

Clinical and Imaging Characteristics of Supratentorial Glioma with *IDH2* Mutation

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Statement

Funding This work was supported by JSPS KAKENHI Grant Number 22K07746, 21K15826, 21K15623, 21K20834.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Institutional Review Board approval was obtained. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (G1124, R2088, R3262).

Informed Consent The requirement for informed consent was waived by the Institutional

Review Board.

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Abstract

Purpose The rarity of *IDH2* mutations in supratentorial gliomas has led to gaps in understanding their radiological characteristics, potentially resulting in misdiagnosis based solely on negative *IDH1* immunohistochemical staining. We aimed to investigate the clinical and imaging characteristics of *IDH2*-mutant gliomas.

Methods We analyzed imaging data from adult patients with pathologically confirmed diffuse lower-grade gliomas and known *IDH1/2* alteration and 1p/19q codeletion statuses obtained from the records of our institute (January 2011 to August 2022, Cohort 1) and The Cancer Imaging Archive (TCIA, Cohort 2). Two radiologists evaluated clinical information and radiological findings using standardized methods. Furthermore, we compared the data for *IDH2*-mutant and *IDH*-wildtype gliomas. Multivariate logistic regression was used to identify the predictors of *IDH2* mutation status, and receiver operating characteristic curve analysis was employed to assess the predictive performance of the model.

Results Of the 20 *IDH2*-mutant supratentorial gliomas, 95% were in the frontal lobes, with 75% classified as oligodendrogliomas. Age and the T2-FLAIR discordance were independent predictors of *IDH2* mutations. Receiver operating characteristic curve analysis for the model using age and T2-FLAIR discordance demonstrated a strong potential for discriminating between *IDH2*-mutant and *IDH*-wildtype

gliomas, with an area under the curve of 0.96 (95% CI, 0.91–0.98, $P = .02$).

Conclusion A high frequency of oligodendrogliomas with 1p/19q codeletion was observed in *IDH2*-mutated gliomas. Younger age and the presence of the T2-FLAIR discordance were associated with *IDH2* mutations and these findings may help with precise diagnoses and treatment decisions in clinical practice.

Keywords Magnetic Resonance Imaging, Glioma, Isocitrate Dehydrogenase, T2-FLAIR Mismatch Sign

Abbreviations *IDH* = isocitrate dehydrogenase; IHC = immunohistochemical; LrGGs = lower-grade gliomas

Introduction

According to the latest edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), the presence of an isocitrate dehydrogenase (*IDH*) mutation is a fundamental genetic feature that characterizes a favorable prognosis [1]. Furthermore, with the advent of a dual inhibitor of mutant *IDH1* and *IDH2* enzymes, the detection of *IDH* mutations has become more clinically significant [2].

IDH2 is a mitochondrial homologue of *IDH1* that plays an important role in various cellular processes. Since both *IDH1* and *IDH2* mutations result in the production of the oncometabolite 2-hydroxyglutarate [3,4], the WHO classification and most current studies have combined them into the same molecular group. However, *IDH2* mutations in gliomas, especially supratentorial ones, are extremely rare compared to *IDH1*-R132H mutations [5,6]. Thus, it remains unclear whether the clinical and imaging features of *IDH1*-mutated and *IDH2*-mutated gliomas can be considered the same. Some studies have shown a higher frequency of 1p/19q codeletions in *IDH2*-mutated gliomas than in *IDH1*-mutated gliomas [5,6].

Although routine genetic testing is mandatory for diagnosis according to the 2021 WHO classification, it could be difficult to cover all cases in practice because of financial and technical issues. Immunohistochemical (IHC) staining is widely used as an important surrogate for genetic testing but is not completely accurate [7]. In particular, IHC analysis fails to detect rarer *IDH* mutations other than *IDH1*-

R132H (such as *IDH1* non-canonical mutations or *IDH2* mutations) and may misdiagnose tumors with these mutations as *IDH*-wildtype.

While the association between *IDH* mutations and imaging features has been elucidated irrespective of the status of 1p/19q [8-16], reports on gliomas with *IDH2* mutations are limited due to their rarity, and no studies have focused on imaging findings [5,6,17,18]. Our aim was two-fold. First, we evaluated the clinical and imaging characteristics of *IDH2*-mutant gliomas. Second, we used these clinical features and imaging biomarkers to create a useful model for differentiating *IDH2*-mutant gliomas from *IDH*-wildtype gliomas, which are similarly negative on IDH1-R132H stains.

