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Ahana Priyanka, G. Kavitha

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# Study of biomarker variation and severity prediction in dementia using intelligent system

Ahana Priyanka* and G. Kavitha

Department of Electronics Engineering,
Madras Institute of Technology,
Anna University,
Chrompet, Chennai, India
Email: ahanachellian@gmail.com
Email: kavithagmit@annauniv.edu
*Corresponding author

**Abstract:** Precise detection of dementia biomarkers in the brain enables early understanding of pathology variations. Owing to which there is a need for studying different dementia biomarker in magnetic resonance (MR) image for its specific changes between normal and severity stages to categorise the prognostic difference. The present study is an attempt to utilise an optimised framework with fused radiomic and deep features based on least absolute shrinkage and selection operator (LASSO) using a hybrid meta-heuristic optimiser for classification. The investigation is attempted on Alzheimer's disease neuroimaging initiative (ADNI) database. The radiomic and deep features were extracted from the considered biomarkers and then fused. Further, the significant features were obtained using LASSO model. Then, those features were input to hybrid meta-heuristic optimiser with machine learning model for classification. From the result, it was identified that hippocampus, along with the brainstem, gave higher classification accuracy of 97.87% to identify prognostic differences for considered classes. Therefore, the quantifiable interpretation was claimed to improve clinical assessment.

**Keywords:** dementia; hybrid optimiser; fused feature; biomarker and prognostic difference; least absolute shrinkage and selection operator; LASSO; Alzheimer's disease neuroimaging initiative; ADNI.

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**Biographical notes:** Ahana Priyanka is currently a research scholar at the Department of Electronics Engineering, MIT Campus, Anna University, India. Her research interests include medical image processing and soft computing techniques.

G. Kavitha is working as an Associate Professor in the Department of Electronics Engineering, MIT Campus, Anna University, Chennai. Her research interests include bio medical image processing and soft computing techniques. She has more than 50 publications in reputed journals and conferences.

## 1 Introduction

Neuro-degenerative disorder, such as dementia, cause irreversible brain deterioration. The chronic disorder is estimated to affect more than 150 million worldwide by 2050 according to the world Alzheimer disease (AD) report of 2018 (Gao, 2021). This kind of disorder is said to cause cognitive and inhibitor function disabilities. This change has a considerable impact on various brain structures and causes atrophy (Mofrad et al., 2021; Veluppal et al., 2022; Rui et al., 2022). Currently, clinical score such as mini mental state examination (MMSE) having a score range of 0–30, prominently evaluate the preliminary changes. The different range of scores in various stages such as normal, early mild cognitive impairment (EMCI), mild cognitive impairment (MCI), late mild cognitive impairment (LMCI) and AD help to categorise the disorder (Jiang et al., 2021). However, this score is ambiguous due to its inconsistent pathological changes during progression. Consequently, there is a need for identifying the appropriate brain biomarkers that indicate the reliable severity changes in progression which might improve the diagnosis. Further, significant biomarkers for severity changes in dementia are less explored (Zhang et al., 2019; Alinsaif et al., 2021).

Studies show that neuro-pathological dysfunctions are highly detected in demented subjects (Xiaoli et al., 2018; Rallabandi et al., 2020; Mustafa and Brittany, 2022). Precise investigation on regions closely related to limbic system, such as ventricle, hippocampus, brainstem and midbrain, could improve the dementia diagnosis (Patel et al., 2020). Sub-cortical structures have synaptic loss in medial temporal lobe which might cause morphometric changes in hippocampus region (Liu et al., 2020; Rallabandi et al., 2020). Enlargement of ventricle and structural changes were observed in ventricle due to tissue loss in the cortex region (Luca et al., 2006). And degeneration of raphe nucleus cause brain stem atrophies (Braun and Van Eldik, 2018). While, midbrain deformation was detected due to significant decline of neuron in posterior region (Lee et al., 2015). Thus, quantitative diagnosis on those biomarker regions helped to understand the transition in severity stages effectively. The intricate biomarker regions were sparsely examined for dementia severity progression. And, the micro and macroscopic structural variations of biomarkers could be revealed using magnetic resonance imaging (MRI) technique. By this, it was proved that the method efficiently examined the biomarkers atrophy in a non-invasive way. Also, it possessed the ability to reveal the intracranial tissue variations with varying contrast and employed in various literatures for dementia differential diagnosis (Feng et al., 2018; Chitradevi et al., 2021; Alinsaif et al., 2021; Veluppal et al., 2022). However, those techniques could not reveal the quantitative information about the progress of this disease. Hence, it lacked to support to improve the sensitivity and specificity of severity stages. Currently, automated machine learning methods are widely employed to capture the pathophysiological changes in considered regions.

Most of the aforementioned methods could extract highly consistent spatial variation and latent information which is found in pixel intensity of sensitive medical image to improve the prediction (Devulapalli et al., 2021). Conventional approaches such as multi-scale transformation, local histogram detection, and statistical features, are widely used to understand the atrophy in dementia (Arco et al., 2021; Hazarika et al., 2021b). However, those features were found to be shallow for prediction and undesirable to characterise the relevant distinction in complex structures. Currently, radiomic features have become prevalent in prognostic prediction of medical images. This image characterisation based feature could provide reliable high level information about the

spatial changes that might improve the stability of detection performance (Hedayati et al., 2021). Further, development in deep learning utilises its capability to extract the discriminative local and global feature from the multilayer network (Cheng et al., 2017). Such features are extensively used in complex medical dataset to identify the pattern changes (Zhang et al., 2021a). Therefore, combining the extracted radiomic and deep features might support to capture the complex elusive difference in medical images. Thus, the fusion of those features support to highlight different intensity and spatial information about the image which might help to improve the borderline in disease categorisation.

Advancement in the feature extraction provides high dimensional data due to various observations in an image. Identification of relevant features, reduction in redundancy and over-fitting require a selection of salient features which might improve the prediction ability of neuro-disorder (Zhang et al., 2021b; Ghaffari et al., 2022). Methods, such as principal component analysis, fisher discriminant analysis, locality preserving projection, mutual information, linear discriminant analysis were attempted to reveal the optimal features for classification (Khaire and Dhanalakshmi, 2019). However, those methods have perturbation in reduction due to increased pairwise selection error and excessive computation while handling the multivariate features. Reliable feature selection provides stable performance with better trade-off between classification error and bias variance (Zhang et al., 2017). Recently, supervised learning sparse logistic regression method, such as least absolute shrinkage and selection operator (LASSO), is considered to handle medical image based on meta-data (Huang et al., 2020). This is based on flexible parameter regularisation and factor adjustment for shrinkage of coefficients. Then non-zero variables from adjustments are assigned to be significant features with less prediction error (Lee and Cai, 2020). This technique has less feature sparsity with enhanced variable association which can avoid over-fitting. This method is widely used in various biomedical applications such as blood vessels, rectal cancer and heart valve analysis. Hence, it could be suitable to improve the classification of dementia differential diagnosis.

Pattern classification and prediction of MR images are extensively applied in support machine (SVM) for classification. This model can learn the distribution of multivariate features using hyper plane and it can identify different classes (Díaz-Vico et al., 2020; Hazarika et al., 2021b). This helps to handle over-fitting of samples and improve approximation ability in multiclass problems based on its error correcting code schemes (Golrokh and Hojjat, 2022). The fore mentioned method has the ability to predict the differences in several medical disorders with improved performance. The states of dynamic features classification accuracy for multiclass could be improved by identifying the appropriate choice of kernels and corresponding feature set. Neural networks model was said to consume more execution and tuning to handle the high-dimensional large medical dataset in classification (Aljuaid and Anwa, 2022; Cai et al., 2020).

