlShehhi, 2024). To help identify the pathophysiology linked to AD, BBBMs are becoming more significant (Dubois, von Arnim, Burnie, Bozeat, & Cummings, 2023).

In clinical contexts, biomarkers comprising amyloid peptide and phosphorylated tau are utilised from both blood (plasma) and cerebrospinal fluid (CSF). Widespread clinical use is limited by the costly and invasive CSF-based biomarker testing procedure, which requires a lumbar puncture. Conversely, the BBBM's detection process is less costly and causes less discomfort for patients. Blood-based biomarkers are hence the patient population's preferred option. (Mandal et al., 2023).

The growing population is likely to increase demand for healthcare services. The healthcare field needs novel strategies to determine how to be more effective and efficient without committing to extra expenses. Artificial intelligence (AI) could significantly enhance patient care and reduce expenses. The use of AI approaches in healthcare is becoming more robust, with the potential to complement healthcare services. AI in healthcare is growing rapidly, particularly for early detection and diagnostic applications (Sunarti et al., 2021). Technologies based on artificial intelligence (AI) present massive opportunities for innovation in knowledge-intensive facilities in healthcare (Lee & Yoon, 2021). AI-enabled systems learn and diagnose using massive quantities of patient data and medical research, which contribute significantly to the improvement of clinicians' diagnosis and treatment decision-making procedures (Manne & Kantheti, 2021). AI-enabled systems supplement clinicians in diagnosing and treating actions for a variety of diseases (Lee & Yoon, 2021) like AD.

Traditional diagnostic approaches include many challenges, such as delayed treatment and misdiagnoses, which may delay treatment progress and increase healthcare expenses. The application of AI techniques, especially machine learning (ML) approaches, is an appropriate solution for addressing these challenges (Naser, Majeed, Alsabah, Al-Shaikhli, & Kaky, 2024). ML is one of the most popular types of AI applied in healthcare (Manne & Kantheti, 2021).

The general principle of ML is to train on the input training data and then trained model evaluated on the new data to get the expected outcomes, so that they may learn to achieve new results while also optimising their own performance based on what they have learned (Lin et al., 2024). ML algorithms may be helpful in diagnosing diseases by analysing related datasets and identifying disease factors from a dataset. ML is outperforming traditional biostatistical techniques by analysing and integrating massive volumes of complex healthcare data in terms of classification, prediction, and clustering. Machine learning has shown exceptional performance in many kinds of tasks, including identifying organs and tissues from segmenting brain tumours, medical images, classifying interstitial lung diseases, reconstructing medical images (An, Rahman, Zhou, & Kang, 2023) and early detection of AD (Ali H Al-Nuaimi et al., 2021)(A.H.H. Al-Nuaimi, Jammeh, Sun, & Ifeachor, 2018). ML algorithms have been widely employed in creating models for efficient early AD detection (Diogo, Ferreira, Prata, & Initiative, 2022).

A Support Vector Machine (SVM) algorithm was used to detect AD patients. A total of 30 BBBMs from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset were investigated, with 108 AD patients, and 58 Normal Cognitive (NC). A panel of five biomarkers (A1M, A2M, C3, IgM and TNC) were identified to detect AD patients, with average performance of 86.5% for sensitivity and 82.1% for specificity (Eke et al., 2018).

The associations between AD and patients with cardiovascular disease (CVD) were examined using the multivariable linear mixed model. 111 subjects with AD, 383 with MCI (mild cognitive impairment), and 410-CVD were included in the 146 plasma proteomic indicators from the ADNI database that were examined. With $p < 0.05$, the study identified 46 biomarkers linked to CVD and 48 linked to AD. 14 biomarkers were linked with AD and CVD (complement C3, ApoH, β2M, α1Micro, BNP, KIM1, cystatin C, PPP, THP, NGAL. TIM1, VEGF, TM, and TFF3), while 12 biomarkers were linked to CVD and MCI (TTR, ApoD, BNP, CD40, AXL Calcitonin, C-peptide, pM, THP, PPP, VEGF and TNFR2) (Theeke et al., 2024).

