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K-fold ensemble 3D convolutional neural network for predicting MGMT promoter methylation in glioblastoma

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ABSTRACT

Medical intervention is necessary for brain tumors, which represent a critical health threat. Chemotherapy response and patient survival outcomes depend on the methylation status of the O-methylguanine-DNA methyltransferase (MGMT) promoter. Biopsy and laboratory testing currently provide the only method to obtain this specific information. This study investigates a non-invasive technique for measuring MGMT promoter methylation through magnetic resonance imaging (MRI) scanning. The BraTS 2021 dataset provided fluid attenuated inversion recovery (FLAIR) and contrast-enhanced T1 (T1ce) MRI data to develop a 3D convolutional neural network (CNN) system. The model used five-fold stratified cross-validation for training and testing to create a reliable assessment method. Prediction accuracy improved through the use of an ensemble that combined the best models from each cross-validation fold. The model achieved an average accuracy of 0.718 and an area under the curve (AUC) of 0.727 on the validation data. The results demonstrate that MRI features can provide essential molecular details despite using restricted imaging techniques. The proposed framework shows that deep learning enables early non-invasive detection of MGMT promoter methylation status in glioblastoma (GBM). The methods help doctors with treatment planning while also identifying patients who will benefit from temozolomide-based therapies.

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1. INTRODUCTION

The World Health Organization classifies glioblastoma, which people commonly refer to as GBM, as a grade IV astrocytoma [1]. The disease progresses rapidly through the brain, which makes it hard to treat even after patients receive surgical intervention, radiation treatment, and chemotherapy. The survival rates for patients experiencing this condition have shown little improvement throughout the years. The methylation status of the O-methylguanine-DNA methyltransferase (MGMT) promoter functions as a critical biological marker that determines therapy outcomes for patients [2]. The MGMT gene produces an enzyme that enables the body to repair DNA damage resulting from the chemotherapy drug temozolomide [3]. The tumor cells that have methylated their promoter region exhibit reduced repair capabilities, which makes them more vulnerable to temozolomide treatment, resulting in better therapeutic outcomes [4]. Tumors that possess unmethylated promoters maintain their DNA repair capacity, which results in minimal response to temozolomide treatment [5].

The current method for testing MGMT methylation requires both biopsy samples and molecular testing techniques [6]. The method delivers direct results yet it cannot provide a complete tumor

representation because of the tumor's internal differences. The procedure increases surgical danger while simultaneously postponing the start of medical care. A non-invasive alternative before surgery can support faster and safer decisions. Magnetic resonance imaging (MRI) technology currently provides detailed brain structure information while researchers investigate how MRI signals connect with genetic patterns in their study of radiogenomics [7]. The features obtained through MRI analysis can predict molecular characteristics, which include MGMT promoter status determination [8]. The BraTS 2021 challenge research dataset has stimulated the creation of image-based prediction models [9].

The current research employs contrast-enhanced T1 (T1ce) and fluid attenuated inversion recovery (FLAIR) MRI data from BraTS 2021 to predict MGMT promoter methylation through a convolutional neural network (CNN), which received training via k-fold cross-validation. CNNs can learn spatial features from MRI slices without manual input [10]. Using k-fold evaluation improves generalization and reduces over-fitting [11]. Multiple folds are combined as an ensemble to balance individual model bias [12]. The study aims to check if two MRI modalities are sufficient for reliable MGMT prediction with lower computation. The model assessment uses accuracy and area under the curve (AUC) as measurement tools. The outcomes suggest that MRI-based CNN models may serve as a practical non-invasive aid for clinical decision-making in GBM management.

The initial research work investigated the capability of MRI, which does not require invasive procedures, to determine the methylation status of the MGMT promoter. Early studies used manually selected features together with semi-automatic tools which included tumor size and shape and region and enhancement, and texture. The features were applied in machine learning models, which included logistic regression and support vector machines [13]. The results showed positive outcomes in certain situations, but the results lacked reliability because the patterns visible in images did not correspond to the actual molecular behavior of the tumor.