Effectiveness of the social algorithms aids to improve the desired function that contributes to overcome the overfitting challenge in precise identification of different disease stages (Zeng et al., 2018). Those methods have the ability to provide a solution in large search space, and also, they support to attain the near optimal solution with effective computation. The algorithms are usually based on the adaptation of an animal or birds social behaviour. The effectiveness of the solution was assessed based on the iteration of fitness function, where, the weaker solutions are eliminated in the search

space. Commonly, particle swarm optimisation (PSO) based SVM is widely used to provide an improved performance in MR based brain tumour detection and various brain abnormalities. This might be due to its exploration ability and speed convergence. Further, this method sometimes has less significance due to its exploration ability leads to local minima. Subsequently, Grey wolf optimisation (GWO) method has adaptability to parameter changes and use hierarchical approach in its search (Şenel et al., 2018). This cause scalable performance and support to find desirable solution due to its exploitation mechanism to handle boarder search space. These algorithms are used in the diagnosis of breast cancer, diabetes and seizure disorders. Recently, hybrid social algorithms play a major role in improvement of classifier performance (Abdulhameed et al., 2021). This work aims to utilise the potential capability of GWO with PSO in local and global search without local fall. Thus, considered hybrid classifiers attain superior performance in classification which improves the discrimination ability of considered classes.

### *1.1 Effectiveness of the proposed study*

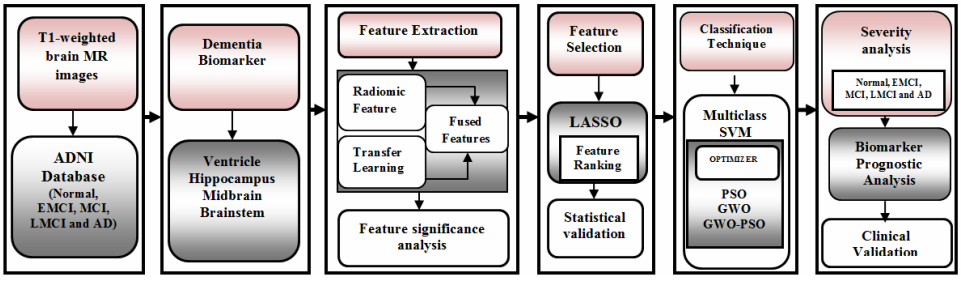
The objective of the study is to recognise the prominent biomarkers in MR images by identifying appropriate textural variations to improve the differential diagnosis of normal, EMCI, LMCI, MCI and AD subjects. The novelty of this study is to use the significant fused feature from radiomic and deep learning models along with dual optimiser for classification. The primary anatomic region such as ventricle, hippocampus, midbrain and brainstem are attempted to observe the quantitative variations in various stages of dementia. The combined ability of radiomic and deep features and dual optimiser for classification in MR images are extensively analysed for discriminative differentiation. Prognostic evaluation is also attempted to identify the discriminative power of biomarker using the novel features and classification model. Experimental and clinical analysis in this study assesses the effect of fused features, ranking, hybrid classification performance for normal, EMCI, MCI, LMCI and AD. This paper is carefully designed based on the goal to identify the appropriate biomarker which captures the transition stage using fused high level features with supervised selection and hybrid optimisers for classification. Section 2 discusses the proposed methodology and the results are explored in Section 3. Section 4 gives the discussions of the present study. Finally, Section 5 concludes overall study.

## 2 Methodology

The proposed work process is represented in Figure 1. The flow comprises of database, extraction of biomarkers, feature extraction, feature selection, and classification of different prognostic severity stages of dementia. Initially, the analysis used ADNI public database which comprised of normal, EMCI, MCI, LMCI, and AD images. The useful biomarkers, such as ventricle, hippocampus, midbrain, and brainstem were obtained using curve constraint and optimised threshold models. Theses segmented biomarkers were subjected to feature extraction. Fusion of radiomic and deep features were carried out to track the pattern change in prognosis. Further, substantial fused features were selected based on LASSO. The SVM classifier was employed to perform classification. Performance of the classifier was improved by parameter tuning using hybrid GWOPSO

optimiser. Finally, various dementia stages discrimination and progostic analysis were done to identify the precise transition of different class.

**Figure 1** Pipeline of the proposed work (see online version for colours)




## *2.1 Image database*

The original T1-weighted structural image acquired with 1.5 Tesla was used in the present analysis from publically available ADNI database (Liu et al., 2020). The primary goal of the database was to develop automated algorithms to compute the clinical indices and computer aided system for dementia disease diagnosis. Totally, 1169 subjects comprising of normal (229), EMCI (200), MCI (398), LMCI (150), and AD (192) were used in the study. The considered subjects were evaluated based on comprehensive dementia screening, such as medical history and MMSE, to determine the neuropsychological capability (Rallabandi et al., 2020). The selected subjects were below 65 years of age and their genders matched in all the classes to avoid the progression related bias. From each class, 500 images were chosen based on visibility, contrast, and appropriate phenotypic information of the considered biomarkers. The structure of the ventricle, white matter, grey matter, and CSF was more visible in axial slices. The anatomical changes of hippocampus, brain stem, and midbrain could be captured prominently in sagittal slices. Those slices could help to reveal the sharp variations of biomarker in MR brain images for dementia severity prognosis.

## *2.2 Feature extraction*

The distinct patterns in an image are extracted through feature extraction process (Lu et al., 2021; Loddo et al., 2022). Recently, convolutional neural networks are widely preferred to extract deep features. In this way, the robust deep features were extracted from pre-trained CNN model AlexNet. It consists of five convolutional layers followed by three pooling layers and two fully connected layers. The convolution layer is the primary layer to extract deep feature maps through convolution kernels. Down sampling is performed in pooling layer (Aditi et al., 2021). The ReLu activation functions are utilised in all the layers to improve the prediction. Each layer captures different features based on their edges, bends and lines. The last layer holds combined deep features from all the considered layers of an image (Qiu et al., 2022). Thus, this model has the ability to learn intricate structures with high level of abstraction due to effective network arrangements. It also helps to localise the appropriate variation in considered images without comprising any pixel information. Hence, subtle changes were captured in the

deep features (Lee et al., 2019; Jain et al., 2019). In this way, the proposed work extracted 1,000 deep features from the fully connected layer.

Along with the deep features, 56 radiomic features were considered for the further process. Radiomic enumerated the textural information to enhance the clinical decisions (Lu et al., 2021). It exhibited the information about inter pixel relationships, grey scale patterns, texture features, and shape features along with spectral properties (Feng et al., 2018; Jiang et al., 2022). This will be useful for personalised diagnosis and clinical decisions for treatment guidance. An intensity-based feature gives grey levels intensity information of input images. Shape based features afford geometrical information in a complex image. The textural features give higher order description about subtle variations. The extracted radiomic and deep features were combined to observe the prognosis difference sharply in the proposed work.

## *2.3 LASSO based Feature Selection*

Selection of robust features is a significant task to attain high prediction accuracy. LASSO is an embedded feature selection method. It conserves the oracle properties of feature subset and removes irrelevant and trivial features (Jin et al., 2021). The feature selection can be done by shrinking regularisation coefficient values to zero. LASSO introduces the regularisation parameter $\lambda$, similar to learning rate which makes the cost function as zero (Fonti and Eduard, 2017). The tuning parameter $\lambda$ controls the strength of penalty. If the value of $\lambda = 0$, then LASSO becomes an ordinary least square regression method. When, the value of $\lambda$ is more, then a greater number of coefficients are shrinked to zero and avoids overfitting. The cost function of LASSO regularisation is given as follows:

$$J(\theta) = \frac{1}{m}\sum_{i=1}^{m} \cos th\left(\theta\left(x_i, y_i\right)\right) + \frac{\lambda}{m}\sum_{j=1}^{n}\left|\theta_j\right| \tag{1}$$

where $x_i$ represents input feature vectors, $y_i$ refers target feature vectors with upper bound value of 'i' as $m$ and $\theta_0$, $\theta_1$, $\theta_2$, $\theta_3$, … $\theta_j$ are the trainable parameters where $j$ varies to the maximum limit of $n$. The different features are denoted as $x_1$, $x_2$, … $x_n$. Both shrinkage and selection of features are performed simultaneously in LASSO. This target to reduce the mean square error by setting upper bound of its parameters. The larger the value of Θ, the larger the impact on feature selection. Depending upon Θ the features were selected, and the remaining values were discarded. This helps to improve the prediction accuracy. The interpretability of the LASSO model was increased by removing irrelevant features.