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A diagnostic method based on ML is the B-HEALED approach was used to identify AD patients. A total of 81 BBBMs from seven cohorts (GeneMatch, AIBL, University of Washington Cohort, SPIN, BioCogBank, Washington University Cohort, Stanford School of Medicine Cohort) were analysed for 126 with mild AD dementia, 123 with prodromal AD, and 96 healthy. The study found a combination of 19 blood biomarkers including gender, APOE4 and amyloid status with age, Age, Mini-Mental State Examination (MMSE), and Clinical Dementia Rating (CDR) scores. The developed model predicts AD dementia with 93.0% specificity and 65.4% sensitivity (AUROC = 81.9%, $p < 0.001$) (Souchet et al., 2024).

Deep-learning and regression analysis approaches were used to detect plasma proteins that predict tau , amyloid, and neurodegeneration (AT[N]) pathologies in AD. A dataset of 3,635 proteins from 881 patients in the European Medical Information Framework for AD Multimodal Biomarker Discovery project (EMIF-AD MBD) was analysed. The study indicated that AUCs for predicting t-tau, Aβ, p-tau, and AT(N) abnormalities were 0.748, 0.662, 0.710, and 0.795, respectively, based only on APOE ε4 status and age (Zhang et al., 2022).

The eXtreme Gradient Boosting (XGBoost) ML algorithm was used to differentiate AD, MCI, and CN. A total of 148 BBBMs from ADNI dataset, including 95 AD, 273 MCI, and 54 NC individuals analysed. The study identified a panel of five biomarkers, including BTC, Calcitonin, EOT3, HBEGF, and PAPP A, as well as MMSE and subject age, with sensitivity and specificity of greater than 90% (Al-Kabi, Al-Tuwaijari, & Al-Nuaimi, 2023).

XGBoost, Random Forest (RF), and deep learning approaches were employed to distinguish CN from AD. The dataset was from the European Medical Information Framework for Alzheimer's Disease Multimodal Biomarker Discovery (EMIF-AD MBD), with 593 plasma samples for 242 NC and 115 with AD who used plasma metabolites (n = 883). This study found that the DL obtained 0.85 for AUC, 0.88 for XGBoost, and 0.85 for RF. When comparing p-tau, CSF amyloid, and t-tau measurements (along with age and gender), the XGBoost achieved AUC values of 0.83, 0.78, and 0.87, respectively (Stamate et al., 2019).

Logistic Regression (LR) were carried out between plasma metabolites (n = 883) and CSF markers, magnetic resonance imaging, cognition, and clinical diagnosis. A total of 593 plasma samples selected from (EMIF-AD MBD) were examined: 242 for NC, 236 for MCI, and 115 for AD. The study found that eight metabolites were related to amyloid b and one with t-tau in CSF, including primary fatty acid amides (PFAMs), lipokines, and amino acids. PFAMs, glutamate, and aspartate are all connected with hippocampus volume and memory (Kim et al., n.d.).

A total of 53 inflammatory proteins from AddNeuroMed, including 259 for NC, 199 for MCI, and 26 for AD. The findings indicated ten LR recognised five (MCP-1, FB, sCR1, FH, eotaxin-1), age/APOε4 adjusted, ideally distinguished AD and proteins in elderly control (AUC: 0.79), and three (sCR1, eotaxin-1, MCP-1) that optimally discriminated AD and MCI (AUC: 0.74). These models were reproduced in a separate cohort (EMIF; AUC = 0.81 and 0.67). Two analytes (FB, FH) together with age indicated MCI progression to AD (AUC: 0.71) (Morgan et al., 2019).

The database plays an essential role in disease diagnosis, representing the fundamentals for data storage and analysis. It may contribute to storing huge amounts of patient data such as e-health records, lab test results, diagnosing reports, and medical history (Luong et al., 2025). Databases are necessary for training AI models which predict diseases depending on test results and recommend appropriate diagnoses for situations like AD (Yang et al., 2025). The accuracy of AI diagnostics models is impacted by the quality and quantity of data stored in databases (Hanif, 2025).