Materials and Methods

Study design

The institutional review board of our institution approved this retrospective observational study (G1124, R2088, R3262) and waived the requirement for informed consent. This study comprised two groups—Cohorts 1 and 2. (Fig. 1). Initially, we retrospectively reviewed pathologically confirmed diffuse gliomas with known *IDH* alterations and 1p/19q co-deletion status at our institute between January 2011 and August 2022 (Cohort 1). The inclusion criteria were as follows: 1) pathologically confirmed lower-grade gliomas (LrGGs; adult-type diffuse gliomas without morphological evidence of necrosis or vascular proliferation, equivalent to grade II/III gliomas according to the 2016 WHO classification); 2) known *IDH* status by

sequencing; 3) known 1p/19q status; and 4) age >18 years. Exclusion criteria were as follows: 1) *IDH1*-mutant glioma (astrocytoma or oligodendroglioma); 2) absence of preoperative images or insufficient sequences for evaluation; 3) atypical location (posterior fossa or spine); and 4) history of brain surgery or radiotherapy. We reviewed preoperative MR images acquired from two datasets containing both genetic and imaging information on gliomas, including *IDH2*-mutant tumors—The University of California San Francisco Preoperative Diffuse Glioma MRI Dataset (UCSF-PDGM, n = 501 [Data Citation 1]) and The Cancer Genome Atlas Low Grade Glioma Collection (TCGA-LGG, n = 199 [Data Citation 2]). The inclusion and exclusion criteria were the same as those described above (Cohort 2). IHC results were not available for Cohort 2. We did not compare *IDH2*-mutant gliomas with *IDH1*-mutant gliomas because even if we could show that there was no statistical difference in the imaging characteristics of these two types of tumors, we would not immediately conclude that they were similar. Instead, emphasis was placed on differentiating *IDH2*-mutant tumors from *IDH*-wildtype tumors, which can be difficult to distinguish from *IDH2*-mutant tumors clinically.

Imaging acquisition

Patients in Cohort 1 were scanned using 3T scanners (Siemens Prisma, Skyra, Trio, Vida, Erlangen, Germany) and underwent standardized protocols for T2-weighted and T2-weighted FLAIR MR imaging: T2-weighted 2D axial: TR, 3200ms; TE, 79 ms; section thickness = 3 mm; matrix, 406 × 448; FOV, 19.9 × 22.0 cm; T2-weighted FLAIR 2D axial: TR, 12000ms; TE, 100ms; Inversion time (TI), 2760 ms; section

thickness = 3 mm; matrix, 280×320 ; FOV, 19.2×22.0 cm. Patients in Cohort 2 were scanned using various scanners. Sequence parameters are as follows: T2WI: TR, 883-6000 ms; TE, 16-120 ms; section thickness, 1.2-5 mm; matrix, 192×256 - 512×512 ; FOV, 18.0×22.0 - 25.6×25.6 cm. FLAIR: TR, 5700-11000 ms; TE, 94-155 ms; TI, 1650-2800 ms; section thickness, 1.2-5 mm; matrix, 160×256 - 348×348 ; FOV, 16.9×24.0 - 25.6×25.6 cm. Detailed information about the MR machines and other imaging parameters of TCIA are available in the following references [19,20].

Image analysis

Brain MR scans were independently reviewed by two neuroradiologists (S.I. and A.S., with 7 and 16 years of experience in neuroradiology, respectively). Preoperative CT images were also obtained for Cohort 1.

We analyzed the following imaging features: location (primary lobe), gliomatosis cerebri, multicentricity (skip lesions not connected by T2/FLAIR-hyperintense signal), corpus callosal invasion, smooth margin, dominant cortical involvement, sinuous, wave-like intratumoral-wall (SWITW) sign, the T2-FLAIR mismatch sign, the T2-FLAIR discordance, contrast enhancement, ring-like enhancement, and calcification/paramagnetic susceptibility. The SWITW sign, recently proposed as a specific finding of oligodendroglioma [15], was identified by the presence of irregular, wave-like intertumoral wall and hyperintensity core on T2WI (Fig. 2). The T2-FLAIR mismatch sign was proposed by Patel et al. as a high specific indicator of *IDH*-mutant astrocytoma (harboring *IDH* mutation but not 1p/19q codeletion) [21]. In addition to the original T2-FLAIR mismatch sign, we evaluated T2-FLAIR discordance in this study. The

T2-FLAIR discordance was judged present if the gliomas had an intratumoral component which was hyperintense on T2-weighted images and showed corresponding matching FLAIR suppression [16]. Even if there were just little areas of discordance inside the tumor, it was regarded positive for the “T2-FLAIR discordance” pattern, but a no discordance (T2-FLAIR full matched) pattern was considered negative. Imaging findings similar to this have been reported previously as a feature that might predict the presence of *IDH* mutation [22]. Although small cysts do not meet the criteria for the original “T2-FLAIR mismatch sign” [21], spongy or honeycomb-like structures, reflecting clusters of tiny cysts with septa, were considered positive for the T2-FLAIR discordance (Fig 2). These variables were evaluated when both T2WI and FLAIR images available for reference. Additionally, we also assessed the presence of calcification/paramagnetic susceptibility in cases where T2*- or susceptibility-weighted imaging was available for reference [23]. For Cohort 1, calcification and hemorrhage were independently evaluated with reference to CT images. Any disagreement was solved by mutual consensus.

Histopathology and Molecular classifications

All surgical tissue samples were histopathologically diagnosed according to the 2016 WHO classification system. For Cohort 1, IHC staining was performed using an antibody specific for the mutant IDH1-R132H protein (Dianova GmbH, Hamburg, Germany). Hotspot mutations in *IDH1/2* were detected using Sanger sequencing. Additionally, 1p/19q codeletion was examined via fluorescence in situ hybridization (FISH) or multiplex ligation-dependent probe amplification [24]. In Cohort 2, histopathological diagnoses and

molecular information were referenced from a study by Ceccarelli et al [25]. *IDH* mutation subtype was characterized using a capture-based targeted next-generation DNA sequencing panel (UCSF500) in UCSF-PDGM [26] and through whole-exome sequencing in TCGA-LGG [25]. Furthermore, the presence of 1p/19q codeletion was assayed via FISH in UCSF-PDGM and confirmed using SNP Array 6.0 (Affymetrix, Santa Clara, California, USA) in TCGA-LGG [25].

