MGMT Promoter Methylation Prediction in Glioblastoma Using 3D CNNs with Advanced MRI Sequences

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Abstract

Accurate determination of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is essential for therapeutic planning in glioblastoma (GBM). Although molecular assays remain the reference standard, they are costly, invasive, and not always feasible in routine practice. This has motivated the development of non-invasive MRI-based deep learning approaches, particularly those leveraging advanced physiological imaging sequences. In this study, we investigated whether arterial spin labeling (ASL) and apparent diffusion coefficient (ADC) imaging provide complementary information for predicting MGMT methylation status in IDH-wildtype GBM. We analyzed 351 patients from the UCSF Preoperative Diffuse Glioma MRI dataset and trained 3D convolutional neural network models based on a ResNet-10 architecture using ASL, ADC, diffusion-weighted imaging (DWI), and conventional T2-FLAIR sequences. Among single-sequence models, ASL achieved the highest performance (accuracy 0.76, precision 0.75, F1 score 0.73). A dual-sequence model combining ASL and ADC further improved prediction, yielding an AUC of 0.83, significantly outperforming both the ASL-only model and the T2-FLAIR model (AUC 0.6524; DeLong test, $p < 0.05$). These results demonstrate that integrating perfusion- and diffusion-based MRI captures complementary physiological characteristics relevant to MGMT methylation, offering a more accurate and fully non-invasive alternative for biomarker assessment. Incorporating advanced MRI sequences into deep learning pipelines may support more informed treatment planning and improve clinical decision-making for patients with GBM.

Keywords: glioblastoma, MGMT methylation, deep learning, arterial spin labeling, apparent diffusion coefficient, MRI, non-invasive diagnosis

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1. Introduction

Gliomas are the most common primary malignant brain tumors, accounting for nearly 80% of cases (Ostrom et al., 2014; Hanif et al., 2017). Arising from glial cells that support neuronal function (Davis, 2018), these tumors are classified into four grades of increasing aggressiveness according to the World Health Organization (WHO) (Louis et al., 2021). Grade IV gliomas, or glioblastomas (GBM), exhibit rapid infiltration, poor therapeutic response, and high recurrence rates, contributing to their exceptionally poor prognosis (Ghosh et al., 2017; Stupp et al., 2014; Rock et al., 2012).

A growing emphasis in GBM management is the stratification of tumors using molecular biomarkers such as isocitrate dehydrogenase (IDH) mutation status and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (Sahm et al., 2023; Sejda et al., 2022; Thomas, 2023; Horbinski et al., 2022). IDH-wildtype gliomas typically show more aggressive biology and worse outcomes (Weller et al., 2015). MGMT promoter methylation, in particular, has substantial therapeutic significance: it predicts sensitivity to alkylating agents such as temozolomide and guides adjuvant treatment decisions (Sonoda et al., 2010; Hegi et al., 2005). However, current molecular assays for assessing MGMT status are invasive, costly, and require specialized laboratory workflows, limiting their availability in many clinical settings (Nguyen et al., 2021; Quillien et al., 2012).

These limitations have motivated efforts to develop non-invasive imaging-based alternatives. Magnetic resonance imaging (MRI) provides rich structural and physiological information, and advanced MRI techniques—including diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), and arterial spin labeling (ASL)—offer measurements of microstructural integrity, water diffusivity, and perfusion, respectively (Hu et al., 2024; Shukla et al., 2017). Such physiological markers may reflect tumor heterogeneity associated with MGMT methylation, making them promising imaging surrogates.

Recent deep learning advances have demonstrated the potential of MRI-based models to predict GBM molecular features (Hu et al., 2024; Yogananda et al., 2021; Faghani et al., 2023). While prior studies have primarily relied on conventional sequences (e.g., T2-weighted and FLAIR), emerging evidence suggests that advanced MRI sequences may capture complementary physiological signatures that improve prediction accuracy (Faghani et al., 2023; Kanas et al., 2017; Han et al., 2018; Saxena et al., 2023). Conventional sequences are effective for visualizing tumor boundaries and edema but often lack the sensitivity to functional and molecular characteristics required for robust biomarker prediction.