The structure of the paper as follows: the materials and methods explained in Section two. Results are shown in Section three and discussion is presented in Section four. Section five is for conclusion

2. Materials and Methods

2.1. Dataset

ADNI proteomic database (http://adni.loni.ucla.edu) was investigated current study. The used dataset includes 146 biomarkers for 150 subjects were used, with 95 AD, and 54 NC. Each biomarker has two values. The Base Line (BL), and 12 Months (M12). The used dataset contains more details about the ADNI proteomic dataset is available at http://www.adniinfo.org. Table 1 shows the explored BBBMs dataset.

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Table 1: Description of the BBBMs dataset

	Total	Age [SD]	MMSE [SD]
AD	95	75.0± 7.9	23.6± 1.9
NC	45	75.3± 5.9	29.0± 1.2

2.2. *Pipeline procedures for detecting the best BBBMs of AD*

A machine learning pipeline is connected sequence of steps that automates the required workflow to develop, train and test, and evaluate machine learning models (Hapke & Nelson, 2020). After downloading the dataset, it was cleaned by removing all record have missing or empty values. The remaining data was 150 subjects. The data cleaning procedure improves machine learning performance by ensuring that the dataset is reliable and appropriate for analysis (Deekshith, 2021). The dataset was spilled into two training and testing subsets. The splitting ratio was 70% for training and 30% for testing. Figure 1 shows the pipeline procedure for identifying the best BBBMs of AD.