Statistical analysis

We compared the prevalence of imaging features between *IDH2*-mutant and *IDH*-wildtype LrGGs using Fisher's exact test or the chi-square test. Multivariate logistic regression analysis was performed to identify the independent indicators of *IDH2* mutations. Receiver operating characteristic curves were generated, and the area under the curve (AUC) was calculated to estimate the diagnostic potential of the prognostic factors for discriminating between *IDH2*-mutant and *IDH*-wildtype gliomas. Statistical significance was set at $P < .05$ for all tests. Interobserver agreement for assessing qualitative features was expressed using the κ coefficients, as follows: <0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; and 0.81–1.00, excellent. All statistical analyses and modeling were conducted using JMP Pro 16.1.0 (SAS Institute) on the Microsoft Windows 10 Pro 64-bit software.

Results

Fifty-nine cases (12 *IDH2*-mutant and 47 *IDH*-wildtype LrGGs) were included in cohort 1, and fifty-four cases (8 *IDH2*-mutant and 46 *IDH*-wildtype LrGGs) were included in Cohort 2. In Cohort 1, 11 patients

with *IDH2*-mutant gliomas and 43 patients with *IDH* wildtype gliomas showed negative results upon IDH1-R132H IHC staining, which indicated that most *IDH2*-mutant gliomas could be determined as wildtype based solely on IHC results.

A total of 20 cases with *IDH2*-mutant LrGGs were identified (Table 1). The median patient age was 35 years (interquartile range, 30.8–46.5 years). The R172K *IDH2* mutation was the most frequent (13 cases), followed by R172W and R172S (two cases each) and R172M, I142T, and A172T (one case each). Of the 20 cases, 75% (n = 15) were oligodendrogliomas with 1p/19q codeletion and 25% (n=5) were astrocytomas with 1p/19q intact. Nineteen tumors (95%) were located in the frontal lobes, with the remaining located in the temporal lobe. There were 10 cases each of grade II and III tumors. The T2-FLAIR mismatch sign was negative in all cases. On the other hand, the T2-FLAIR discordance was found in 16 cases (84.2%) for *IDH2*-mutant gliomas and in 8 cases (9%) for *IDH*-wildtype ones. Representative cases are shown in Figure 3.

Univariate analysis revealed associations of age ($P < .001$), tumor location ($P < .001$), smooth margins ($P < .001$), the absence of a gliomatosis cerebri pattern ($P = .02$), SWITW sign ($P < .001$), and T2-FLAIR discordance ($P < .001$) with *IDH2* mutations (Table 2). The results for Cohorts 1 and 2 are presented in Table 2. Multivariate logistic regression identified age (OR 0.93 [0.87–0.99], $P = .04$) and T2-FLAIR discordance (OR 43.6 [3.16–603.3], $P = .005$) as independent predictors of *IDH2* mutation. Receiver operating characteristic curve analysis developed using age and T2-FLAIR discordance showed

discriminatory potential between *IDH2*-mutant and *IDH*-wildtype gliomas, with an area under the curve of 0.96 (95% CI, 0.91–0.98, $P = .02$) (Fig 4).

Interobserver agreement on each variable was good-to-excellent, except for dominant cortical involvement (moderate; $\kappa = 0.53$). The κ values are shown in Table 3.

Discussion

We evaluated the clinical and radiological features of *IDH2*-mutant supratentorial gliomas. These tumors predominantly occurred in the frontal lobes of young adults, with 75% of tumors being oligodendrogliomas exhibiting 1p/19q codeletions. Radiologically, the *IDH2*-mutant tumors showed a significant association with T2-FLAIR discordance, which could aid in their diagnosis, especially considering the potential for misclassification based on IHC results.

Previous studies have indicated a higher incidence of oligodendrogliomas in *IDH2* mutant tumors than in those with *IDH1* mutations. For instance, Appay et al. demonstrated 1p/19q co-deletion in 91% of *IDH2*-mutant gliomas, in contrast to 48% in *IDH1*-mutant gliomas [5], consistent with our findings. The prevalence of young-onset cases and frontal lobe localization in our study further supports the high frequency of oligodendrogliomas harboring 1p/19q codeletion.

Our analysis revealed that *IDH2*-mutant supratentorial gliomas often exhibited smooth margins and the SWITW sign, consistent with imaging characteristics typically observed in oligodendrogliomas.

These results suggest a similarity in radiological features between *IDH2*-mutant and *IDH1*-mutant gliomas, particularly those with 1p/19q co-deletion. Although several previous studies have demonstrated an association between 1p/19q codeletion and indistinct tumor borders, these studies compared gliomas with the 1p/19q codeletion to those without the 1p/19q deletion; *IDH*-mutant astrocytomas in the current classification, which are known to be more clearly demarcated tumors [27-29]. It has been shown that tumors with sharp borders are more frequently *IDH*-mutant, whereas tumors with indistinct borders are more frequently *IDH*-wildtype [29], which appears to support our results.