To address these limitations, this study investigates whether combining advanced perfusion- and diffusion-based MRI modalities enhances the non-invasive prediction of MGMT promoter methylation status in IDH-wildtype GBM. Using a retrospective MRI dataset, we develop and compare several 3D convolutional neural network (CNN) models trained on individual and combined MRI sequences, focusing particularly on ASL and ADC. Our goal is to evaluate whether integrating complementary physiological information can improve predictive performance beyond that of conventional MRI alone.

2. Materials and Methods

An overview of the study workflow is shown in Figure 1. The analysis began with MRI data from 351 IDH-wildtype GBM patients. Each scan, originally provided in NIfTI format, was

converted to DICOM for standardized handling across preprocessing and modeling steps. The dataset was split into a training cohort (n = 280) and a held-out testing cohort (n = 71). For each patient, the central 100 axial slices—corresponding to the region most likely to contain the tumor—were extracted and processed through a standardized pipeline comprising resizing, augmentation, and normalization. Separate 3D CNN models were trained using individual MRI sequences (ASL, ADC, and DWI), and a dual-sequence fusion model was constructed by combining ASL and ADC inputs along the channel dimension. A comparative model based on conventional T2 and FLAIR sequences was also evaluated. Model performance was assessed on the independent test set.

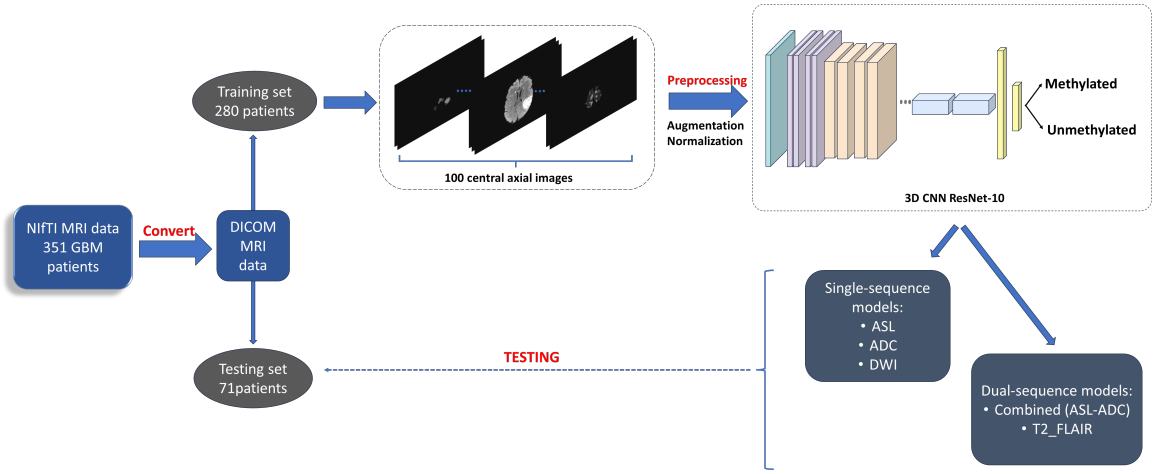

Figure 1: Overview of the proposed workflow for MRI-based MGMT methylation prediction. The pipeline includes MRI acquisition, NIfTI-to-DICOM conversion, slice extraction, preprocessing, and model development using 3D convolutional neural networks (3D CNNs) based on a ResNet-10 architecture. ASL, ADC, DWI, and conventional sequences are processed individually or in combination to generate prediction outputs. Abbreviations: CNN = Convolutional Neural Network; ResNet = Residual Network; NIfTI = Neuroimaging Informatics Technology Initiative; DICOM = Digital Imaging and Communications in Medicine.

2.1. Patient data

This study used the University of California, San Francisco Preoperative Diffuse Glioma MRI (UCSF-PDGM) dataset (Calabrese et al., 2022), which contains imaging and molecular profiling data from 501 patients who underwent a standardized preoperative 3T MRI protocol between 2015 and 2021. Institutional review board approval and an exemption from patient consent were granted by the UCSF IRB.

