Letter to the Editor

eISSN 2005-8330
https://doi.org/10.3348/kjr.2023.0925
Korean J Radiol 2023;24(12):1303-1305

Korean Journal of Radiology
KJR

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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Keywords: Isocitrate dehydrogenase (IDH); Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B); Medical statistics; Deep learning; Machine learning

We read with great interest the article entitled "Qualitative and Quantitative Magnetic Resonance Imaging Phenotypes May Predict CDKN2A/B Homozygous Deletion Status in Isocitrate Dehydrogenase-Mutant Astrocytomas: A Multicenter Study" by Park et al. [1], which used a multivariable logistic regression model to predict cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) homozygous deletion status in isocitrate dehydrogenase (IDH)-mutant astrocytoma using preoperative magnetic resonance imaging (MRI). The authors utilized multiple MRI sequences, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and three-dimensional post-contrast T1-weighted images, as well as diffusion-weighted imaging and dynamic susceptibility contrast imaging. These data were collected for 88 patients (12 with CDKN2A/B homozygous deletion, 76 without). The authors derived qualitative MRI features including tumor location, involvement with the surrounding tissue, and MRI findings.

In addition to these qualitative factors, quantitative factors such as maximum diameter, volume, apparent diffusion coefficient, and normalized cerebral blood volume (nCBV) were automatically analyzed using dedicated software. The multivariable logistic regression model with backward elimination revealed three independent risk factors for CDKN2A/B homozygous deletion status: the presence of an infiltrative pattern, larger maximal diameter, and an nCBV > 95th percentile. The model achieved outstanding performance with an area under the receiver operating characteristic curve (AUC-ROC) of 0.83 (95% confidence interval, 0.72–0.91).

As Park et al. [1] mentioned, the comprehensive evaluation of the qualitative and quantitative MRI features helps predict CDKN2A/B homozygous deletion status in IDH-mutant astrocytoma. We recognize, in particular, that one strength of that study was their variable selection for input into the multivariable logistic regression model using three statistical methods: univariable analysis, calculation of variance inflation factor, and backward elimination.

These statistical methods are pivotal processes for addressing multicollinearity. Multicollinearity is a condition in which there is an approximately linear relationship between two or more independent variables. Preventing multicollinearity avoids the decrease in precision that results from the interdependence of variables in the multivariable logistic regression model [2].

We argue that the meticulous feature selection in that study constitutes a crucial approach in medical statistics. However, their statistical analysis has two concerning pitfalls. First, little attention was paid to the interrelation of MRI features in the multivariable logistic regression analysis. A multivariable logistic regression assumes that

Received: September 19, 2023 **Accepted:** September 25, 2023
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all of the explanatory variables are independent of each other. In clinical practice, a patient with multiple MRI risk features can be at interrelation-associated risk of CDKN2A/B homozygous deletion. Second, linear regression-based classification, such as with univariable and multivariable logistic regression models, is sometimes a limitation [3]. This is because non-linear processing may provide the opportunity to gain new insights into characteristic features beyond what linear processing can offer [4].

Deep convolutional neural networks (DCNNs), which combine a series of linear and non-linear processing layers, can analyze multiple datasets without addressing multicollinearity or performing subsequent feature selection [4]. Gao et al. [5] achieved an AUC-ROC of 0.943 (0.815–0.993) using a machine learning model combining DCNN features with radiomics features for predicting CDKN2A/B homozygous deletion status in IDH-mutant astrocytoma using CE-T1WI and T2FLAIR. Zhang et al. [6] also achieved an AUC-ROC of 0.9704 with a ConvNeXt-based fused multi-sequence network model using four different MRI sequences. In addition to these two recent studies, new deep learning techniques have been investigated by incorporating a wider range of clinical and imaging data for paying attention to the interrelations.

The development of effective multimodal fusion approaches is becoming increasingly important to capture features of complex diseases [7]. For example, a deep learning model with a cross-attention mechanism extracts the correlated features between MRI sequences and electronic health records [8]. Another example is the proposed variable Vision Transformer (vViT), in which a multi-head attention mechanism integrates multiple MRI and other relevant datasets [9]. These deep learning techniques are capable of relating MRI sequences to clinical information and can facilitate the development of a comprehensive model that Park et al. [1] aimed to achieve for guiding treatment decisions and predicting prognosis of CDKN2A/B homozygous deletion status in IDH-mutant astrocytoma. On the other hand, we should recognize that deep learning features challenges not present in medical statistics. The results obtained through deep learning are not always reproducible, even if produced under the same conditions, because of complicated non-linear processing (i.e., frequent calculations by activation functions) [10]. Thus, medical statistics versus deep learning may pose a trade-off between technical reproducibility and feature interrelations.

In conclusion, medical statistics is a specialized tool for comparative verification that opens the door for further research using deep learning. We argue that Park et al. [1] indeed knocked on the gateway to further research aimed at predicting the prognosis of CDKN2A/B homozygous deletion status in IDH-mutant astrocytoma. We deeply appreciate the authors' contribution to this field and are grateful for the opportunity to discuss their paper.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kengo Takahashi, Takuma Usuzaki. Investigation: all authors. Project administration: Kengo Takahashi, Takuma Usuzaki. Supervision: Kengo Takahashi, Takuma Usuzaki. Writing—original draft: all authors. Writing—review & editing: all authors.

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Funding Statement

None

REFERENCES

1. Park YW, Park KS, Park JE, Ahn SS, Park I, Kim HS, et al. Qualitative and quantitative magnetic resonance imaging phenotypes may predict CDKN2A/B homozygous deletion status in isocitrate dehydrogenase-mutant astrocytomas: a multicenter study. *Korean J Radiol* 2023;24:133-144.
2. Alin A. Multicollinearity. *Wiley Interdiscip Rev Comput Stat* 2010;2:370-374.
3. Chan JYL, Leow SMH, Bea KT, Cheng WK, Phoong SW, Hong ZW, et al. Mitigating the multicollinearity problem and its machine learning approach: a review. *Mathematics* 2022;10:1283.
4. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015;521:436-444.
5. Gao J, Liu Z, Pan H, Cao X, Kan Y, Wen Z, et al. Preoperative discrimination of CDKN2A/B homozygous deletion status in isocitrate dehydrogenase-mutant astrocytoma: a deep learning-based radiomics model using MRI. *J Magn Reson Imaging* 2023 Aug 9. [Epub]. https://doi.org/10.1002/jmri.28945

6. Zhang L, Wang R, Gao J, Tang Y, Xu X, Kan Y, et al. A novel MRI-based deep learning networks combined with attention mechanism for predicting CDKN2A/B homozygous deletion status in IDH-mutant astrocytoma. *Eur Radiol* 2023 Aug 8. [Epub]. https://doi.org/10.1007/s00330-023-09944-y
7. Rudin C. Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead. *Nat Mach Intell* 2019;1:206-215.
8. Sun X, Guo W, Shen J. Toward attention-based learning to predict the risk of brain degeneration with multimodal medical data. *Front Neurosci* 2023;16:1043626.
9. Usuzaki T. Splitting expands the application range of vision transformer -- variable vision transformer (vVit). arXiv:2211.03992 [Preprint]. [posted Nov 8, 2022; revised Mar 25, 2023; cited Sep 15, 2023]. https://arxiv.org/abs/2211.03992
10. Gil IS, Dong L. Real world large scale recommendation systems reproducibility and smooth activations. arXiv:2202.06499 [Preprint]. [posted Feb 14, 2022; cited Sep 15, 2023]. https://arxiv.org/abs/2202.06499