In the present study, SWITW sign were more commonly observed in *IDH2* mutant tumors. The SWITW sign was originally proposed as an imaging biomarker for oligodendroglioma with 1p19q codeletion [15], and thought to reflect the distinctive growth pattern of oligodendrogliomas: the high cell density and compact growth behavior in the cortex and loosely diffuse infiltration in the subcortical white matter. We speculate that the high prevalence of oligodendrogliomas in *IDH2*-mutant tumors is directly attributable to the association of the SWITW sign.

Although gliomatosis cerebri was not an independent predictor in the multivariate logistic analysis, its frequency seemed to differ between the two groups: *IDH2*-mutant and *IDH*-wildtype gliomas. The term "gliomatosis cerebri" has long since disappeared from the WHO classification, from an imaging perspective, it remains an important part of diffuse glioma as a very characteristic pattern. One study that classified the molecular subgroups of gliomatosis showed that tumors presenting with the gliomatosis

pattern often belonged to the anaplastic astrocytoma, *IDH* wildtype group, while the *IDH* mutant group, especially those with 1p19qcode1, was extremely rare [30]. This tendency supports our results, and the presence or absence of gliomatosis cerebri on preoperative imaging may have some value in differentiating *IDH* mutation in gliomas.

No cases showing T2-FLAIR mismatch signs were observed in either *IDH2*-mutant or *IDH*-wildtype gliomas. On the other hand, our study showed that *IDH2*-mutant tumors have a significantly higher frequency of T2-FLAIR discordance when compared to *IDH*-wildtype tumors. The T2-FLAIR mismatch sign was proposed as a highly specific indicator of *IDH*-mutant lower-grade astrocytoma in 2017 [21]. In utilizing this sign for gliomas diagnosis, it is crucial to adhere to the specific inclusion/exclusion criteria outlined by Jain et al [31]. For example, when the tumor exhibits heterogeneity on T2WI or includes areas of contrast enhancement, this sign may not be applicable. Conversely, Juratli et al. highlighted the potential to exclude *IDH*-wildtype tumors based on the presence of the T2-FLAIR mismatch sign within certain subregions of gliomas, even in cases of T2WI heterogeneity and contrast enhancement [22]. Indeed, reports have shown that oligodendrogliomas contain such textures in certain regions [31-33]. This “relaxed” version of the T2-FLAIR mismatch sign has also been identified as predictive of *IDH* mutations in the WHO grade 4 astrocytomas (termed the partial T2-FLAIR mismatch sign) [34] as well as LrGGs [16]. Our study identified T2-FLAIR discordance in some *IDH2*-mutant supratentorial gliomas, including oligodendrogliomas, albeit less frequently in *IDH*-wildtype LrGGs. Notably, this feature was significantly

more prevalent in *IDH2*-mutant gliomas, potentially aiding in their differentiation from *IDH*-wildtype LrGGs. Pathologically, the classic T2-FLAIR mismatch sign is considered indicative of microcystic formation or myxomatous changes [35,36]. Pathologic studies have reported the presence of mucin-filled microcystic cavities in oligodendrogliomas with *IDH* mutations and 1p/19q deletions [37], and it is possible that these pathologic changes are similarly reflected as T2-FLAIR discordance, but further pathologic-radiologic association studies are needed.

We developed a model using patient age and the T2-FLAIR discordance to differentiate *IDH2*-mutant gliomas from *IDH*-wildtype gliomas, which demonstrated good diagnostic performance, although we were unable to establish a validation cohort due to the small number of cases. MRI findings may suggest the possible presence of a rarer *IDH* mutation in the tumor, even if the IHC results misclassify it as *IDH*-wildtype. According to the 2021 WHO classification, genetic testing is recommended when IDH1-R132H IHC staining is negative; however, costs and technological issues make it difficult to perform it in most cases. Furthermore, genetic information is not entirely specific. Patel et al. reported that imaging analysis can correct the diagnosis of gliomas misdiagnosed by FISH results [23]. We believe that our results also support the notion that radiogenomics has the potential to overcome some of the limitations of histologic assessment [38]. Especially in facilities where genetic sequencing results are known later than morphological and immunohistochemical diagnoses, it may be advisable to note in the radiology report the possibility of *IDH* mutation based on the presence or absence of intratumoral T2-FLAIR discordance and

to use this information in deciding the treatment strategy.

This study had several limitations. First, this was a retrospective study with a relatively small sample size. Larger datasets are required to validate the preliminary results. Second, images from different facilities and scanners were evaluated. However, there were no marked differences in the results between Cohorts 1 and 2, suggesting reproducibility with respect to qualitative assessment, regardless of the acquisition method or equipment. Third, *IDH2*-mutant gliomas are a heterogeneous group (mixed tumor types, oligodendrogliomas, and astrocytomas), and *IDH2*-mutant astrocytomas are extremely rare, which makes the evaluation of their inherent features difficult. Finally, we did not evaluate gliomas with non-canonical *IDH1* mutations. This is because only one case with such a mutation was identified in Cohort 1; in that case, the preoperative images were insufficient for evaluation.