All MRI examinations were acquired on a 3T Discovery 750 scanner (GE Healthcare) equipped with an eight-channel head coil (Invivo). The imaging protocol included 3D T2-weighted, FLAIR, pre- and post-contrast T1-weighted, susceptibility-weighted, DWI, 2D

high-angular-resolution diffusion imaging (HARDI), and 3D ASL. As described in prior work (Calabrese et al., 2020, 2021), images were registered and resampled to a 1-mm isotropic space using Advanced Normalization Tools, with T2-FLAIR serving as the reference volume. Skull stripping was performed using standardized pipelines validated in these earlier studies.

The dataset includes molecular annotations such as IDH mutation status and MGMT promoter methylation. Among the 501 cases, 403 (80%) were WHO grade IV gliomas, of which 63% were MGMT-methylated. IDH mutation testing was performed using Sanger or next-generation sequencing (Kline et al., 2017), and MGMT methylation status was assessed using a quantitative methylation-specific PCR assay (Kitange et al., 2009), with two or more methylated loci considered positive (Ratai et al., 2018).

For this study, all IDH-wildtype GBM patients (n = 351) were selected, consisting of 247 MGMT-methylated and 104 unmethylated cases. Patients were randomly assigned to training and testing sets using an 8:2 ratio. Representative examples of the conventional and advanced MRI sequences used in the analysis are shown in Figure 2.

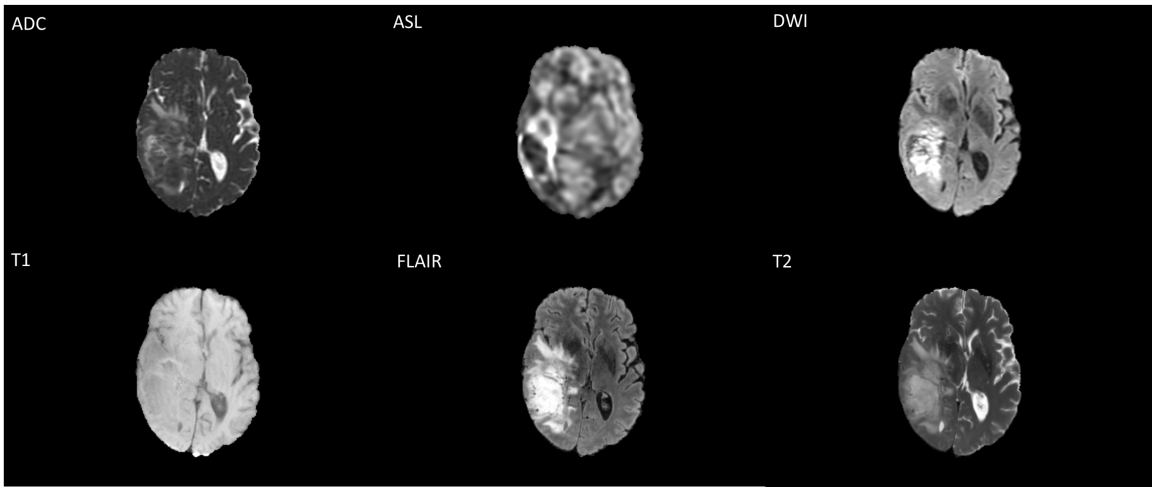

Figure 2: Representative conventional and advanced MRI sequences from a glioblastoma patient. Shown are examples of T1-weighted, T2-weighted, and FLAIR images (conventional sequences), alongside ASL, ADC, and DWI (advanced physiological sequences), illustrating the multimodal information used for MGMT promoter methylation prediction.

2.2. Data preprocessing

MRI scans were initially converted from NIfTI to DICOM using Python to standardize downstream processing. Each scan consisted of 155 axial slices (240×240 pixels), of which the first 133 slices contained cerebral anatomy. To ensure consistent anatomical coverage, we selected the central 100 slices for model input.

Formally, an MRI volume is represented as an ordered set of slices:

$$V = \{v_1, v_2, \ldots, v_{155}\}.$$

Let the cerebral region span slices 1–133; the central subset is extracted as:

$$V_{\text{central}} = \{v_{28}, \ldots, v_{127}\},$$

providing a fixed-length input of 100 slices per subject.