## *2.4 Hybrid GWO-PSO based SVM classifier*

Optimisation based classification has recently become an effective prediction system for various diagnostic. The performances of the SVM mainly depend on kernel parameter and consider feature set (Sun et al., 2018; Amol et al., 2021). Usually, those parameters are selected randomly. Instead of random selection, meta-heuristic algorithms such as PSO and GWO are adopted to optimise these parameters to improve the performance of classification.

GWO is a population-based optimisation algorithm based on social hierarchies and hunting behaviour of wolves. This population algorithm has a leader that manages the

swarm according to the role distributed for its searching to find the optimal solution. Here, alpha, beta, delta, and omega wolves were considered to have the different ranks in wolf packs. Usually, the team leads with alpha which holds the best position for selection in the population. Other ranked wolves follow the instruction of alpha. The position of the prey is considered to be the global position. Chasing, tracking, encircling, and attacking the prey are the major processes involved in hunting mechanism. Based on the position of alpha the population modelled their next position in the team during hunting. Encircling determine the strategy to surround the prey to attack. The mathematical model of encircling the prey is given as follows:

$$D = \left| C.X_p(t) - X(t) \right| \tag{2}$$

$$X_{t+1} = x_p(t) - A.D \tag{3}$$

where $x_p(t)$ and $x(t)$ are the positions of prey and wolf, and $D$ represents the distance between the prey and wolf. Here, $t$ denotes the number of iterations, and $A$ and $C$ are the vector coefficients. Finally, attacking is the decision process of the pack to attack the current prey or find the new prey in the search space. Thus, the GWO algorithm was highly focused such that, no wolf gets struck in local minimum. Hence the obtained optimum solution could enhance the parameters of SVM. Further, PSO algorithm exhibits the detection of potential features with optimised solution by exploring search space (Zeng et al., 2018). The generalisation error of the classification model was also reduced. PSO is a meta-heuristic algorithm resembles the behaviour of bird flock (Bao et al., 2013). The best position of each particle was stored and further updated by the following equation.

$$x_{n+1} = x_n + v_{n+1} \tag{4}$$

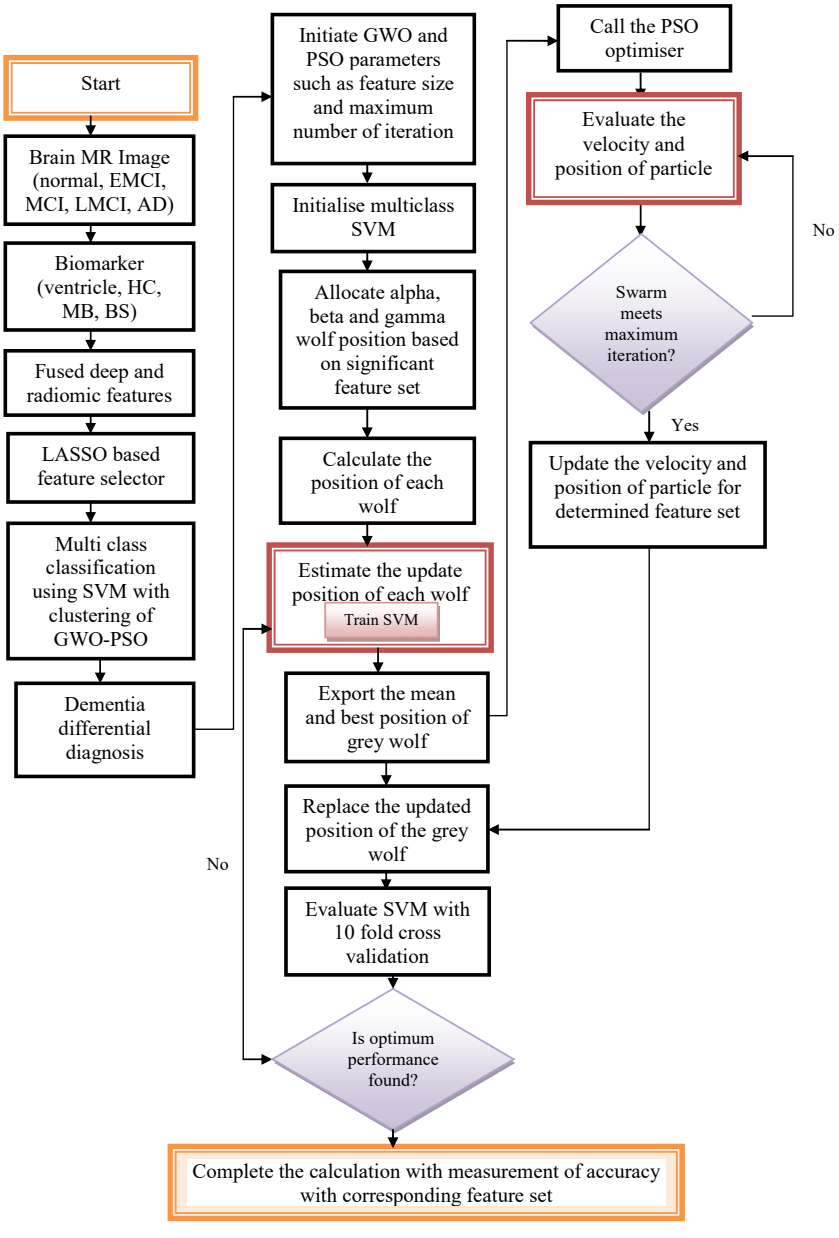
$$v_{n+1} = \omega v_n + c_1 r_1 \left( p_n - x_n \right) + c_2 r_2 \left( {p_n}^g - x_n \right) \tag{5}$$

where $n$ denotes the number of iterations, $x_{n+1}$ represents updated position of the particular swarm particle, $r_1$ and $r_2$ are the random numbers in the range [0, 1]. $\omega$ represents inertia weight. The values $c_1$ and $c_2$ are acceleration coefficients which can be used as optimisation parameters. The velocity of the particle is represented by 'v'. The position of particle is given as $p$, whereas, the best position is denoted by png. The search for optimum solution is carried out with pre-defined maximum number of iterations reached.

The hybrid GWO-PSO algorithm was implemented in the proposed work by adopting the highlighted features in the considered algorithms. The various types of demented MR images were obtained from the database. The biomarkers, such as ventricle HC, MB and BS are given for feature extraction. The CNN model based deep features and radiomic features are fused together. LASSO based feature selection was adopted to select the prominent features. The selected features were given to SVM classifier whose parameters were optimised by hybrid GWO-PSO algorithm as shown in Figure 2. The required parameters of GWO and PSO were initialised. Then, the fitness function using SVM model was calculated. The positions were also updated for the wolves. Then, those positions are considered for PSO to determine the optimum features set and accuracy. This process helped to update the modified best position as optimal solutions. Finally, the process id repeated until it reached maximum iterations. Thus, the considered LASSO

feature selection and meta-heuristic algorithms were trained in order to get the maximum accuracy for diagnosis.

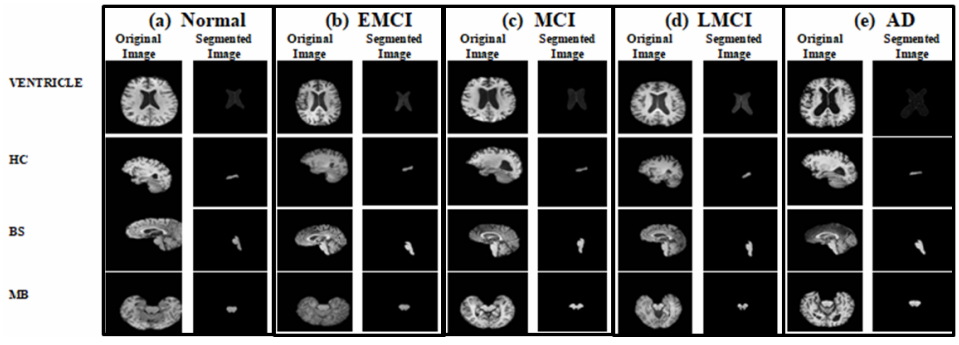
**Figure 2** Flow diagram of hybrid PSGWO optimisation (see online version for colours)



## 3 Observations attained from considered framework

The cohort utilised 2,500 images which consisted of normal, EMCI, MCI, LMCI, and AD from ADNI database. The T1 weighted axial and saggital view MR images were used to detect the prognosis variation of dementia disorder. The biomarker, such as ventricle, hippocampus, midbrain, and brainstem structures were more clearly noticeable in the middle slices of the considered views as shown in Figure 3. From the figure, ventricle is filled with CSF which in turn reflects as black contrast, hippocampus is found to be a grey matter intricate structure, and the brainstem and midbrain exist as white matter structure. These anatomical regions were precisely extracted using optimised threshold and curve based evolution methods to avoid complexity in the analysis. Further, the considered biomarkers were observed to have morphological change in considered severity levels. Though, the area variability is visible in prognosis for considered biomarkers of normal, EMCI, MCI, LMCI and AD subjects as portrayed in Figures 3(a)–3(e). However, the change is not considered to be prominent and consistent in severity progression. Furthermore, it did not reveal the subtle anatomical changes and homogenous characteristic of the considered biomarkers for differential diagnosis. Thus, the quantitative analysis of the atrophy was attempted using fusion of radiomic and deep features.