Conclusion

A high frequency of oligodendrogliomas with 1p/19q codeletion was observed in *IDH2*-mutated gliomas. Younger age and the presence of the T2-FLAIR discordance were associated with *IDH2* mutations. These combined clinical and radiological findings may be useful for discriminating *IDH*-wildtype gliomas.

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Data Citations

1. Calabrese E, Villanueva-Meyer J, Rudie J, et al. The University of California San Francisco
Preoperative Diffuse Glioma MRI (UCSF-PDGM). <https://doi.org/10.7937/TCIA.BDGF-8V37>.
2. Pedano N, Flanders AE, Scarpance L, et al. The Cancer Genome Atlas Low Grade Glioma Collection
(TCGA-LGG). <https://doi.org/10.7937/K9/TCIA.2016.L4LTD3TK>.

Table 1

Results of all 20 cases with *IDH2*-mutant gliomas.

No.	Cohort	Age	Sex	Tumor type	Histological grade	Mutation	IHC IDH1- R132H	FISH 1p/19q codeletion
1	1	24	M	OD	III	R172K	(–)	(+)
2	1	27	M	OD	II	R172K	(–)	(+)
3	1	34	F	OD	II	R172K	(–)	NA ^a
4	1	29	M	OD	II	R172K	(–)	(+)
5	1	42	M	OD	III	I142T	(+)	(+)
6	1	35	F	OD	III	R172K	(–)	NA ^a
7	1	30	M	OD	III	R172K	(–)	(+)
8	1	49	M	AC	III	R172M	(–)	(–)
9	1	69	M	AC	II	R172K	(–)	NA
10	1	68	M	OD	III	R172S	(–)	(–) ^a
11	1	39	M	OD	III	R172K	(–)	(–) ^a
12	1	38	M	OD	II	R172K	(–)	NA ^a
13	2	48	M	OD	II	R172K	NA	NA ^b
14	2	41	F	OD	III	R172S	NA	NA ^b
15	2	33	F	OD	II	R172W	NA	NA ^b
16	2	26	M	AC	II	R172K	NA	NA ^b
17	2	35	M	OD	III	R172W	NA	NA ^b
18	2	48	M	OD	II	R172K	NA	NA ^b
19	2	34	F	AC	II	R172K	NA	(–)
20	2	35	F	AC	III	A172T	NA	(–)

Note: IHC, immunohistochemistry; *IDH*, isocitrate dehydrogenase; FISH, fluorescence in situ

hybridization; OD, oligodendroglioma; AC, astrocytoma.

a 1p/19q codeletion confirmed via multiplex ligation-dependent probe amplification

b 1p/19q co-deletion was confirmed using SNP Array 6.0 (Affymetrix, Santa Clara, California, USA).

Table 2 Comparison of clinical and radiological findings between *IDH2*-mutant and *IDH*-wildtype glioma

All cases				Cohort 1			Cohort 2		
	<i>IDH2</i> mutant	<i>IDH</i> wildtype	<i>P</i>	<i>IDH2</i> mutant	<i>IDH</i> wildtype	<i>P</i>	<i>IDH2</i> mutant	<i>IDH</i> wildtype	<i>P</i>
N [†]	20	93		12	47		8	46	
Age (years (IQR))	35 (30.8–46.5)	60.0 (49.0–68.0)	<.001	36.5 (29.3–47.3)	63 (45.0–72.0)	<.001	35 (33.3–46.3)	57.5 (51.0–62.0)	<.001
Sex (male/female)	15/5	51/42	.13	10/2	27/20	.18	5/3	24/22	.71
Location			<.001			<.001			<.001
Frontal lobe	19 (95.0%)	24 (25.8%)		12 (100.0%)	15 (31.9%)		7 (87.5%)	9 (19.6%)	
Temporal lobe	1 (5.0%)	40 (43.0%)		0	17 (36.2%)		1 (12.5%)	23 (50.0%)	
Other	0	29 (31.2%)		0	15 (31.9%)		0	14 (30.4%)	
Gliomatosis cerebri	0	20 (21.5%)	.02	0	12 (25.5%)	.10	0	8 (17.4%)	.34
Multicentricity	1 (5.0%)	21 (22.6%)	.12	0	9 (19.1%)	.18	1 (12.5%)	12 (26.1%)	.66
Corpus callosal invasion	6 (30.0%)	23 (24.7%)	.59	3 (25.0%)	17 (36.2%)	.73	3 (37.5%)	6 (13.0%)	.12
Smooth margin	20 (100%)	49 (52.7%)	<.001	12 (100.0%)	26 (55.3%)	.005	8 (100.0%)	23 (50.0%)	.02
Dominant cortical involvement	17 (85.0%)	60 (64.5%)	.11	9 (75.0%)	23 (48.9%)	.19	8 (100.0%)	37 (80.4%)	.33
SWITW sign	11 (55.0%)	8 (8.6%)	<.001	7 (58.3%)	5 (10.6%)	.001	4 (50.0%)	3 (6.5%)	.006
T2-FLAIR mismatch sign	0	0	1.00	0	0	1.00	0	0	1.00
T2-FLAIR discordance	16 (84.2%) ^a	8 (9.0%) ^b	<.001	9 (75.0%)	6 (12.8%)	<.001	7 (100.0%) ^c	2 (4.8%) ^d	<.001
Contrast enhancement	8 (40.0%)	50 (53.8%)	.32	5 (41.7%)	27 (57.4%)	.35	3 (37.5%)	23 (50.0%)	.70
Ring-like enhancement	1 (5.0%)	19 (20.4%)	.19	1 (8.3%)	13 (27.7%)	.26	0	6 (13.0%)	.58
Calcification/paramagnetic susceptibility	5 (35.7%) ^e	16 (30.8%) ^f	.75	5 (41.7%)	15 (31.9%)	.52	0	1 (20.0%) ^g	1.00
Calcification	3 (25.0%) ^h	4 (8.5%) ⁱ	.14	3 (25.0%)	4 (8.5%)	.14	NA	NA	NA
Hemorrhage	4 (33.3%) ^h	12 (25.5%) ⁱ	.72	4 (33.3%)	12 (25.5%)	.72	NA	NA	NA