All selected slices were resized to 224×224 pixels to match the ResNet-10 input specification. Data augmentation included four rotational transforms (0°, 90° clockwise, 90° counterclockwise, and 180°) to improve robustness to spatial variability. Intensities were standardized using min–max normalization. For single-sequence models, the 100 slices were stacked into a 3D tensor, whereas dual-sequence models concatenated two corresponding MRI sequences along the channel dimension to form a two-channel 3D input.

2.3. Deep learning model implementation

MGMT promoter methylation prediction was formulated as a binary classification task. Each MRI input volume was represented as a 3D tensor:

$$X \in \mathbb{R}^{C\times H\times W\times S},$$

where C is the number of MRI channels (1 for single-sequence, 2 for fused ASL+ADC inputs), and S is the number of axial slices. The 3D ResNet-10 model f_θ produced a methylation probability:

$$\hat{y} = \sigma(f_\theta(X)),$$

and network parameters were optimized using binary cross-entropy:

$$\mathcal{L} = -\left[y \log(\hat{y}) + (1-y)\log(1-\hat{y})\right], \quad y \in \{0, 1\}.$$

Architecture. All models were built using a 3D ResNet-10 backbone consisting of:

- an initial 7×7×7 3D convolution (64 filters, stride 1, padding 3),
- BatchNorm3d and ReLU activation,
- a 3×3×3 max-pooling layer (stride 2),
- four residual blocks with hierarchical downsampling (stride 2 where appropriate), and
- an AdaptiveAvgPool3d layer yielding a global feature vector before the final fully connected classifier.

Each residual block computes:

$$\mathbf{z}_{l+1} = \mathbf{z}_l + F(\mathbf{z}_l; \theta_l),$$

where F denotes a two-layer 3D convolutional transformation. This skip-connection structure facilitated stable training of deep 3D networks.

Single-sequence and fused models. Separate models were trained using ASL, ADC, and DWI inputs. For dual-sequence fusion, ASL and ADC volumes:

$$X^{(\mathrm{ASL})},\ X^{(\mathrm{ADC})} \in \mathbb{R}^{H\times W\times S}$$

were concatenated channel-wise:

$$X_{\mathrm{fusion}} = \mathrm{Concat}\left(X^{(\mathrm{ASL})},\ X^{(\mathrm{ADC})}\right) \in \mathbb{R}^{2\times H\times W\times S}.$$

This fused representation was processed by a shared 3D ResNet-10 encoder. A T2_FLAIR model served as a conventional MRI baseline.

Training protocol. Training was performed using stratified 5-fold cross-validation for 15 epochs per fold. The Adam optimizer was used with an initial learning rate of 1×10^{-4}, reduced to 5×10^{-5} during training.

2.4. Statistical analysis

Performance was quantified using accuracy, recall, precision, and F1 score. Overall discriminative performance was evaluated using the area under the receiver operating characteristic curve (AUC). The DeLong test was used to assess statistical differences between the dual-sequence model and single-sequence baselines. Group comparisons for age were performed using the Mann–Whitney U test, and categorical variables (sex and MGMT status) were analyzed using Fisher's exact test. A significance threshold of $p < 0.05$ was applied.

All preprocessing and model development were performed using Python 3.10.12 on a high-performance computing workstation equipped with an NVIDIA A100-SXM4-40GB GPU, an Intel® Xeon® 2.20GHz CPU, 83.5 GB RAM, and 201.2 GB storage.

3. Results

3.1. Patient characteristics

The demographic and clinical characteristics of the study cohort are summarized in Table 1. There were no significant differences between the training (n = 281) and testing (n = 70) sets in terms of age, sex distribution, or MGMT promoter methylation status. The mean age was 61.43 ± 11.28 years in the training set and 63.53 ± 10.63 years in the testing set (Mann–Whitney U, $p = 0.253$). The proportion of male patients was similar across subsets (59.1% vs. 65.7%; Fisher's exact test, $p > 0.05$). The prevalence of MGMT promoter methylation was also comparable (70.46% vs. 70.00%; $p > 0.05$), confirming balanced distributions of key covariates following random split.