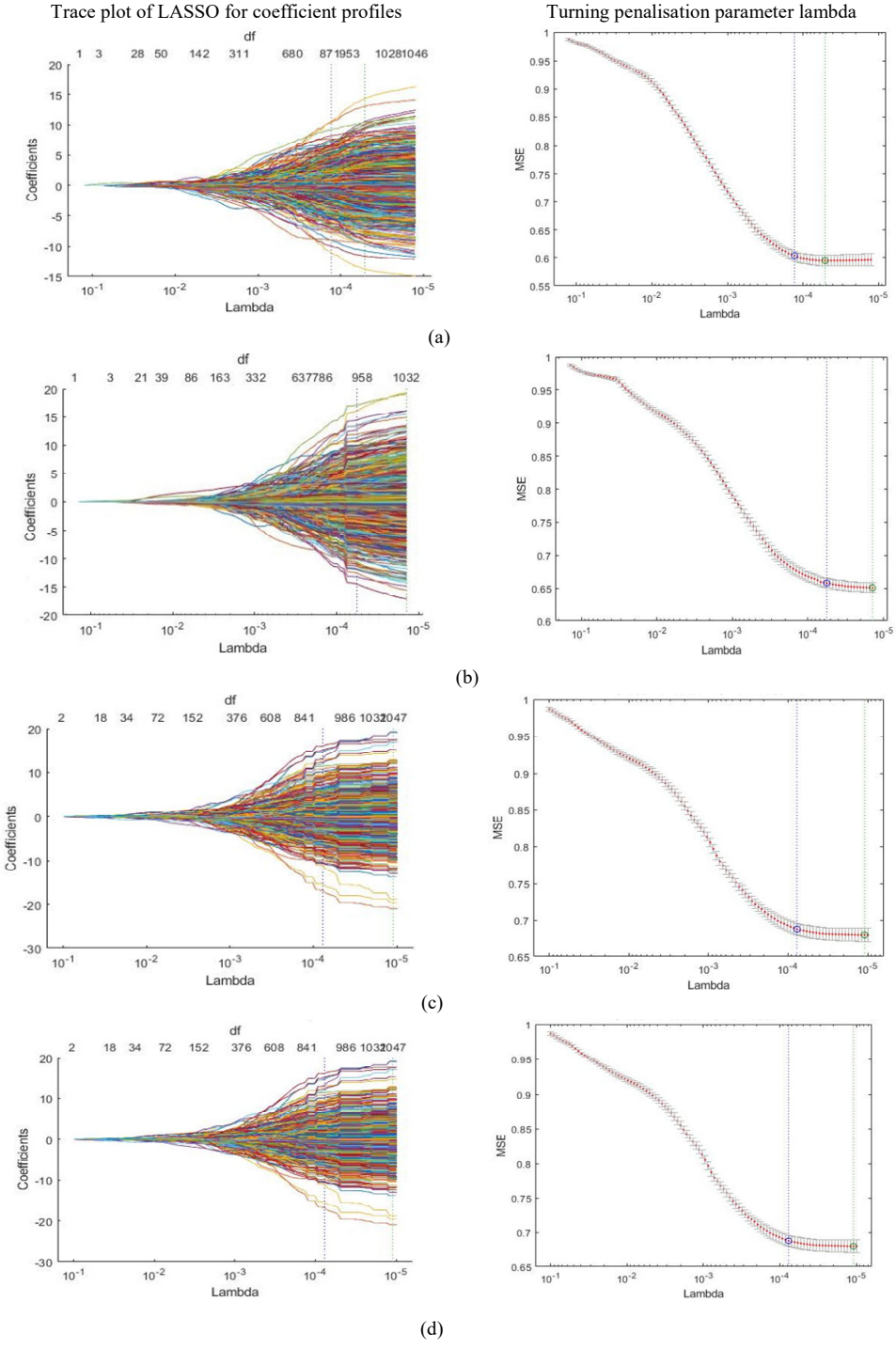
**Figure 3** Biomarkers of considered work for (a) normal, (b) EMCI, (c) MCI, (d) LMCI, (e) AD




Note: HC – hippocampus; BS – brain stem; MB – mid brain.

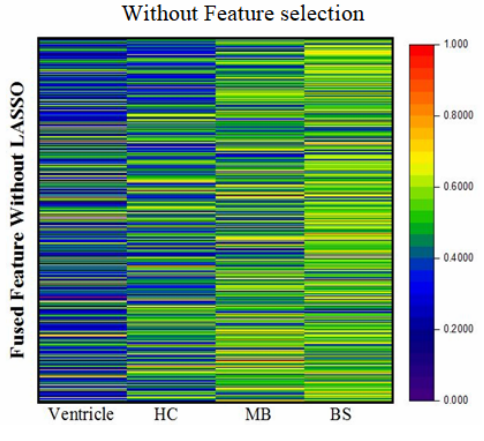
Here, the anatomical and structural changes of ventricle, hippocampus, midbrain and brainstem were analysed using shape and texture features. In total 56 quantitative radiomic features were used to characterise the reason behind the progression. Consequently, deep features were derived from last fully connected layer of AlexNet model. The learned 1,000 features from the considered model had the ability to perform an exhaustive quantitative and qualitative analysis of the pattern changes in the considered region with clear semantic that can tolerate the intra-class variation. After the extraction, fusion of radiomic and deep features were performed. The fused feature has the ability to identify intricate structures with high level of abstraction, and was able to localise the appropriate variation in considered normal and pathological images.

**Figure 4** LASSO based feature selection for (a) ventricle, (b) hippocampus, (c) midbrain, (d) brainstem (see online version for colours)

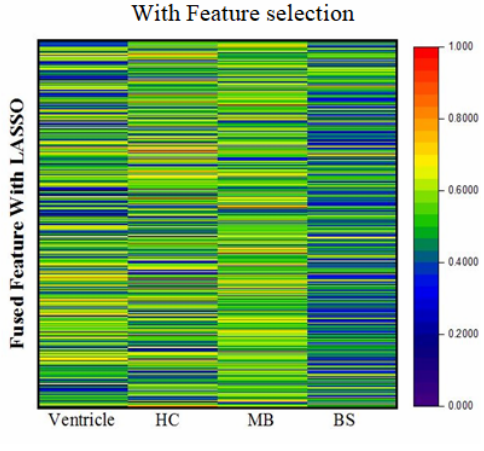


After that LASSO logistic regression technique was employed to identify the distinctive fused feature set for the considered biomarker regions. The LASSO parameters were tuned in various combination of $\lambda$ = [0.01, 0.1, 0.2, 0.3, 0.5, 0.6, and 0.9] and $\Theta$ = [0.1, 0.001, 0.05, 0.006, and 0.007] for significant performance of considered 1056 feature vectors. Here, the 10-fold cross-validation was applied. The regularisation parameter $\lambda$ = 0.5 and $\Theta$ = 0.007 were optimal to find the minimum deviance coefficients. The robust features were identified based on its intra correlation coefficient performance. The correlation was performed for each pair of fused feature to observe nature of correlation. Highly correlated and non-zero features were selected for further evaluation. Finally, fused feature score was obtained using linear combination of significant features that were weighted by their respective coefficients. Figures 4(a)–4(d) represent the least absolute shrinkage and selection operation parameter regularisation and coefficient plot. The vertical grey line in the plot indicates the selection of cross validation with optimal $\lambda$ to obtain the significant fused features.