This task received its fresh research approach through deep learning methods. CNNs enabled pattern recognition directly from MRI data without requiring human experts to choose the necessary features. Researchers studied both 2D and 3D CNNs because the 2D version processes slices, while the 3D version manages complete MRI volumes [8], [14]. The networks achieved superior results when compared to standard machine learning algorithms. Researchers adopted ensemble learning techniques, which combined results from multiple CNNs to achieve more accurate predictions with reduced bias [15]. Medical images which show different patterns across various scanners and patients present challenges that this method effectively addresses.

K-fold cross-validation has remained a preferred evaluation method for smaller medical datasets. The method enables evaluation of model performance on new data that it has not encountered before [11]. In recent BraTS challenges, teams applied different deep models, including hybrid CNN-RNN designs, for MGMT classification [16], [17]. Early radiomics methods used hand-crafted features with linear or kernel classifiers [18]. While new studies have tested combined radiomics and deep learning frameworks with external validation [19], [20].

The present work continues from these studies by developing a CNN model trained with k-fold cross-validation and finalized as an ensemble of the best folds. The model operates exclusively with T1ce modality, while previous studies required multiple MRI modalities for their research. The research tests whether restricted MRI data can effectively forecast MGMT outcomes while developing a standardized method for supporting clinical decisions during GBM treatment.

2. METHOD

This section describes the materials and methodological framework adopted in this study for MGMT promoter methylation prediction. The section begins by explaining the dataset which was used in the study, together with the methods which were used to process the MRI volumes into a standardized form. The section begins with a detailed description of the 3D CNN architecture, which follows the explanation of the five-fold stratified cross-validation method, together with the training approach that was used to accomplish effective learning. The section presents the evaluation metrics that researchers used to evaluate model performance.

2.1. Dataset

The Centre for Biomedical Image Computing and Analytics (CBICA) and the Medical Segmentation Decathlon made the BraTS 2021 MGMT promoter methylation dataset available to the public [21]. The dataset used in this study belongs to the BraTS 2021 competition. The 585 GBM patients received four different types of preoperative MRIs, which include T1-weighted, T2-weighted, T1ce, and FLAIR imaging. T1-weighted reveals complete brain structural information together with the duration required for brain tissue to return to its natural state. T1-weighted with gadolinium contrast enhancement (T1ce) these are the areas where the blood-brain barrier is disrupted. The presence of this symptom typically

indicates that the tumor is currently developing. T2-weighted imaging detects changes in water content, which assists in determining the total dimensions of tumors and their accompanying edema, while FLAIR works to eliminate signals from cerebrospinal fluid which lets through peritumoral edema and lesions. The image files exist in 3D NIfTI format, which has already undergone pre-alignment and skull stripping. The case annotation contains MGMT promoter methylation status, which indicates positive results for methylated cases and negative results for unmethylated cases. Out of 585 cases, 304 cases tested positive for methylation while 281 cases tested negative for methylation. The problem presents itself as a balanced binary classification task. The dataset serves as an effective foundation for creating and evaluating non-invasive MRI-based methods to predict MGMT status. Figure 1 showcases the data set sample, which contains four different modalities and their corresponding mask that researchers can utilize for segmentation purposes.