3.2. Performance of single-sequence models

Performance metrics for models trained on individual MRI sequences are presented in Table 2. Among the advanced MRI modalities, the ASL-based model achieved the strongest results, with an accuracy of 0.7571, recall of 0.6361, precision of 0.7333, and an F1 score of 0.6814. The ADC model yielded comparable accuracy (0.7559) but slightly lower recall (0.6062) and F1 score (0.6093). The DWI model demonstrated reduced performance overall, with an accuracy of 0.7042 and an F1 score of 0.5834.

Table 1: Demographic and clinical characteristics of the study population.

Parameter	**Training set (n=281)**	**Testing set (n=70)**	**p-value**
Age (mean ± SD)	61.43 ± 11.28	63.53 ± 10.63	0.2530
Gender			
Male	166 (59.07)	46 (65.71)	0.3095
Female	115 (40.93)	24 (34.29)	
MGMT status			
Methylated (%)	198 (70.46)	49 (70.00)	0.9395
Unmethylated (%)	83 (29.54)	21 (30.00)	

Table 2: Performance of single-sequence models for predicting MGMT promoter methylation.

Model	**Accuracy**	**Recall**	**Precision**	**F1 score**
ASL	0.7571	0.6361	0.7333	0.6814
DWI	0.7042	0.5552	0.6151	0.5834
ADC	0.7559	0.6062	0.6129	0.6093
T2_FLAIR	0.6857	0.5442	0.5829	0.5628

The model based on conventional T2_FLAIR sequences exhibited the lowest predictive performance, with metrics ranging from 0.5442 to 0.6857. These results highlight that advanced MRI sequences—particularly ASL and ADC—provide more informative features for MGMT promoter methylation prediction than structural imaging alone.

3.3. Performance of combined ASL+ADC model

The dual-sequence model integrating ASL and ADC inputs achieved the highest overall performance, with an AUC of 0.8163 (Table 3). This represented a significant improvement over the single-sequence ASL model (AUC 0.7580; DeLong test, $p < 0.0001$) and the conventional T2_FLAIR model (AUC 0.6524; $p = 0.0203$). The corresponding ROC curves for the combined and baseline models are shown in Figure 3. These results indicate that

Table 3: Comparison of AUC values for the combined ASL+ADC model and baseline models.

Model	**ASL**	**Combined**	**T2_FLAIR**
AUC score	0.7580	0.8163	0.6254
p-value	< 0.0001		0.0203

combining perfusion- and diffusion-based physiological information yields a complementary

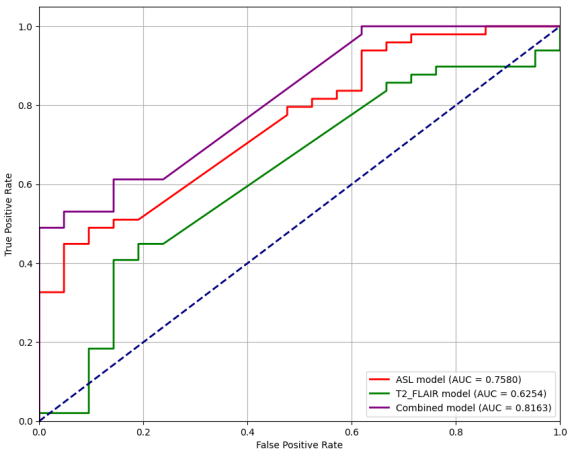

Figure 3: Receiver operating characteristic (ROC) curves for MGMT methylation prediction models. Comparison of ROC curves for the combined ASL+ADC model, the ASL-only model, and the T2_FLAIR baseline, demonstrating the improved discriminative performance of integrating advanced MRI sequences.

representation that enhances the non-invasive prediction of MGMT promoter methylation status in GBM.

4. Discussions

The increasing availability of multimodal neuroimaging datasets such as UCSF-PDGM (Calabrese et al., 2022) has accelerated research on MRI-based artificial intelligence (AI) approaches for characterizing glioblastoma. Leveraging this resource, the present study demonstrates that advanced physiological MRI sequences—particularly ASL and ADC—carry complementary information that improves non-invasive prediction of MGMT promoter methylation status, an important biomarker for treatment planning and prognosis in GBM.