**Figure 5** Representation of heat-map for (a) without feature selection, (b) with feature selection method (see online version for colours)




(a)




(b)

Figures 5(a)–5(b) illustrate the heat map for fused features without and with LASSO for considered biomarker regions. It depicts the amount of correlation between the considered features. The deep colour indicates the prominent biomarker features. The result revealed that the LASSO had the ability to identify the significant coefficients from fused feature set. It indicated that those prominent fused features have higher potential to differentiate the considered groups which could improve the performance of classification decision for normal and severity prognosis.

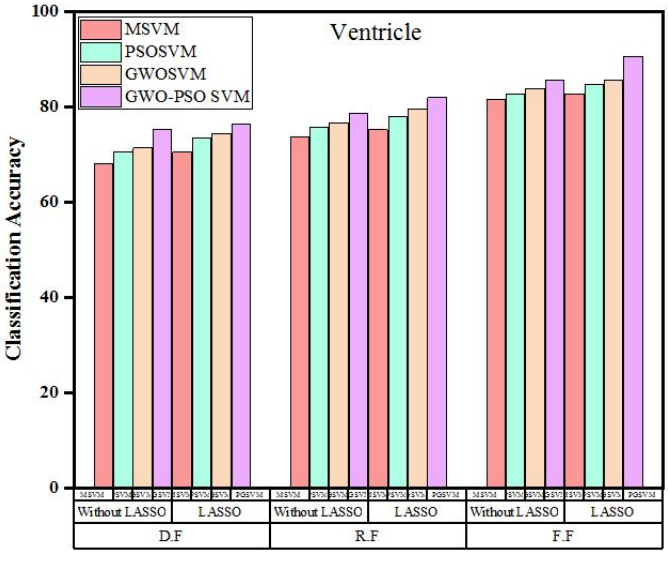
Further, the selected deep feature (D.F), radiomic feature (R.F), fused features set (F.F) based on LASSO selection were tested using ANOVA. Initially, Shapiro-Wilk based normality test was conducted to determine the distribution fit of the selected features. Based on the observation the considered test showed $\alpha = 0.05$ for selected features from the biomarkers. It indicated that the considered features were normally distributed and suitable for ANOVA test to check its significance. The ANOVA test determined the efficiency of features in differentiating the considered classes based on *p*-value. The *p*-value less than 0.05 are considered to have significant features. This is done by comparing the variance across the mean of considered groups. This statistical test result indicates that selected features from LASSO gives a *p*-value of ($p < 0.001$) which is considered to be highly significant. This shows that identified features is capable to offer the precise variation in considered biomarker which will be suitable for further evaluation.

Further, the features with and without LASSO were given to the multiclass SVM (MSVM), PSOSVM, GWOSVM and GWO-PSO SVM classifier. These methods are trained with fivefold cross validation. The present study considered 20 wolves with search range of 2 in GWO. Similarly, the inertia maximum and minimum weights of PSO varied as: [0.2, 0.9], [0.4, 0.9], [0.1, 1.2], and [0.9, 1.2]. It was noted that the minimum weight of 0.1 and maximum weight of 1.2 helped to balance the global and local the search effectively. The acceleration coefficients varied from 0.5 to 2.5 and found 0.5 seemed to show desired influence in particles. Finally, 100th iteration was considered as stopping criterion, as any change could not be observed after varying the range of the iterations. The values of this parameter were carefully chosen based on various trials to attain maximum efficiency of the considered optimiser in search space.

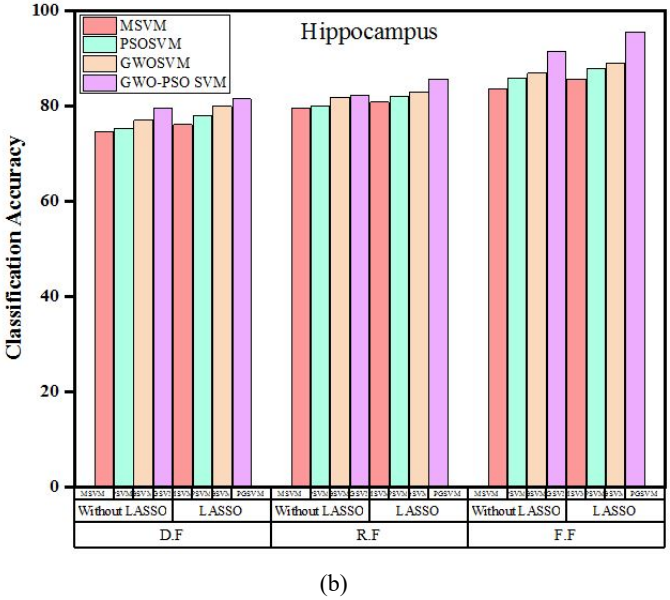
Figure 6 shows that ventricle, hippocampus, midbrain and brainstem show better variation in classification accuracy. This evaluation metric determine the robustness of the considered biomarker features in a classifier. It indicated that those regions showed pathology changes which are highly permissive to the severity progression of dementia. It is evident that LASSO based D.F, R.F, and F.F perform better for the considered biomarkers. Further, it was observed that classification accuracy of significant F.F was found to be superior when compared to D.F and R.F in the considered classification techniques of the considered biomarkers. Compared to MSVM, PSOSVM and GWOSVM classifier, GWO-PSO SVM achieves peak accuracy of 90.53%, 95.6%, 93.87%, and 94.8% in all the considered biomarkers. It showed that GWO-PSO SVM could provide more reliable and robust prediction about severity prognosis of biomarker. This might be due to the capability of GWO-PSO SVM synchronous search and rapid convergence without falling in local optima which improve the prediction performance. Furthermore, GWO-PSO SVM evaluation suggests hippocampus based significant F.F achieved higher accuracy than the other biomarkers. This is due to the influence of neurogenesis alteration in hippocampus tissue for normal and severity classes which was

well captured by significant F.F and GWO-PSO SVM which contributed to better differentiation.

**Figure 6** Classification accuracy of (a) ventricle, (b) hippocampus, (c) midbrain, (d) brainstem using different techniques with and without feature selection method (see online version for colours)

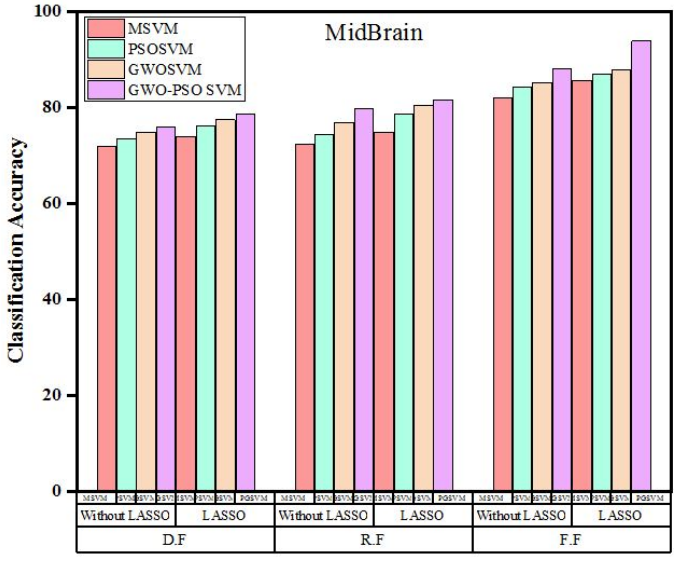



(a)