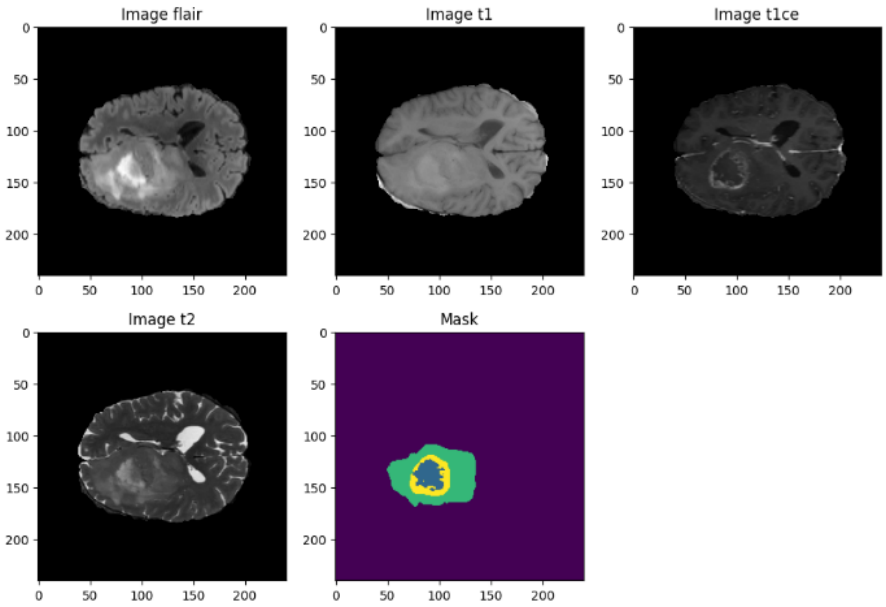

Figure 1. BraTS 2021 dataset sample image

2.2. Data pre-processing

The BraTS 2021 MGMT dataset provides 3D MRI scans for each patient in four modalities. The study used T1ce modality which shows tumor boundaries better than other methods and researchers use it for MGMT classification. All scans were resized to a fixed dimension of 128×128×128 and normalized using the z-score method to keep image intensity consistent across subjects. The multi-channel volume recorded T1ce and FLAIR information through first and third channel selection because these two channels contained essential tumor data.

The dataset showed a slight imbalance between methylated and unmethylated samples during its preparation. The unmethylated group required extra transformations which were developed to address this problem. The team created new image variations by applying random rotations and flips and using elastic deformations. The system applied 3D rotations with a range of rotation limit set at ±10° and it applied random spatial axis flips with a 0.5 probability and it applied elastic deformations which maintained anatomical accuracy through low-intensity displacement. The validation loss showed decreased variability across folds when augmentation was used which helped training stability while AUC values showed better consistency during cross-validation. The network learned to recognize multiple examples from the minority class which helped decrease bias that occurred during its training process. The resized sample images are presented in Figure 2.

2.3. Convolutional neural network architecture

The system uses a 3D CNN model which performs binary classification to determine MGMT promoter methylation status through analysis of two selected MRI imaging techniques FLAIR and T1ce. The network receives input through a 3D image whose size measures 128×128×128 with two channels that show the selected MRI imaging techniques. The network base comprises three essential convolutional processing

units. The blocks include a 3D convolutional layer, which links to batch-normalization and ReLU activation and max-pooling and dropout layers that precede the fully connected classification layers. Figure 3 shows the block diagram that represents the proposed model.