Prior studies have explored a range of imaging planes and acquisition strategies for MRI-based glioma characterization (Batra et al., 1988; Ren et al., 2021; Ding et al., 2021). Although 3D volumetric analysis provides rich contextual information, axial slices remain the most clinically interpretable and are commonly used in radiological workflows (Koh et al., 2010). Our slice-based 3D CNN approach aligns with this clinical convention while enabling efficient model training. The selection of ResNet-10 was motivated by its favorable balance between representational capacity and computational complexity (Faghani et al., 2023; Saxena et al., 2023; Korfiatis et al., 2017; Saeed et al., 2023), making it suitable for high-dimensional MRI inputs without requiring extensive model tuning.

Among the advanced MRI modalities evaluated, ASL and ADC emerged as the most informative single-sequence predictors. Their physiological underpinnings help explain this outcome. ASL provides direct measurements of tissue perfusion, which may relate to tumor vascularity and hypoxia—features that differ between methylated and unmethylated

MGMT phenotypes. ADC, by contrast, captures diffusivity and microstructural integrity, reflecting variations in cellularity and necrosis. Each modality therefore probes distinct biological processes. The combined ASL+ADC model harnessed these complementary characteristics, achieving a significantly higher AUC (0.8163) than either modality alone and outperforming a model based on conventional T2_FLAIR sequences. This suggests that perfusion–diffusion fusion provides a richer characterization of tumor physiology relevant to MGMT methylation.

Our findings are consistent with earlier studies that reported limited performance when relying solely on conventional MRI for MGMT prediction. For example, Yogananda et al. achieved an AUC of 0.6588 using T2-weighted imaging with a 3D Dense-UNet (Yogananda et al., 2021), while Saxena et al. reported an AUC of 0.753 using 3D ResNet-18 (Saxena et al., 2023). By incorporating advanced physiological sequences, our ASL and combined models exceed these benchmarks, reinforcing the value of moving beyond purely structural imaging for molecular phenotype estimation.

Despite these encouraging results, several limitations must be acknowledged. First, the study relied on a single model architecture; alternative architectures, such as DenseNet, EfficientNet, or transformer-based 3D models, may further improve performance. Second, although ASL and ADC provided strong predictive signals, additional advanced sequences (e.g., perfusion-weighted imaging, spectroscopy) were not evaluated and may contribute additional complementary information. Third, no clinical variables or radiomic features were incorporated. Prior work has suggested that multimodal fusion of imaging and clinical data can lead to more holistic and robust predictors (Huang et al., 2020). Finally, this study focused exclusively on axial-plane data from a single institutional dataset; assessing cross-plane fusion or testing on external cohorts would be important for evaluating generalizability.

Future research should therefore explore multi-view fusion strategies, integration of clinical metadata, and broader architectural comparisons. Incorporating explainability techniques such as saliency mapping or attention-driven visualization may also improve clinical trust and interpretability. As advanced MRI acquisition becomes increasingly common in neuro-oncology, combining physiological imaging with deep learning holds promise for non-invasive molecular profiling and aiding precision medicine in glioblastoma.

5. Conclusion

This study evaluated advanced physiological MRI sequences for non-invasive prediction of MGMT promoter methylation status in IDH-wildtype glioblastoma and demonstrated that ASL and ADC offer complementary information that substantially improves predictive performance. The combined ASL+ADC 3D CNN model achieved the highest accuracy and discriminative ability, outperforming both single-sequence models and a conventional T2_FLAIR baseline. These findings highlight the value of integrating perfusion- and diffusion-based imaging for molecular phenotype estimation and support the potential clinical utility of advanced MRI–based deep learning tools in guiding treatment planning for GBM.

Future research should extend these results by incorporating additional data modalities, such as clinical variables or multi-plane imaging, and by exploring more diverse model archi-

tectures to enhance generalizability. Continued development of multimodal, physiologically informed deep learning frameworks may further advance non-invasive biomarker prediction and precision neuro-oncology.

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