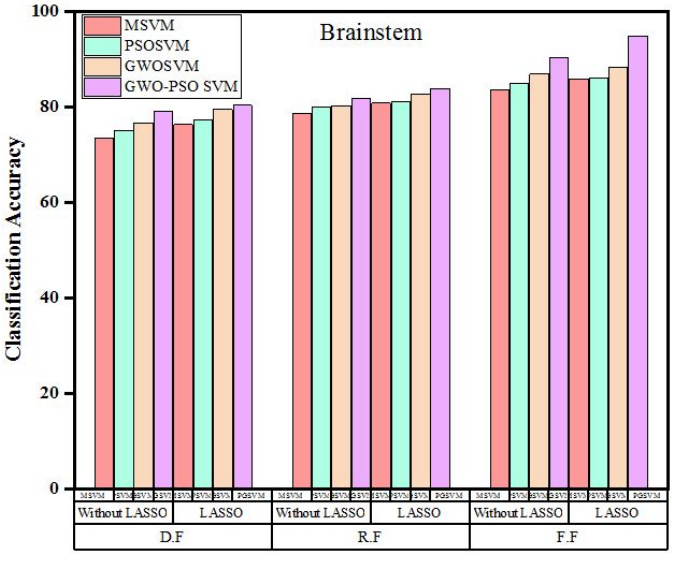



(b)

**Figure 6** Classification accuracy of (a) ventricle, (b) hippocampus, (c) midbrain, (d) brainstem using different techniques with and without feature selection method (continued) (see online version for colours)




(c)

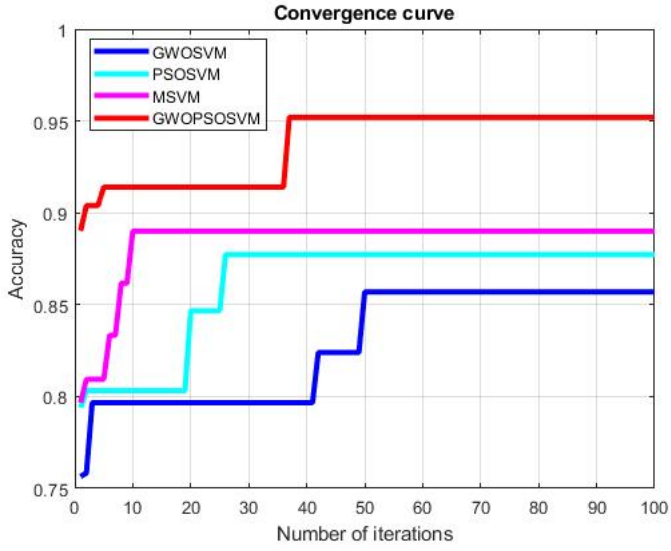



(d)

Figure 7 vividly expresses the convergence process of hippocampus region for the considered classification techniques. This method runs for 100 iterations to obtain optimal performance. The obtained graph depicts that MSVM, PSOSVM, and GWOSVM have slow convergence capability due to search acceleration in finding optimum feature set to attain maximum accuracy. However, GWO-PSO SVM provides a

superior exploration in the search and provides reliable convergence with higher accuracy.

**Figure 7** Convergence curve of MSVM and optimiser based MSVM for hippocampus region (see online version for colours)

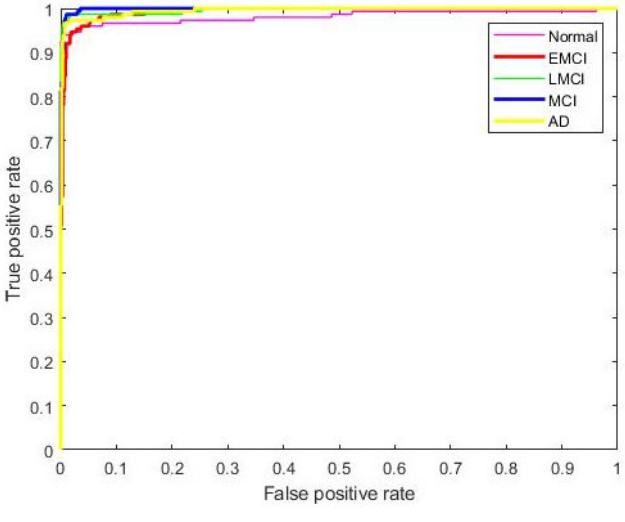



Confusion matrix for hippocampus region based on GWO-PSO SVM classifier for the considered class is represented in Figure 8(a). It showed that normal, EMCI, MCI, LMCI, and AD are prominently classified. The result specified that hippocampus based significant fused features with GWO-PSO SVM showed better prediction in progression. Figure 8(b) indicates ROC curve of normal and severity class. The area under the curve (AUC) for the hippocampus region show desirable performance of 0.999, 0.999, 0.992, 0.996, and 0.991 for normal, EMCI, MCI, LMCI, and AD respectively.

The classifier performance such as accuracy, F1score, precision, sensitivity and specificity for normal, EMCI, MCI, LMCI and AD in hippocampus region using GWO-PSO SVM is shown in Figure 9(a). The measure helped to evaluate the stability of the hybrid classifier when handling different features from considered classes. From the figure it is observed normal and AD is distinctly varied in all employed measures. Higher sensitivity and specificity are evident in considered groups. Precision is found to be 99.3%, 96.1%, 97.3%, 92.2%, and 92.9% for normal, EMCI, MCI, LMCI, and AD respectively. Finally, F1 score is 99.3% for normal, 98% for EMCI, 96.9% for MCI, 93.4% for LMCI and 90% for AD. The results revealed more significant atrophy changes of hippocampus region for normal and severity classes. Consequently, inter class variation was observed for hippocampus region as given in Figure 9(b). This violin plot depicts the statistical inter class relation for considered class with *p*-value. The finding suggested the considered groups were statistically significant with $p < 0.001$. Most of the inter class variations with respect to EMCI, MCI, LMCI were tedious to observe the prognosis. This might be due to early unstable change in pyramidal cells of hippocampus region which is not evident in the image pixels.

**Figure 8** Representation of (a) confusion matrix, (b) ROC curve for hippocampus region using GWO-PSO SVM classifier (see online version for colours)


(a)



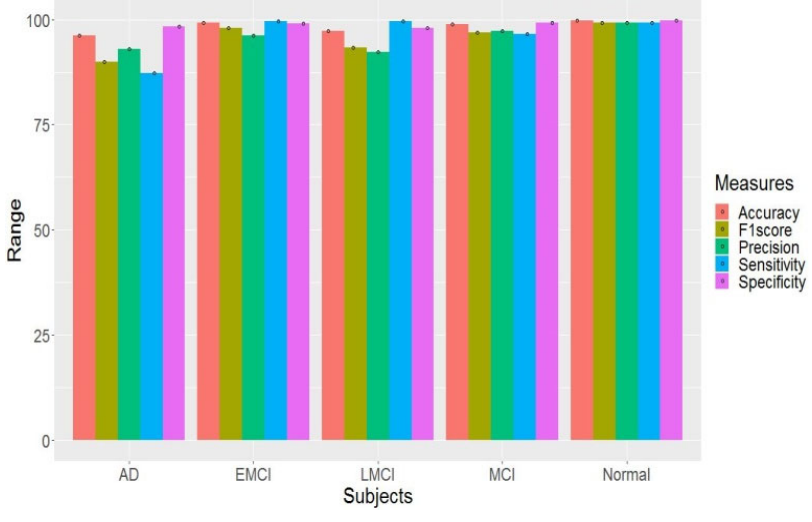

(b)

Additionally, to improve the prediction capability prognostic analysis is considered. This analysis used multiple significant features sets which aimed to get distinct differences among groups. This method strengthened the significant feature correlation, reduced the classifier variance error, and result in accurate classification. Table 1 describes the prognostic analysis of considered biomarker using GWO-PSO SVM classifier. Hippocampus region was fused with the other biomarker regions based on the existing results. Two, three, and four regions prognostic combinations were attempted to observe appropriate variations among the considered groups.