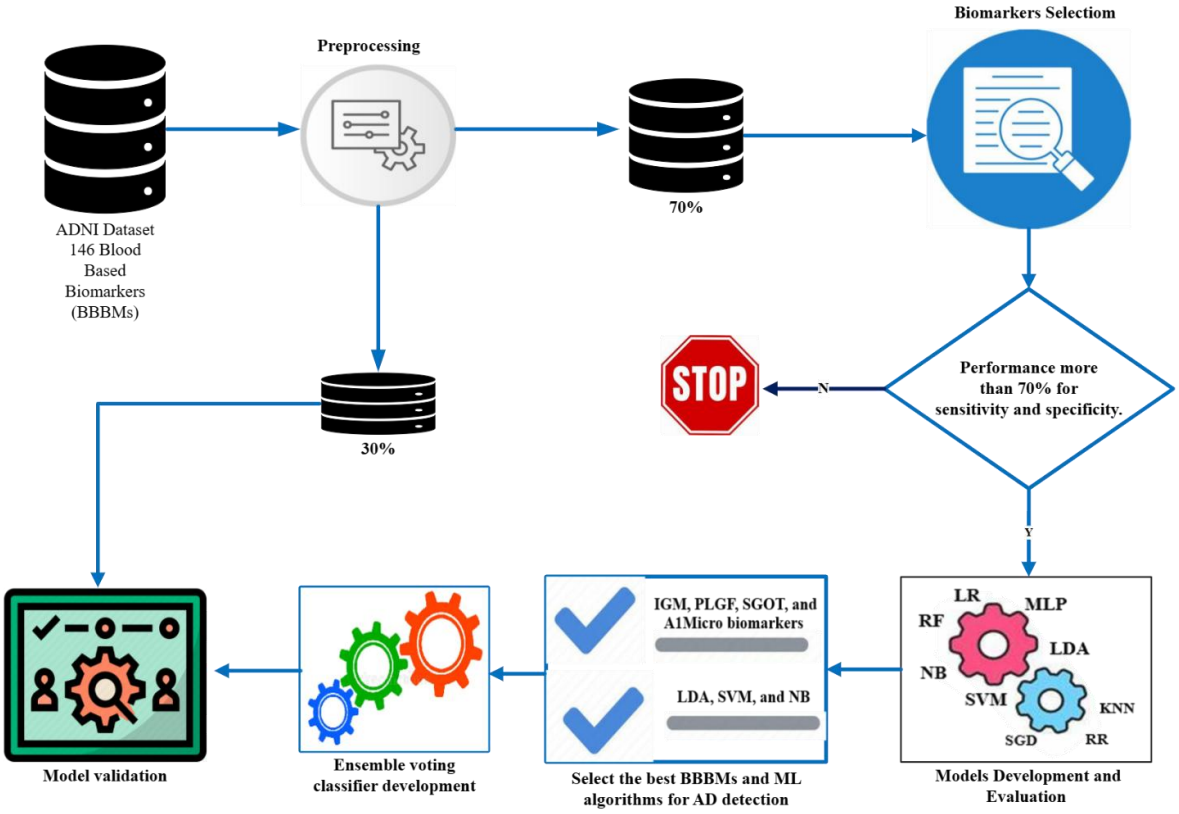

Figure 1: Pipeline procedure for identifying the best BBBMs of AD

2.2.1. Biomarkers Selection

Four different feature selection approaches were investigated to select the BBBMs which have great value in AD detection using the training dataset. These methods include Recursive Feature Elimination (RFE) using LR, RFE with cross-validation, permutation feature importance, and LASSO (Least Absolute Shrinkage and Selection Operator) feature importance. The biomarkers were ranked based on their impact in AD detection from high to low. For each method, the top 10 biomarkers were selected for the next levels of investigation. This approach increases accuracy, decreases training time, and minimizes overfitting for ML development models, and only the most "informative" biomarkers should be selected; noisy, irrelevant, and redundant biomarkers should be eliminated (Pudjihartono,

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Fadason, Kempa-Liehr, & O'Sullivan, 2022). Selecting different methods for biomarkers selection because each method works in a different way, this could lead to select all biomarkers have an impact in AD detection.

1. RFE using LR.

Table 2 shows the top 10 BBBMs when applying the RFE using the LR method.

Table 2: RFE using LR

#	**Selected biomarkers**
1	Angiotensinogen (AGT)
2	Apolipoprotein H (Apo H)
3	Brain Natriuretic Peptide (BNP)
4	CD40 Ligand (CD40-L)
5	C-Reactive Protein (CRP)
6	Epidermal Growth Factor (EGF)
7	Epidermal Growth Factor Receptor (EGFR)
8	E-Selectin
9	Fibrinogen
10	Follicle-Stimulating Hormone (FSH)

2. RFE with cross-validation.

Table 3 shows the top 10-BBBMs when applying the RFE with cross-validation method.

Table 3: RFE with cross-validation

#	**Selected biomarkers**
1	Immunoglobulin M (IGM)
2	Peptide YY (PYY)
3	Apolipoprotein A-II (Apo A-II)
4	Alpha-1-Microglobulin (A1Micro) α 1-Microglobulin (α 1 m)
5	Interleukin-16 (IL-16)
6	Apolipoprotein E (Apo E)
7	Brain Natriuretic Peptide (BNP)
8	Proinsulin- Total (pM)
9	Serotransferrin (Transferrin)
10	Placenta Growth Factor (PLGF)

3. Permutation feature importance.

Table 4 shows the top 10-BBBMs when applying the permutation feature importance method.

Table 4: Permutation feature importance

#	Selected biomarkers
1	Immunoglobulin M (IGM)
2	Apolipoprotein A-II (Apo A-II)
3	Interleukin-16 (IL-16)

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4	Brain Natriuretic Peptide (BNP)
5	Alpha-1-Microglobulin (A1Micro)
6	Apolipoprotein E (Apo E)
7	Peptide YY (PYY)
8	Ferritin (FRTN)
9	Serum Glutamic Oxaloacetic Transaminase (SGOT)
10	Apolipoprotein B (Apo B)

4. LASSO feature importance.

Table 5 shows the top 10-BBBMs when applying the LASSO method.

