Letter to the Editor

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Response to "Medical Statistics Unlock the Gateway to Further Research: Using Deep Learning to Predict CDKN2A/B Homozygous Deletion in Isocitrate Dehydrogenase-Mutant Astrocytoma"

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We have carefully reviewed the Letter for our recent article by Takahashi et al. [1] with great interest. In short, the comments highlight the constraints of linear-based classifications such as logistic regressions (in strict terms, logistic regression uses a logistic function rather than a linear equation), which we employed in our study to predict CDKN2A/B homozygous deletion in IDH-mutant astrocytomas using qualitative and quantitative imaging features. They further suggest the potential benefits of non-linear processing with deep learning, which could provide insights beyond what linear processing can offer. While we acknowledge the promising results of deep learning in neuro-oncology imaging, we would like this opportunity to discuss several limitations of deep learning, drawing from our own experience, and to explain why logistic regression is a better approach for our current study. Moreover, we would like to raise a question regarding the proportion of CDKN2A/B homozygous deletion in IDH-mutant astrocytomas, as presented in several articles.

First, when constructing a classification model with deep learning in a relatively small dataset without true external validation, there is a notable risk of overestimating the performance. Thus, the results should be interpreted with caution [1]. The use of a small training dataset may lead to overfitting of the model, particularly when dealing with complex deep learning models with various hyperparameters [2]. While cross-validation or split-sample validations are well-known internal validation methods commonly used for preliminary evaluation of model performance, they cannot replace external validation, which is crucial for verifying an overparameterized classification model [1,3]. In contrast, a logistic regression model, as an extension of the linear model, is less prone to overfitting and typically results in better generalizability [4]. Therefore, as our study has a data imbalance (only 13.6% of patients exhibit CDKN2A/B homozygous deletion among a total of 88 IDH-mutant astrocytoma patients) [5], logistic regression is a more suitable approach. Additionally, utilizing visual transformers may not be advisable in the context of comparatively rare tumor types in neuro-oncology. This is because visual transformers require a larger amount of data and high memory requirements, even much more than convolutional neural networks [6].

Another advantage of logistic regression is its interpretability, which aligns with the primary objective of our study to provide simple imaging information that will directly aid neuroradiologists in real-world practice. In cases where interpretability is crucial, logistic regression models yield straightforward and easily interpretable results, setting them apart from deep learning approaches [7], which is well-known for its "black box" nature, despite efforts to improve its interpretability or explainability [8,9].

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Furthermore, our imaging results, such as infiltrative pattern, maximal diameter, and higher cerebral blood volume, which indicate a higher probability of CDKN2A/B homozygous deletion in IDH-mutant astrocytomas, are simple and intuitive, and can be directly applied in clinical practice.

Third, multivariable logistic regression involves the assumption that all of the explanatory variables are independent of each other. In our study, we assessed the interrelation of imaging features, using variance inflation factor (VIF) to detect multicollinearity between the variables (all variables showed a VIF < 10 in our study) [5].

Lastly, the data imbalance of CDKN2A/B homozygous deletion in IDH-mutant astrocytomas is inevitable. The reported frequencies of CDKN2A/B homozygous deletions using various datasets range from 0%–12% in histological grade 2, 6%–20% in histological grade 3, and 16%–34% in histological grade 4 [10]. Moreover, the reported frequency of CDKN2A/B homozygous deletion in all IDH-mutant astrocytomas ranges from 11%–13.8% [11-13]. A recent systematic review of IDH-mutant gliomas reported a median incidence of CDKN2A/B homozygous deletion of 22% across studies [10]. In our study encompassing 88 IDH-mutant astrocytoma patients, only 13.6% of patients exhibited CDKN2A/B homozygous deletion [5]. Consistently, a recent pathology article utilized the Cancer Genome Atlas (TCGA) dataset, where 31 out of 224 IDH-mutant astrocytoma patients (13.8%) had CDKN2A/B homozygous deletion, which aligned with this reported frequency [11]. However, in the recent articles on radiomics and/or deep learning using the TCGA dataset, 111 out of 234 patients (47.4%) exhibited CDKN2A/B homozygous deletion among IDH-mutant astrocytomas [14,15]. In our view, this proportion appears considerably higher than other reports using the TCGA dataset. To validate this, we examined the Supplementary Data provided in these articles [14,15]. Unfortunately, we could not find any information on the CDKN2A/B homozygous deletion status in the mentioned TCGA dataset. Hence, we gently suggest the authors from the previous articles [14,15] to collaborate with other experts, such as neuropathologists or bioinformaticians, to present the detailed molecular information from the TCGA dataset.

Although we have experience in deep learning, we do not believe that deep learning can be a "silver bullet" to all of the questions encountered in neuro-oncology imaging. Logistic regression, despite its simplicity and conventional nature, remains a potent statistical tool with distinct advantages, especially in rare neuro-oncology tumors. Due to the inevitable limitation of our study, that is, the small dataset as well as data imbalance, we consider our current results as a "work in progress". We emphasize that future multicenter validation is mandatory to validate our findings. Finally, we would like to thank the reviewers for their interest and insightful comments on our article.

Conflicts of Interest

Kyunghwa Han, the Statistical Consultant of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. All authors have declared no conflicts of interest.

Author Contributions

Conceptualization: all authors. Data curation: Yae Won Park. Formal analysis: Yae Won Park. Investigation: Yae Won Park. Methodology: Kyunghwa Han. Project administration: Yae Won Park. Resources: Se Hoon Kim. Software: Yae Won Park. Supervision: Se Hoon Kim. Validation: Yae Won Park. Visualization: Yae Won Park. Writing—original draft: all authors. Writing—review & editing: all authors.

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