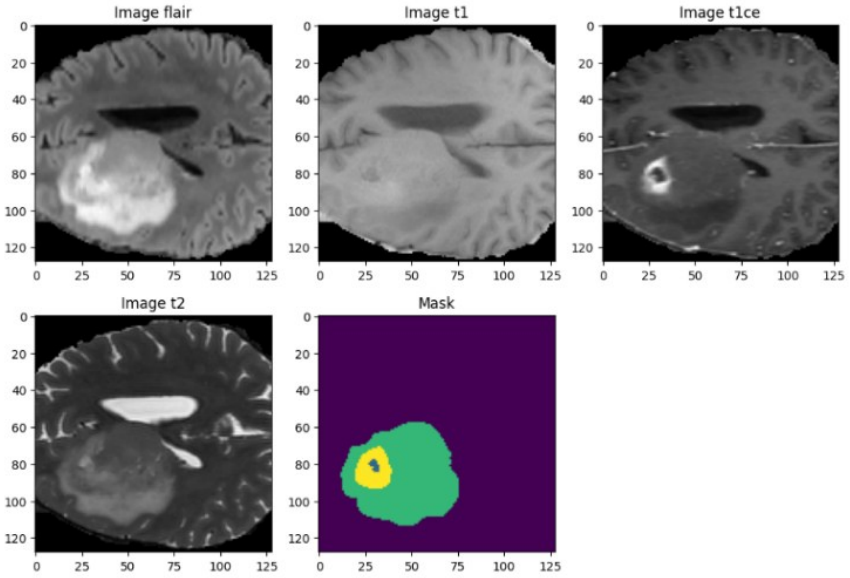

Figure 2. Sample image after cropping to resize for 128×128×128

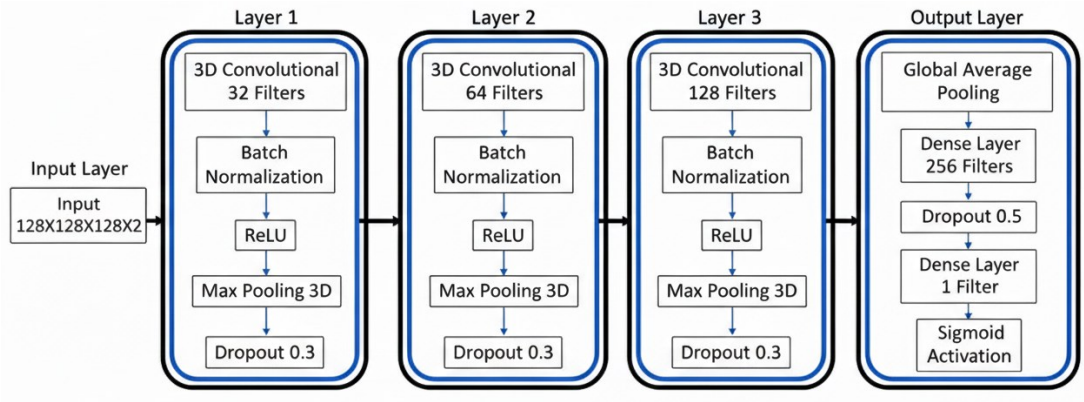

Figure 3. CNN network with 3 hidden layers used in this work

The output layer consists of a single neuron that uses sigmoid activation to produce a probability output which ranges from 0 to 1 to indicate the probability of MGMT promoter methylation. The design protects against overfitting by enabling the model to identify spatial patterns within MRI data which becomes challenging to learn from limited medical datasets. The system requires only two imaging modalities because this choice keeps processing expenses affordable while delivering sufficient data to support accurate classification. The researchers decided to keep the system architecture shallow because their tests showed that deeper models would lead to overfitting problems. The researchers used dropout techniques at various points in the system to achieve better results because this method worked well with their class augmentation system which handled fewer common classes. Table 1 provides a complete overview of the 3D CNN configuration which includes information about kernel dimensions and filter quantities and methods for managing overfitting. The research team selected a shallow network design after they discovered through initial testing that deeper networks would quickly experience overfitting effects which would result in unpredictable validation results because of the restricted dataset and the limited radiogenomic features of MGMT promoter methylation.

Table 1. CNN architectural parameters

Layer	Filters	Kernel size	Stride	Pooling	Dropout
Conv block 1	32	3×3×3	1	2×2×2	0.3
Conv block 2	64	3×3×3	1	2×2×2	0.3
Conv block 3	128	3×3×3	1	2×2×2	0.3
FC layer	256	–	–	–	0.5
Output	1	–	–	–	–

2.4. K-fold cross-validation pipeline for ensemble

The researchers used five-fold stratified cross-validation because it provided accurate assessment results while preventing overfitting when researchers had only small datasets. The data were split into five equal sized portions with balanced class distribution in each. For each model training run, four-folds were used for training and the remaining one for validation. This process was conducted five times so that each validation fold would be used exactly once. The assessment method provides stronger model performance evaluation than using one train-test split.

The training process saved all five models after they reached their peak validation AUC performance. The testing phase used prediction probabilities from the trained models which were combined through averaging to build an ensemble model that produced better network performance with increased stability and improved generalization capabilities. The ensemble method reduced bias which could have occurred from using just one data split for analysis. The main components of k-fold ensemble processing are presented in Algorithm 1, while Figure 4 demonstrates how the process operates on the BraTS 2021 dataset. External validation on independent datasets was not performed in this study due to the limited availability of publicly accessible MRI cohorts with standardized MGMT annotations and harmonized acquisition protocols; a detailed discussion of these constraints and their clinical implications is provided in sub-section 3.2.