Table 5: LASSO feature importance

#	**Selected biomarkers**
1	Apolipoprotein B (Apo B)
2	Osteopontin
3	Cortisol (Cortisol)
4	Glutathione S-Transferase alpha (GST-α)
5	Prostatic Acid Phosphatase (PAP)
6	C-peptide
7	Clusterin (CLU)
8	Trefoil Factor 3 (TFF3)
9	Follicle-Stimulating Hormone (FSH)
10	CD 40 antigen (CD40)

To select the top AD biomarkers, tables 1-4, were combined in one table with no repetition, as shown in Table 6.

Table 6: Selected the top biomarkers out of 147 for AD detection

#	**Selected biomarkers**
1	A1Micro
2	Angiotensinogen
3	Apo A-II
4	Apo B
5	Apo E
6	Apo H
7	BNP
8	CD40
9	CD40-L
10	CLU
11	Cortisol
12	C-peptide
13	CRP
14	EGF
15	EGFR
16	E-Selectin

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17	FRTN
18	Fibrinogen
19	FSH
20	GST-α
21	IGM
22	IL-16
23	Osteopontin
24	PYY
25	PLGF
26	pM
27	PAP
28	Transferrin
29	SGOT
30	TFF3

Table 6 shows the top 30 biomarkers out of the total 146-BBBMs which have an impact on the detection of AD.

2.2.2. Models Development and Evaluation

Twelve machine learning algorithms were investigated to select the best biomarkers out of 30 for AD detection based on their performance. The sensitivity (Sen), specificity (Spec), accuracy (Acc), and ROC-AUC (Receiver Operating Characteristic Area Under the Curve) scores were computed to assess the performance of each biomarker (BBBM). These algorithms are Naiive Bayes (NB), stochastic gradient descent (SGD), RF, k-nearest neighbours (KNN), multi-layer perceptron (MLP), SVM, bootstrap aggregation (bagging) classifier, LR, ridge regression classifier (RR), XGBoost, Linear Discriminant Analysis (LDA), and Categorical Boosting (Catboost) classifier. Each of the 30 bi-omarkers was evaluated on those 12 ML algorithms. It means 12 ML models were developed and evaluated for each of the 30 biomarkers. This process may provide a comprehensive understanding of each biomarker, and the ML algorithm has an impact value on AD detection based on analysing their BBBMs. Table 6 shows all biomarkers and ML algorithms achieved performance of more than 70% for sensitivity and specificity.

3. Results

The biomarker selection process explored all 146 BBBMs and 30 were selected that have an impact on AD detection. To select the best subset of these 30, their performance on AD detection was investigated. Table 7 shows only the biomarkers that achieved more than 70% of sensitivity and specificity, and the ML detection models. These bi-omarkers and ML models were selected for further investigation.

Table 7: Top BBBMs for AD detection achieved more than 70% of sensitivity and specificity

Biomarker	**Method**	**Sen %**	**Spec %**	**Acc %**	**ROC-AUC %**
A1Micro	LDA	76.47	72.73	75.56	69.83
A1Micro	SVM	74.29	70.00	73.33	66.70
Apo A-II	SGD	83.33	73.33	80.00	77.48
Apo E	SVM	74.29	70.00	73.33	66.70
BNP	LDA	71.05	71.43	71.11	62.18
CRP	NB	74.36	100	77.78	68.75
GST-α	NB	71.05	71.43	71.11	62.18
IGM	Bagging	71.79	83.33	73.33	63.9
IGM	Catboost	71.79	83.33	73.33	63.90

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IGM	LDA	71.05	71.43	71.11	62.18
IGM	LR	72.50	100	75.56	65.62
IGM	MLP	71.79	83.33	73.33	63.9
IGM	SVM	72.50	100	75.56	65.62
PYY	LDA	75.00	77.78	75.56	68.43
PLGF	Bagging	73.68	85.71	75.56	67.03
PLGF	MLP	73.68	85.71	75.56	67.03
PLGF	NB	81.25	76.92	80.00	76.08
PLGF	RF	85.71	70.59	80.00	78.88
PLGF	SGD	80.65	71.43	77.78	74.35
PLGF	SVM	80.00	90.00	82.22	76.40
SGOT	Catboost	72.97	75	73.33	65.3
SGOT	LDA	73.68	85.71	75.56	67.03
SGOT	LR	70.73	100	73.33	62.5

Table 7 shows 10 BBBMs out of the 30 investigated biomarkers. Each biomarker of the 30 (as shown in Table 5) was investigated by 12 ML algorithms. Some of those biomarkers occurred many times, while others did not, as shown in Table 6. Biomarkers that achieved high performance with different ML algorithms might have an impact on AD detection. Similarly, the same ML algorithms have occurred many times with various biomarkers, and they might play a crucial role in developing detection models.