Data are presented as number (%) unless otherwise indicated

† N is the number of all subjects. However, the number of subjects differs where the following notes are given. a N=19, b N=89, c N=7, d N=42, e N=14, f N=52, g N=5, h N=12, I N=47.

Note: - *IDH*, isocitrate dehydrogenase; SWITW, sinuous, wave-like intratumoral wall

Table 3

Interobserver agreement for categorical variables.

Variable	κ value	95% CI
Location	0.91	(0.84–0.97)
Gliomatosis cerebri	0.77	(0.61–0.92)
Multicentricity	0.68	(0.51–0.86)
Corpus callosal invasion	0.79	(0.66–0.92)
Smooth margin	0.68	(0.54–0.82)
Dominant cortical involvement	0.53	(0.37–0.69)
SWITW sign	0.87	(0.74–0.99)
T2-FLAIR mismatch sign	1.00	(1.00–1.00)
T2-FLAIR discordance	0.77	(0.64–0.91)
Contrast enhancement	0.84	(0.74–0.94)
Ring-like enhancement	0.88	(0.76–1.00)
Calcification/paramagnetic susceptibility	0.83	(0.69–0.97)

SWITW; sinuous, wave-like intratumoral wall

Fig. 1

Flow chart. **a** Data from our institute; **b** Data from the Cancer Imaging Archive (TCIA) dataset.

Fig. 2

Areas with markedly high signal on T2-weighted images (**a**) show signal suppression on FLAIR images (**b**) (arrowhead), consistent with the T2-FLAIR discordance. Spongy or honeycomb-like structure (arrowhead), which show markedly high signal on T2-weighted images (**c**) and low signal with septa on FLAIR images (**d**) is also positive for this sign. However, a large cyst (arrow) does not meet the definition of this sign (**a**, **b**). It also should be noted that such signal attenuation on FLAIR images shown here is not consistent with classic T2-FLAIR mismatch signs. Case 7 is considered positive for the SWITW sign on T2-weighted images (**e**, **f**).