Algorithm 1. Ensemble CNN for MGMT classification

```
Input: Dataset D = {(x₁, y₁), (x₂, y₂), ..., (xₙ, yₙ)}, where xᵢ ∈ R^(128 X 128 X 128 X 2)
          CNN model architecture 𝓜
          Loss function ℒ_focal
          Learning rate η, batch size B, number of epochs E
Output:   Ensemble model ℰ consisting of K trained CNNs
Initialize:
              𝓜_ensemble ← ∅
              Number of folds K ← 5
Partition D into K stratified folds: D₁, D₂, ..., D_K
For each fold k = 1 to K do
          Set validation set D_val ← D_k
          Set training set D_train ← D − D_k
          Apply augmentation to all (x, y) ∈ D_train
           where y = 0
          Normalize all x ∈ D_train ∪ D_val using z-score:
                   x' ← (x − μ_x) / (σ_x + ε)
          Initialize model 𝓜_k with random weights θ_k
          Compile 𝓜_k with:
                  optimizer ← Adam(learning rate = η)
                  loss ← ℒ_focal
                  metrics ← {accuracy, AUC}
          Train 𝓜_k on D_train for E epochs of batch size B
          Monitor validation AUC
          Save best model weights θ_k* based on max AUC
          Append trained model 𝓜_k(θ_k*) to 𝓜_ensemble
End
Define ensemble model ℰ:
          For any input sample x do
                  Predict each model: ȳ_k ← 𝓜_k(x) for all 𝓜_k ∈ 𝓜_ensemble
                  Compute average prediction: ȳ_ensemble ← (1 / K) · Σ_k ȳ_k
                  Final label: ŷ ← 1 if ȳ_ensemble > 0.5 else 0
          End
Return ℰ
```

2.5. Training strategy

The five-fold stratified cross-validation method established for model training delivered unbiased complete assessment results. Every testing round used one-fold for validation purposes while the remaining four folds served as training data. Researchers used three-dimensional random rotation and flip and intensity

augmentation techniques to create additional samples of the smaller class because they faced a class imbalance problem. The network required these transformations to learn about the special features possessed by the minority group. The two MRI modalities underwent normalization procedure which used mean and standard deviation values derived from the training sample. The model achieved its optimization through binary focal and Dice loss combination which improved its capacity to handle difficult and imbalanced situations. The Adam optimizer with a learning rate starting at 1×10^{-4} was used for weight updates. The system used dropout with 0.3 probability and early stopping at ten epochs to reduce overfitting risks.

The system saved the best validation AUC model from each training fold after completing all fold training. The five models produced outputs which were combined through soft-voting to create a single result. The ensemble delivered more consistent predictions which achieved better results during testing of unfamiliar data.

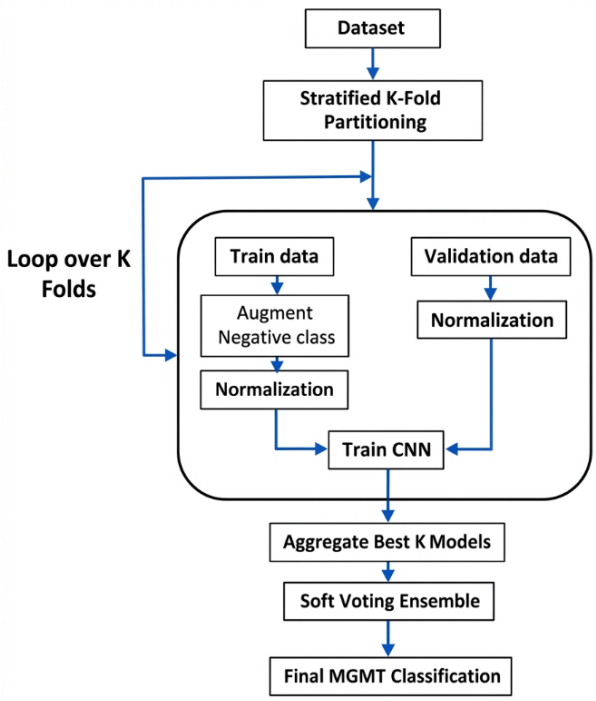

Figure 4. K-fold cross validation on CNN

2.6. Evaluation metrics

The model assessment used standard classification performance indicators to measure its performance. The measurement system enables prediction assessment through evaluation of various model operational components. The MGMT dataset contained a slight class imbalance which required multiple performance metrics to assess how the model handled both case types. The following metrics were used to evaluate the performance of the system:

i) Accuracy gives how many cases predicted accurately, it may not always show the true balance between both classes.