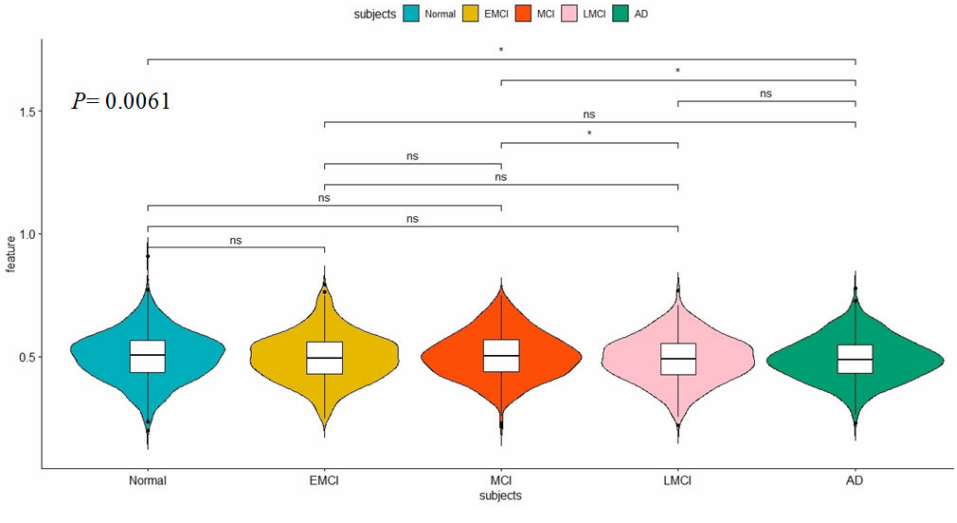
The constructed prognostic analysis consist of the following combinations: HC+ ventricle, HC+MB, HC+BS, HC+MB+BS, HC+MB+ ventricle, HC+BS+ ventricle and HC+MB+BS+ ventricle with promising accuracy. However, HC+BS were found to be 97.87% which was due to the reason that the combined significant features of hippocampus and brainstem region captured the trivial tissue changes in normal, EMCI, MCI, LMCI, and AD more accurately in progression. Figure 10 represents the confusion

matrix and ROC curve of prognostic analysis. It indicated normal, EMCI, MCI, LMCI, and AD showed desirable difference in dementia progression. The AUC value of ROC curve for normal and severity groups are 0.981, 0.993, 0.996, 0.998 and 0.995. This determines that hippocampus and brainstem region predicted the difference by reducing the homogenous disparity of significant features in classification.

**Figure 9** Representation of (a) performance measures, (b) interclass performance of hippocampus region for normal and severity classes (see online version for colours)




(a)



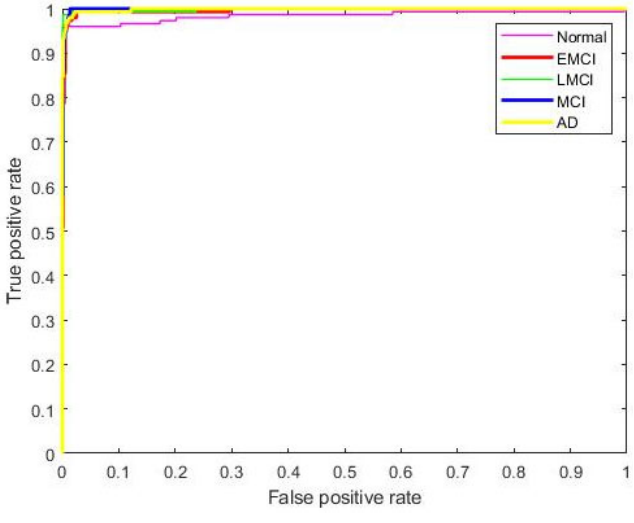

(b)

**Table 1** Prognostic analysis of biomarker regions using GWO-PSO SVM classifier

| *Region* | *Accuracy of GWO-PSO SVM (%)* |
|---|---|
| HC+ Ventricle | 89.66 |
| HC+MB | 93.83 |
| *HC+BS* | *97.87* |
| HC+MB+BS | 91.68 |
| HC+BS+ Ventricle | 96 |
| HC+MB+ Ventricle | 92.74 |
| HC+MB+BS+ Ventricle | 91.59 |

**Figure 10** Representation of (a) confusion matrix, (b) ROC curve for hippocampus and brainstem regions (see online version for colours)

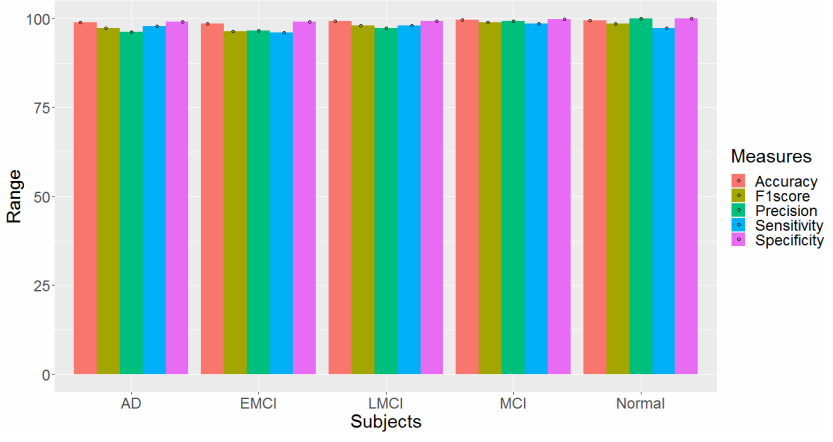

(a)



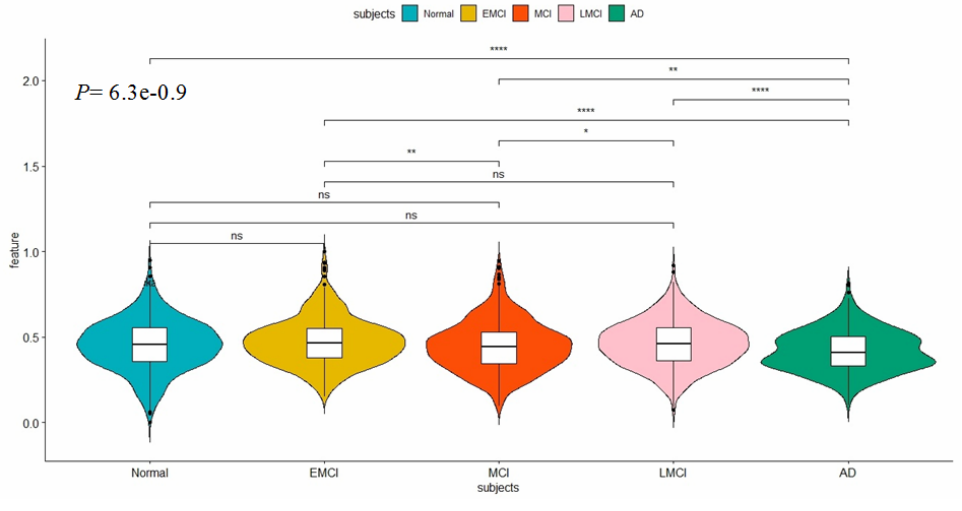

(b)

Subsequently, the classifier performance measures are depicted in Figure 11(a). Accuracy, sensitivity, specificity, precision and F1 score for individual class are illustrated in the figure. For normal, EMCI, MCI, LMCI, and AD shows 99.4%, 98.5%, 99.6%, 99.2% and 98.9% of accuracy were obtained. The sensitivity was achieved for normal, EMCI, MCI, LMCI, and AD; they are 97.3%, 96%, 98.6%, 98%, and 97.8% respectively. An improvement was also noticed in specificity obtained for normal (100%), EMCI (99.1%), MCI (99.8%), LMCI (99.3%), and AD (99%) classes. Similarly, precision was observed for normal, EMCI, MCI, LMCI, and AD as 100%, 96.6%, 99.3%, 97.3%, 92.2%, and 92.9%. Finally, F1 score resulted 99.3% for normal, 98% for EMCI, 96.9% for MCI, 93.4% for LMCI, and 90% for AD. They indicated that there was a reduction false positive rate in severity prediction. Further, the intra class variation hippocampus and brainstem region prognostic analysis is represented in Figure 11.