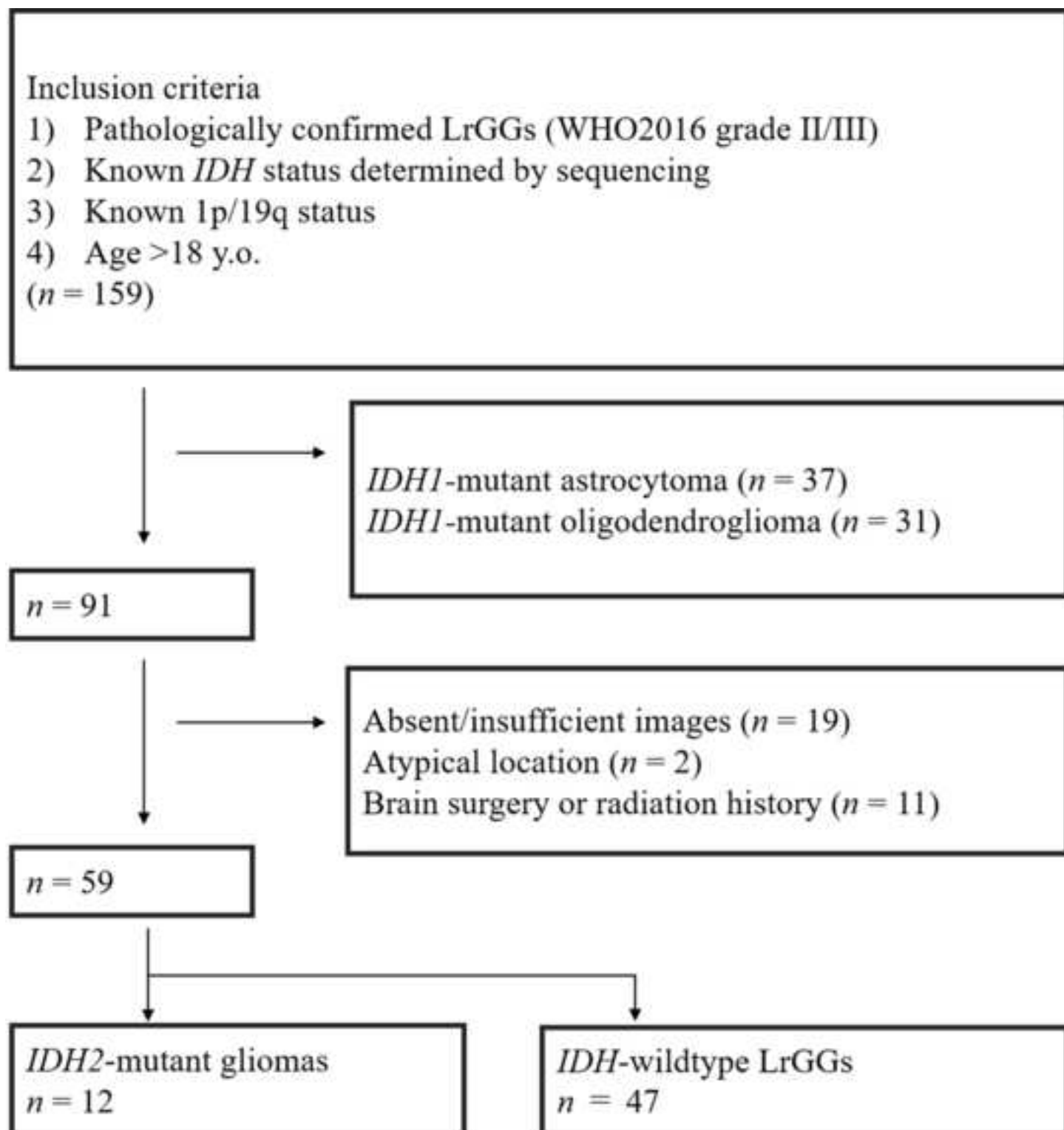
Fig. 3

Representative cases of *IDH2*-mutant gliomas (Case 2, a 27-year-old male. **a**; T2-weighted images, **b**; FLAIR images, **c**; contrast-enhanced T1-weighted images). The tumor is located in the left frontal lobe and shows cortical involvement. The lesion shows heterogeneous hyperintense signal on T2-weighted (**a**) and FLAIR (**b**) images and no contrast enhancement on contrast-enhanced T1-weighted (**c**) images. Arrowheads indicate areas of T2-FLAIR discordance.

Fig. 4

Receiver operating characteristic curve for the model developed using age and T2-FLAIR discordance to predict *IDH2* mutation status.