ii) Precision which is very important in medical diagnosis using deep learning techniques as it explains how reliable and accurate the positive predictions are given. It tells what part of the samples predicted as methylated were actually methylated. When precision is high, model makes fewer false positive decisions.

iii) Recall (or sensitivity) focuses on how many true methylated cases were correctly identified. It shows how well the network captures positive cases without missing them.

iv) F1-score merges precision and recall into a single number. It is useful when the data have unequal class sizes because it maintains balance between detecting positives and avoiding false detections.

v) AUC-receiver operating characteristic (ROC) is used to indicate the separation performance of the. In the ROC curve, the x-axis is for false positive rates while the y-axis is for true positive rates, and the AUC ranges from 0 to 1. The larger the value of AUC, the better the discrimination between methylated and unmethylated tumors.

3. RESULTS AND DISCUSSION

The section demonstrates complete assessment of the MGMT promoter methylation prediction framework which has been proposed. The first step involves assessment of classification accuracy and training performance through analysis of quantitative results which were obtained from five-fold cross-validation testing. The research results are compared with current MRI-based MGMT studies to demonstrate the research strengths and weaknesses and their potential impact on clinical practice.

3.1. Performance evaluation using five-fold cross-validation

The research utilized 585 MRI samples from the BraTS 2021 MGMT dataset for its investigation. The dataset achieved near balanced distribution after creating a dataset from 304 methylated samples and 281 unmethylated samples which the researchers used for training. BraTS guidelines required researchers to exclude all clinical and demographic information from their study. The proposed 3D CNN was trained using five-fold stratified cross-validation, where each split was handled independently, and the best-performing model was saved based on validation AUC.

The researchers achieved stable results through the ensemble averaging method which combined outputs from all five separate evaluation sections. The validation set results showed that the model achieved 0.718 accuracy, 0.727 ROC-AUC, 0.867 precision, 0.825 recall, and F1-score 0.844. The research demonstrates that T1ce and FLAIR modalities can achieve reliable MGMT prediction despite showing lower results than previous multi-modal studies. The selection of these two sequences was based on their ability to show both tumor enhancement and peritumoral edema which medical professionals use to assess GBM status [8].

The confusion matrix in Figure 5 displays 202 true negatives and 219 true positives as correctly identified results while 79 incorrect positive predictions and 85 missed positive cases occurred. This balance means that the classifier worked evenly for both methylated and unmethylated tumors. The study found a slight advancement in methylated tumor detection which matches earlier research that discovered stronger signal uniformity in methylated lesions [14], [15]. The accuracy and AUC measurements for five folds of testing showed a range from 0.70 to 0.75 which demonstrated stable learning performance across various data splits. The model demonstrated consistent performance results across different test folds because it showed minimal link between test results and model operation. All the performance future work will incorporate confidence interval estimation to further quantify statistical robustness. The loss curves decreased smoothly for both training and validation sets and stabilized near 0.35 to 0.40 after 30 epochs which indicates that the network successfully prevented overfitting. The research in [16], [19] reported similar steady convergence trends in their BraTS-based CNN research. The detailed five-fold cross-validation performance metrics are summarized in Table 2.

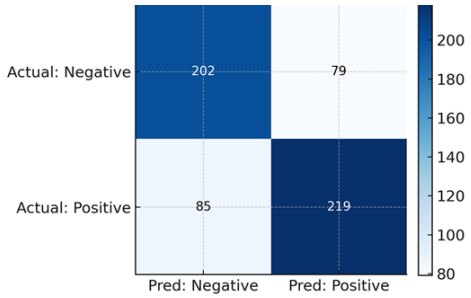

Figure 5. Aggregated confusion matrix

Table 2. Fold wise accuracy and AUC comparison

Split	Accuracy	AUC	Precision	Recall	F1-score
Fold 1	0.720	0.740	0.740	0.720	0.730
Fold 2	0.730	0.750	0.760	0.730	0.745
Fold 3	0.710	0.720	0.730	0.700	0.715
Fold 4	0.700	0.700	0.710	0.690	0.700
Fold 5	0.730	0.730	0.750	0.720	0.735
Ensemble avg.	0.718	0.728	0.738	0.712	0.725

The ensemble model ROC curve results are displayed in Figure 6. The curve demonstrates continuous performance above the diagonal line because it reaches an AUC value of 0.727 which enables the model to differentiate between methylated and unmethylated tumors. The model achieves

consistent and understandable classification results through its use of a basic network structure and two MRI imaging techniques.