Table 8 shows a summary of each BBBM, how many times occurred, and ratio of occurrences during detection. For example, IGM occurred six times (ratio of occurrences is 26.09%) using Bagging, Catboost, LDA, LR, MLP, and SVM detection models. While PYY occurred one time with LDA only (ratio of occurrences is 4.35%).

Table 8 The BBBMs have great value in AD detection and their frequencies

Biomarker	**Occurrences**	**Ratio of occurrences %**
IGM	6	26.09
PLGF	6	26.09
SGOT	3	13.04
A1Micro	2	8.70
Apo A-II	1	4.35
Apo E	1	4.35
BNP	1	4.35
CRP	1	4.35
GST-α	1	4.35
PYY	1	4.35

Table 9 shows a summary of each ML algorithms, how many times occurred, and ratio of occurrences during detection. For example, LDA occurred 5 times (ratio of occurrences is 21.74%) with A1Micro, BNP, IGM, PYY, and SGOT biomarkers. While RF occurred one time with PLGF biomarker only (ratio of occurrences is 4.35%).

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Table 9: ML algorithms and their frequencies in AD detection

ML algorithm	Occurrences	Ratio of occurrences %
LDA	5	21.74
SVM	4	17.39
NB	3	13.04
Bagging	2	8.70
Catboost	2	8.70
LR	2	8.70
MLP	2	8.70
SGD	2	8.70
RF	1	4.35

Table 8 ranks the BBBMs based on their impact on AD detection, from high to low. Similarly, Table 2 ranks the ML algorithms from high to low based on their sensitivity to the developed models for AD detection.

3.1. Ensemble voting classifier development

According to tables 8 and 9, can conclude that IGM, PLGF, SGOT, and A1Micro blood-based biomarkers can be used to develop a robust ensemble ML model to detect AD in its prodromal stages using LDA, SVM, and NB classifiers.

The three ML algorithms i.e., LDA, SVM, and NB were ensembled into one voting model to develop a new robust detection model. This leads to enhancing the overall performance through integrating the predictions of several models. The four biomarkers with high impact in AD detection (first four in Table 8) were used into the development.

The results of the ensemble voting model are 92.86%, 82.35%, 88.89%, and 88.58% for Sen, Spec, Acc, and ROC-AUC, respectively. The results of the ensemble voting model are performed on the results of all 12 ML models that were investigated, as shown in Table 7.

4. Discussion

Table 7 summarises each BBBMs performance in AD detection. The results of the present study found that IGM, PLGF, SGOT, A1Micro, Apo A-II, Apo E, BNP, CRP, GST-α, and PYY are associated with dementia development.

The first protein is IGM, which is the most ancient antibody class and an important modulator of the essential immune response (Sutton, 2023). It is the initial type of antibody generated during a primary antibody response and generated by the immune system early in an infection (Boes, 2000). The results showed that IGM achieved an average performance of 71.90%, 86.90%, 73.70%, and 64.19% for Sen, Spec, Acc, and ROC-AUC respectively. This finding is consistent with other results that found that IGM happens in a considerable proportion of dementia patient (Doss et al., 2014), and Busse et al. (Busse et al., 2018), demonstrating that IGM is associated with MCI and dementia. The IGM protein might be considered as an initial indicator of people who are more likely to develop dementia.