**Figure 11** Representation of (a) performance measure, (b) interclass performance of HC+BS regions for normal and severity classes (see online version for colours)



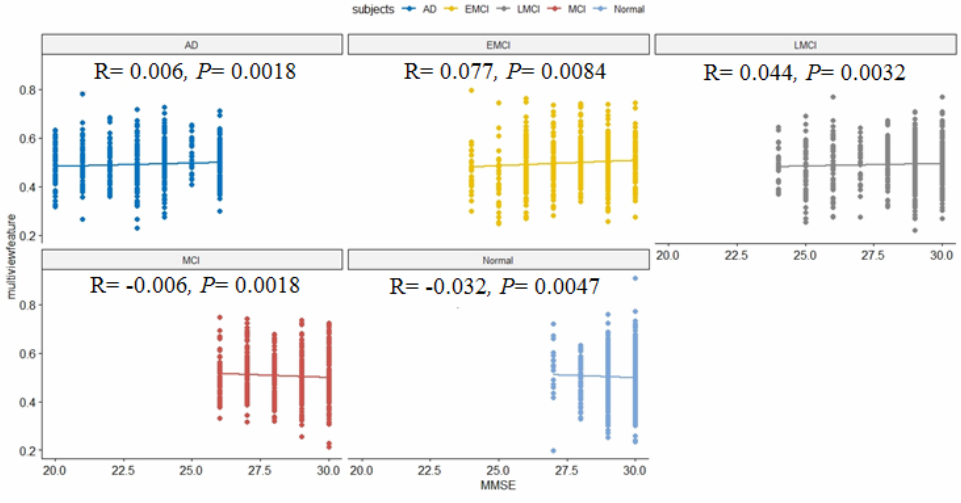

(a)




(b)

The intermediate severity group such as MCI, EMCI, and LMCI variation was found to be statistically significant with higher *p*-value ($p$ < 6.3e-0.9). Figure 12 shows the correlation plot of different diagnostic group with respect to prognostic analysis features and MMSE score. It can be witnessed that considered features are reliable to discriminate normal and severity groups. Thus, hippocampus and brainstem region prognostic analysis based significant features could capture the dementia progression under different extent of severity.

**Figure 12** Clinical correlation of hippocampus and brainstem region based features for normal, EMCI, MCI, LMCI and AD subjects (see online version for colours)




## 4 Discussion

Demented subject underwent brain deformation which directly affects the structural and functional activities of brain. This caused a difficulty in understanding the prognostic changes of biomarker in various severity stages. Identification of relevant biomarker in MR images can be helpful in performing effective diagnostic assessments. Hence, the present study is an attempt to understand the brain biomarkers in MR images such as ventricle, hippocampus, midbrain, and brainstem anatomical variations in MR images using fused features and hybrid optimiser based classification for dementia prognosis.

The images of normal, EMCI, MCI, LMCI, and AD were obtained from ADNI database. This database has a complete clinical scoring of a subject based on neurological assessments. The considered biomarkers could show edges and structural changes in considered classes. However, these changes are not quantitative due to the limited ability of the human eye to identify the subtle, intrinsic and heterogeneous characteristics of certain tissues. Therefore, radiomic and deep features were extracted from considered biomarkers for normal, EMCI, MCI, LMCI, and AD subjects. Radiomic features could extract the microstructural in patterns from ventricle, hippocampus, midbrain and brainstem regions. Likewise, deep features revealed the relative quantitative and qualitative changes in biomarkers based on its sophisticated network layer arrangements.

Thus, the extracted feature which captures the sharp anatomical changes was fused to improve the prediction ability. Then, significant features were selected from fusion of radiomic and deep features using LASSO logistic regression model. This model identified the highly informative features based on coefficient shrinkage from fused feature set which support the high prediction ability in classification. The heatmap revealed the distinct difference of feature selection based on colour map. Row determined the subject and column indicated the biomarkers in the heatmap. It was observed from the heat map that each biomarker hold a different range of fused feature information based on its colour.

**Table 2** Comparison of proposed work with existing work

| *Reference* | *Dataset* | *Image* | *Class* | *Method* | *Average accuracy* |
|---|---|---|---|---|---|
| Cheng et al. (2017) | ADNI | MRI | 3 class | Multi-domain transfer classification (MDTC) | 94% |
| Zeng et al. (2018) | ADNI | MRI | 4 class | SDPSO + SVM (switching delayed PSO) | 85% |
| Feng et al. (2018) | ADNI | MRI | 3 class | Quantitative radiomic features and SVM | 70.51% |
| Sun et al. (2018) | ADNI | MRI | 4 class | Group lasso SVM + SAR | 89% |
| Jain et al. (2019) | ADNI | MRI | 3 class | 2D convolution neural network | 95% |
| Lee et al. (2019) | ADNI | MRI | 3 class | RNN | 81% |
| Arco et al. (2021) | ADNI | MRI | 3 class | Data fusion+ PCA+ SVM | 80.9% |
| Liu et al. (2020) | ADNI | MRI | 3 class | 3D convolution neural network with instance normalisation, small-sized kernels and wider network | 80% |
| Rallabandi et al. (2020) | ADNI | MRI | 4 class | Freesurfer +SVM | 75% |
| Veluppal et al. (2022) | ADNI | MRI | 2 class | Corpus callosum texture features estimated using KDE | 81.3% |
| Hazarika et al. (2021a) | ADNI | MRI | 3 class | Improved DenseNet-121 | 90.22% |
| Alinsaif et al. (2021) | ADNI | MRI | 4 class | Wholebrain+ shearlet based descriptor with deep features | 94.4% |
| Ghaffari et al. (2022) | ADNI | MRI | 3 class | Grey matter+ deep features | 93.33% |
| *Proposed method* | *ADNI* | *MRI* | *5 class* | *Fused feature+ LASSO+ hybrid GWOPSO SVM classification* | *97.87%* |

Further, the selected features from ventricle, hippocampus, midbrain and brainstem regions are given to meta-heuristic classifier such as MSVM, PSOSVM, GWOSVM, and GWO-PSO SVM. The classification performance measures indicate that hybrid optimiser such as GWO-PSO SVM shows an effective classification result in all considered

biomarkers compared to the other methods. Moreover, hippocampus region based on GWO-PSO SVM technique achieved superior classification result (accuracy = 95.6%) than ventricle, midbrain, and brainstem regions. This could be due to the ability of superior search of GWO and effective updation of PSO for global solution which resulted in reliable generalisation in SVM classification. Consequently, to reveal the EMCI, MCI and AD variations of hippocampus region prognostic analysis was carried out. Various combinations of the considered biomarkers were also performed. However, combined hippocampus and brainstem features showed a promising result in observing the variations in normal, EMCI, MCI, LMCI, and AD due to effective recognition of inter-relation tissue transitions. Thus, hippocampus and brainstem regions micro and macro level changes were well captured by fused features in each considered stages and GWO-PSO SVM provide better insight about the borderline differences.

In addition, the intra relation between the considered classes and significant biomarkers were significant with $p$-value ($p < 0.001$). Then, the clinical correlation showed the stability of significant fused features to identify each class. Finally, the proposed pipeline was compared with various conventional methods as represented in Table 2. Thus, the strength of this work relies on effective assessment of dementia biomarker trivial changes in MR images using fusion, selection and optimised classification techniques which improved the differentiation of healthy and severity groups effectively.

## 5 Conclusions

The present study concluded by characterising the potential changes in extracted ventricle, hippocampus, brainstem, and midbrain in dementia progression. The pipeline was evaluated for important biomarker region of normal, EMCI, MCI, LMCI and AD images with fused feature extraction, significant feature selection and hybrid optimiser based classification techniques. The inclusion of LASSO effectively supported for a better identification of the distinct fused radiomic and deep features. The classifier based on GWO-PSO SVM showed distinct performance in HC+BS based significant fused features. The normal, EMCI, MCI, LMCI, and AD classification accuracy for HC+BS prognostic analysis was found to be 97.87%. The present study found that the observation of brainstem and hippocampus had greater potential to reveal progression in normal and severity classes. Hence, this framework was proved to facilitate the understanding of anatomical changes in neurodegenerative disorder efficiently.

Conversely, this study also has a few limitations such as extracting and selecting appropriate higher level features from the network which consume more computation time. The parameter used in LASSO and meta-heuristic optimiser requires proper attention to attain maximum performance in diagnosis. The proposed approach could be used for unlabelled images. This framework could be suitable to identify the different stages of progression in various cancer, lung, and heart disorder to improve clinical decisions.

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