The model's stability across various data splits is demonstrated through its fold-wise performance which testing reveals. Accuracy and AUC values obtained from the five-fold stratified cross-validation remained consistent, with accuracy ranging between 0.70 and 0.73 and AUC values between 0.70 and 0.75, as summarized in Table 2 and visualized in Figure 7. The three-dimensional convolutional network model achieved consistent performance across multiple test periods because it learned universal features instead of becoming too specialized to one validation set. The ensemble model, which combines predictions from all top models selected during each testing period, attained an overall accuracy of 0.718 and an AUC of 0.727, which shows better prediction stability and model strength than single testing periods.

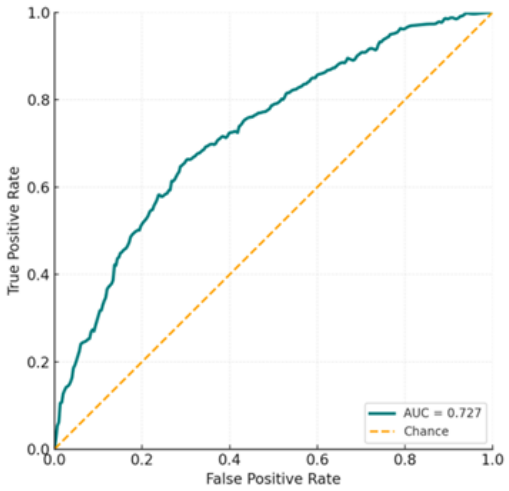

Figure 6. ROC curve of the proposed model

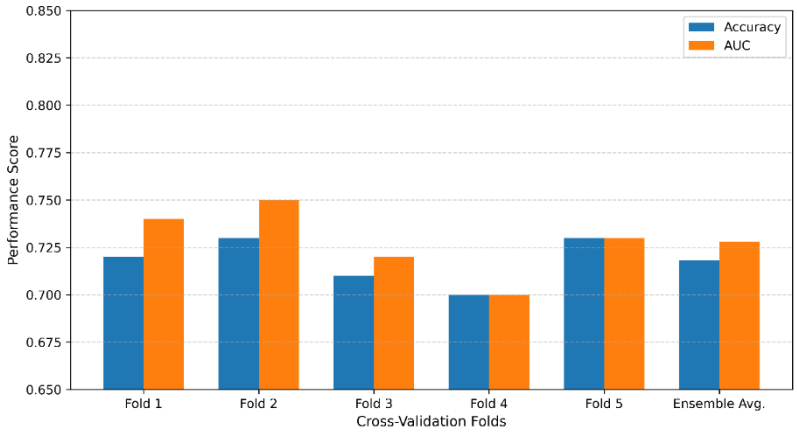

Figure 7. Accuracy and AUC across the folds

3.2. Discussion: comparative analysis, limitations, and clinical implications

The proposed model performed in line with several recent single- and dual-modality approaches reported in the literature. T1ce and FLAIR together provide complete tumor enhancement and peritumoral infiltration details which researchers use to study MGMT promoter methylation through radio genomic studies [22]. The model delivers competitive results through its use of clinically relevant sequences which require less computational resources than complex multimodal systems. The weighted voting method of alternative ensemble systems costs more to implement than simple averaging solution which provides essential data protection.

Ensemble averaging across cross-validation folds improved consistency and reduced prediction variability because it had been used in previous BraTS-based MGMT classification studies which aimed to

decrease split-dependent bias [23]. The achieved AUC score of 0.728 shows moderate performance for non-invasive tasks which require biological testing but still demonstrates effective signal distinction. Previous investigations have shown that MGMT methylation leads to changes in tissue microstructure and edema and enhancement patterns which enables CNNs to detect subtle but consistent predictive patterns from T1ce and FLAIR training.