The second protein is PLGF, which belongs to the VEGF (Vascular Endothelial Growth Factor) family of six proteins. It is a homologous form of VEGF that induces angiogenesis by activating endothelial cells through binding to VEGFR1 (Vascular Endothelial Growth Factor Receptor 1) and neuropilin1 (NRP1) (eun Lee, Lee, & Kim, 2024). The results showed that PlGF achieved an average performance of 79.16%, 80.06%, 78.52%, and 73.30% for Sen, Spec, Acc, and ROC-AUC respectively. This finding is compatible with other findings that showed the plasma PlGF may be used as a diagnostic biomarker to evaluate the degree of vascular damage in those at risk of cognitive impairment and dementia, which lead to baseline cognitive dysfunction (Hinman et al., 2023). Also, the levels of serum PlGF were shown to be higher in AD patients than in cognitively impaired people with no dementia (Ankeny, Bacci, Decourt, Sabbagh, & Mielke, 2024).

The third indicator is SGOT, which is also known as AST (aspartate aminotransferase). This enzyme is widely distributed in human tissues, with the highest level found in the cardiac tissue, liver, and skeletal muscle containing the

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highest quantities, while the kidneys, pancreas, and erythrocytes contain the lower levels (Michael L. Bishop, 2018). The results showed that SGOT achieved an average performance of 72.46%, 86.90%, 74.07%, and 64.94% for Sen, Spec, Acc, and ROC-AUC respectively. This finding is consistent with other results that showed change in SGOT level is a sign of hepatic dysfunction (Ganeshpurkar et al., 2024), and liver dysfunction may affect brain function and might lead to brain damage (Butterworth, 2003). It was discovered that AST levels showed a substantial positive association with cognitive function and were significantly lower in AD (Han, Park, Jang, Nho, & Kim, 2022).

The next indicator is A1Micro protein, which is characterized as a tissue housekeeping protein that removes and protects as opposed to dangerous oxidants, as well as macromolecule repair. A1M protein has been shown to function as a physiological antioxidant that protects cells and tissues. Several internal or external factors might cause kidney damage as a result of a relatively high A1M level in the kidney (Bergwik, Kristiansson, Allhorn, Gram, & Åkerström, 2021). The results showed that A1Micro achieved an average performance of 75.38%, 71.37%, 74.45%, and 68.27% for Sen, Spec, Acc, and ROC-AUC respectively. The results of other studies showed that kidney dysfunction is a risk factor for AD (Stanciu et al., 2020). A protective impact of the kidneys on A1M from a range of factors that cause oxidative stress-related damage (Bergwik et al., 2021). Oxidative stress is a significant element in the progression of AD (Stanciu et al., 2020)(Bai, Guo, Ye, Xie, & Xie, 2022). As a result, variations in A1M levels may be used to diagnose Alzheimer's disease. This finding is compatible with the findings of this study, which indicate that A1M is an indicator of AD progression.

The fifth indicator is Apo A-II protein. The main function of apoA-II protein is linked to lipid metabolism. Since it is the second most abundant protein in high-density lipoprotein (HDL) particles, it is related to cardiovascular diseases (CVD) (Cho, 2022). In particular, ApoA-II contributes significantly to incident CVD in women (Anagnostis, Lambrinoudaki, Stevenson, & Goulis, 2022). Cardiovascular risk factors' influence on AD has been shown at both the clinical and pathological level (Bettcher, Tansey, Dorothée, & Heneka, 2021). The results of the present study showed that A1Micro achieved a performance of 83.33%, 73.33%, 80%, and 77.48% for Sen, Spec, Acc, and ROC-AUC respectively. This is consistent with the results of other researchers that indicated changes in A1Micro might assist in AD prediction.

The sixth indicator is Apo E protein, which is mostly generated by liver parenchymal cells, is essential for preserving the structural integrity of lipoproteins and enhancing their solubility in blood circulation (Ben Khedher, Haddad, Laurin, & Ramassamy, 2021a). APOE ε4 has been linked to increased dementia risk and impaired cognitive function (Llibre-Guerra et al., 2023), as well as Lewy body disease (Gal et al., 2022). The relationship between the APOE ε4 allele and oxidative stress may contribute to increased risk of AD (Ben Khedher, Haddad, Laurin, & Ramassamy, 2021b). Oxidative stress is a crucial factor in the development of AD (Stanciu et al., 2020)(Bai et al., 2022). The findings in the present study showed that Apo E is related to AD development, which is compatible with other findings. Apo E achieved performances of 74.29%, 70%, 73.33%, and 66.70% for Sen, Spec, Acc, and ROC-AUC respectively, as shown in Table 7.