Multiple studies conducted during recent times demonstrate that MGMT promoter methylation functions as a molecular and epigenetic alteration which does not show consistent results through standard MRI examinations [24], [25]. The first factor establishes the maximum limit which MRI-only prediction methods can reach while the second factor accounts for performance saturation which multiple researchers have found. CNN-based MGMT classifiers show lower generalization ability according to large-scale evaluations which test their performance outside the development distribution, thus emphasizing the need for careful interpretation of cross-validation results [26]. External validation remains a key challenge for MRI-based MGMT promoter methylation prediction.

The medical test shows MGMT methylation through imaging methods which reflect the genetic change but the change needs to be viewed through medical scan results which show patient movement and display issues. The public databases which offer standardized multi-modal MRI data and trustworthy MGMT annotations remain inaccessible, thus preventing effective cross-dataset validation, while institutional differences in preprocessing methods make external testing more challenging. The current research operates as an exploratory radiogenomic analysis which uses a controlled benchmark dataset for its investigation rather than a medical diagnostic system ready for clinical use.

The results demonstrate that minimal-modality CNNs maintain stable performance when their models undergo testing through stratified cross-validation and ensemble learning. Table 3 presents comparative results which show how the proposed method performs against both single-modality baseline systems and hybrid deep–radiomics approaches. Future research will use attention mechanisms and radiomic descriptors to perform better tumor region tracking which leads to accurate predictions, because this study lacked interpretability analysis. The organization needs to develop harmonization strategies while testing their system across different healthcare institutions to achieve better system reliability and understanding of their technology and user trustworthiness.

Table 3. Comparison with existing MGMT classification studies

Reference	Dataset/Modality	Model/method	Accuracy	AUC	Remarks
Proposed study	BraTS 2021 (T1ce+FLAIR)	3D CNN+five-fold ensemble	0.718	0.728	Two-modality and lightweight framework
Koska and Koska [22]	BraTS 2021 (T1-weighted, T1ce, T2-weighted, FLAIR)	3D ResNet+Radiomics fusion	0.880	0.900	Multi-modal with handcrafted features
Kim *et al.* [17]	BraTS 2020 (All modalities)	Hybrid CNN–RNN	0.760	0.780	Temporal aggregation improves sensitivity
Calabrese *et al.* [26]	Preoperative MRI (multi-institutional)	CNN-based MGMT classifier	0.66	0.70	CNN-only performance comparable to MRI-only methods
Saeed *et al.* [8]	BraTS 2021 dataset (T1ce+Flair)	Multiple DL models	0.62–0.71*	0.65–0.74*	Performance varies across architectures and limited generalization
Qureshi *et al.* [19]	BraTS 2021	Deep–Radiomics fusion	0.730	0.745	Combines deep and radiomic features

* Performance is reported as a range due to evaluation of multiple deep learning methods.

4. CONCLUSION

The process of estimating the methylation status of the MGMT promoter through pre-operative MRI data analysis becomes difficult because the biomarker shows molecular changes that cannot be seen with standard imaging methods, different scanner equipment, and tumor growth patterns. The researchers developed a small 3D CNN model, which scientists used to train their system through five-fold stratified cross-validation while using ensemble averaging to predict MGMT promoter methylation from T1ce and FLAIR MRI images. The architectural design achieved 0.718 accuracy and 0.727 AUC performance while maintaining consistent results without displaying any overfitting behavior. The study demonstrates that basic system performance achieves satisfactory results without using multimodal systems, which contain multiple layers, because training stability and testing standards become the deciding factors. The results show that dual-modality models can be developed as lightweight systems that serve as standard bases for non-invasive MGMT estimation, although they cannot yet be used in clinical practice. The results expand research possibilities by requiring external validation and testing of additional features.

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AUTHOR CONTRIBUTIONS STATEMENT

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Burra Vijaya Babu	✓	✓	✓	✓	✓	✓				✓		✓	✓	

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

DATA AVAILABILITY

The data used in this study are publicly available from the RSNA-MICCAI Brain Tumor Radiogenomic Classification dataset hosted on Kaggle at https://kaggle.com/competitions/rsna-miccai-brain-tumor-radiogenomic-classification, reference number [21]. No new dataset was generated in this study.

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