The seventh indicator is BNP, which belongs to a class of structurally related peptide hormones. BNP is released by both atrial and ventricular myocytes. However, the left ventricle is the primary site of production (Cowie et al., 2003). As shown in Table 7, the BNP achieved performances of 71.05%, 71.43%,71.11%, and 62.18% for Sen, Spec, Acc, and ROC-AUC respectively. That is consistent with the findings of other studies that concluded that BNP is considered as a risk factor for cognitive decline and the onset of dementia (Kerola et al., 2010).

The eighth indicator is CRP protein, which belongs to the protein family known as pentraxins. The liver releases CRP in response to several inflammatory cytokines. CRP levels increase quickly in response to trauma, inflammation, and infection, then fall rap-idly as the condition resolves (Du Clos, 2000). MCI individuals with decreased CRP levels showed a faster progression to AD dementia (Fernandes et al., 2020). The findings in the current study stated that CRP might be associated with AD progression, which is consistent with other results. The findings showed that CRP achieved performance of 74.36%, 100%, 77.78%, and 68.75% for Sen, Spec, Acc, and ROC-AUC respectively, as shown in Table 7.

The ninth indicator is GST-α, which is a key detoxifying enzyme that retains cellular health by counteracting oxidative and chemical stress associated with aging. GSTα activity could point to oxidative stress, a key factor in the

pathogenesis of neurodegenerative diseases. It is well acknowledged as a key pathogenic element in the development of MCI and AD. GSTα protein might serve as a biomarker for AD and AD (Tang, Li, Dai, Wang, & Lai, 2024). This finding is also stated in the present study, that GST-α achieved performances of 71.05%, 71.43%, 71.11%, and 62.18% for Sen, Spec, Acc, and ROC-AUC respectively.

The last indicator is PYY, which is a 36-amino acid peptide that is excreted into the bloodstream from the intestine and colon following a meal. It has been demonstrated to reduce appetite in men and rodents (Morris et al., 2020). Individuals with AD had a significantly higher meal-stimulated response to glucose, insulin, and PYY (MacKenzie, 2006). The gastrointestinal tract excretes peptides such as PYY, GLP-1 (glucagon-like peptide-1), and GIP (glucose-dependent insulinotropic polypeptide) to increase the insulin response and regulate blood glucose levels. These effects are crucial because elevated glucose levels and im-paired glucose control have been linked to increased AD clinical progression and markers of AD development (El-Ghazawi, Eyo, & Peirce, 2024). The investigation of the current study stated that PYY has an implication in AD detection, which is consistent with the findings of others. The performance of PYY achieved was 75%, 77.78%, 75.56%, and 68.43% for Sen, Spec, Acc, and ROC-AUC respectively.

5. Conclusions

The investigation of 146 AD blood-based biomarkers utilising multiple types of machine learning algorithms (12 ML) to identify the best blood-based biomarkers has an influence on early AD detection. The current investigation discovered that BBBMs offer robust markers, and risk factors are associated with AD progression. Some BBBMs are directly linked to Alzheimer's disease progression, whereas others are indirectly linked. The BBBMs might be employed as markers and risk factors to assist in AD prediction during the prodromal stages. Furthermore, integrating different biomarkers to create a fusion marker of Alzheimer's disease improves the efficiency, reliability, and credibility of the findings. In further studies, we will assess the proposed approach using different BBBMs datasets including people with AD, MCI, and NC.

Supplementary Materials: The ADNI proteomic dataset used in this study is available at http://adni.loni.ucla.edu. Extra information about the ADNI proteomic dataset is available at http://www.adni-info.org

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