Fig.1a



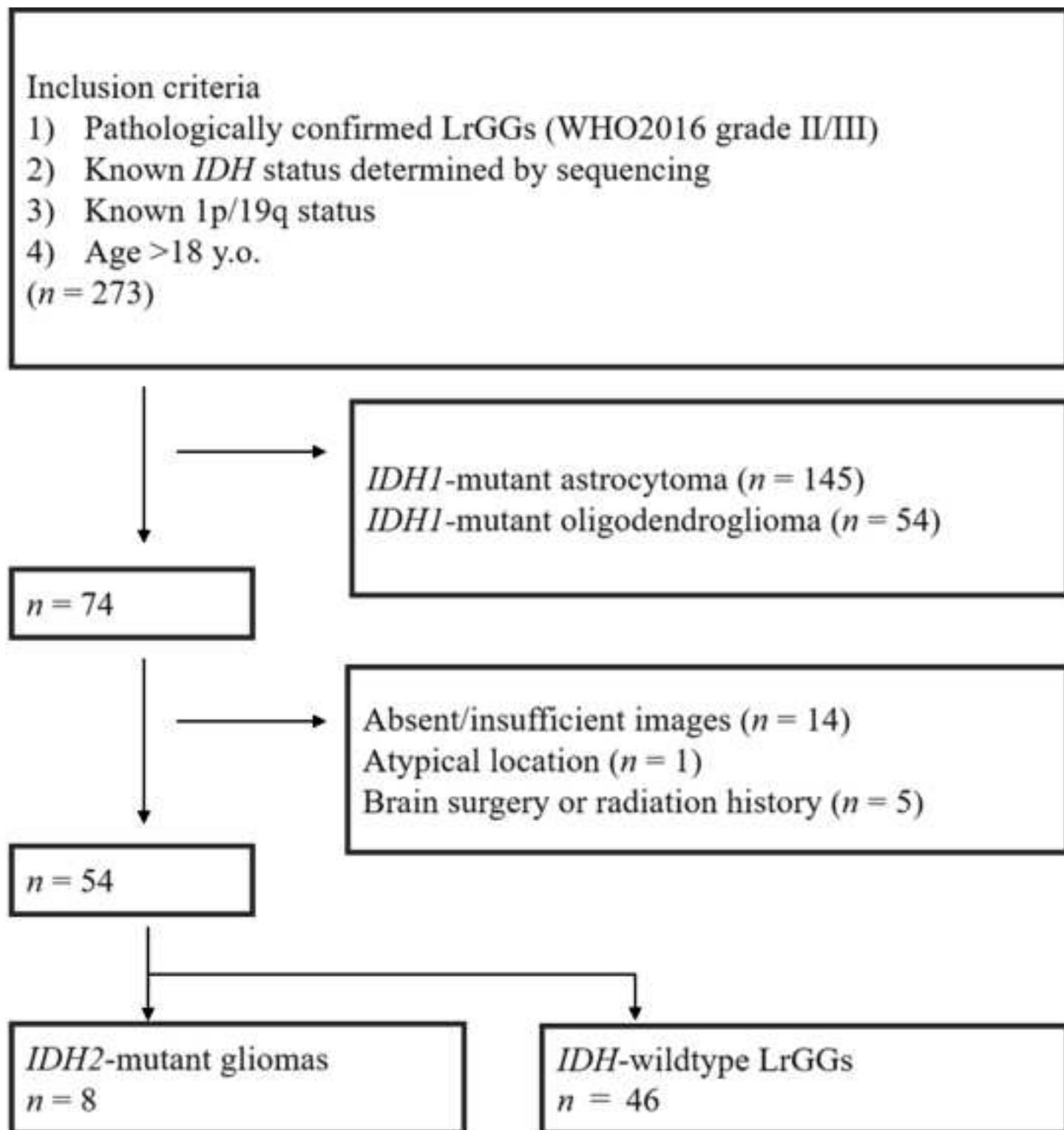


Fig. 4

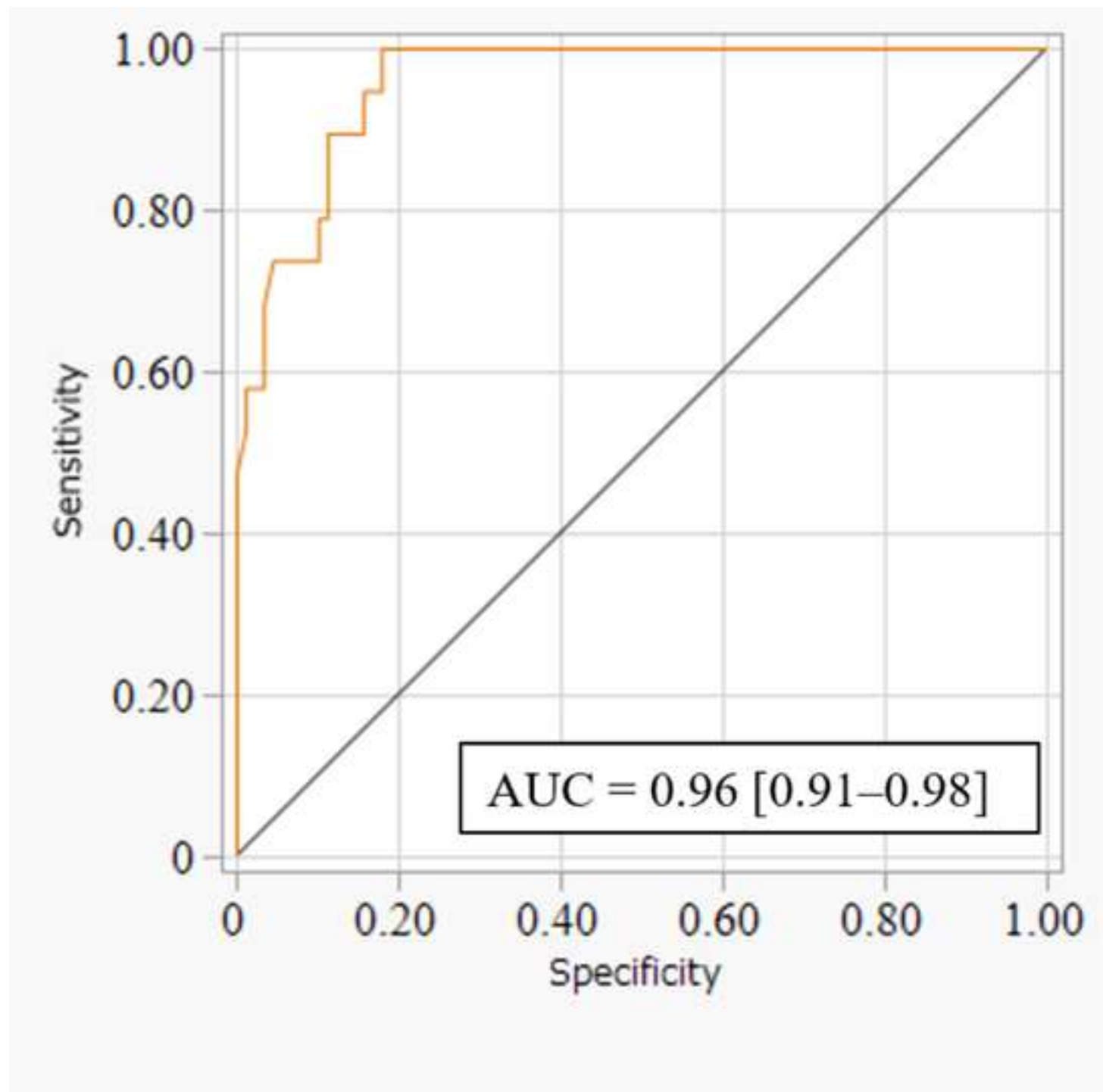


Fig.2a

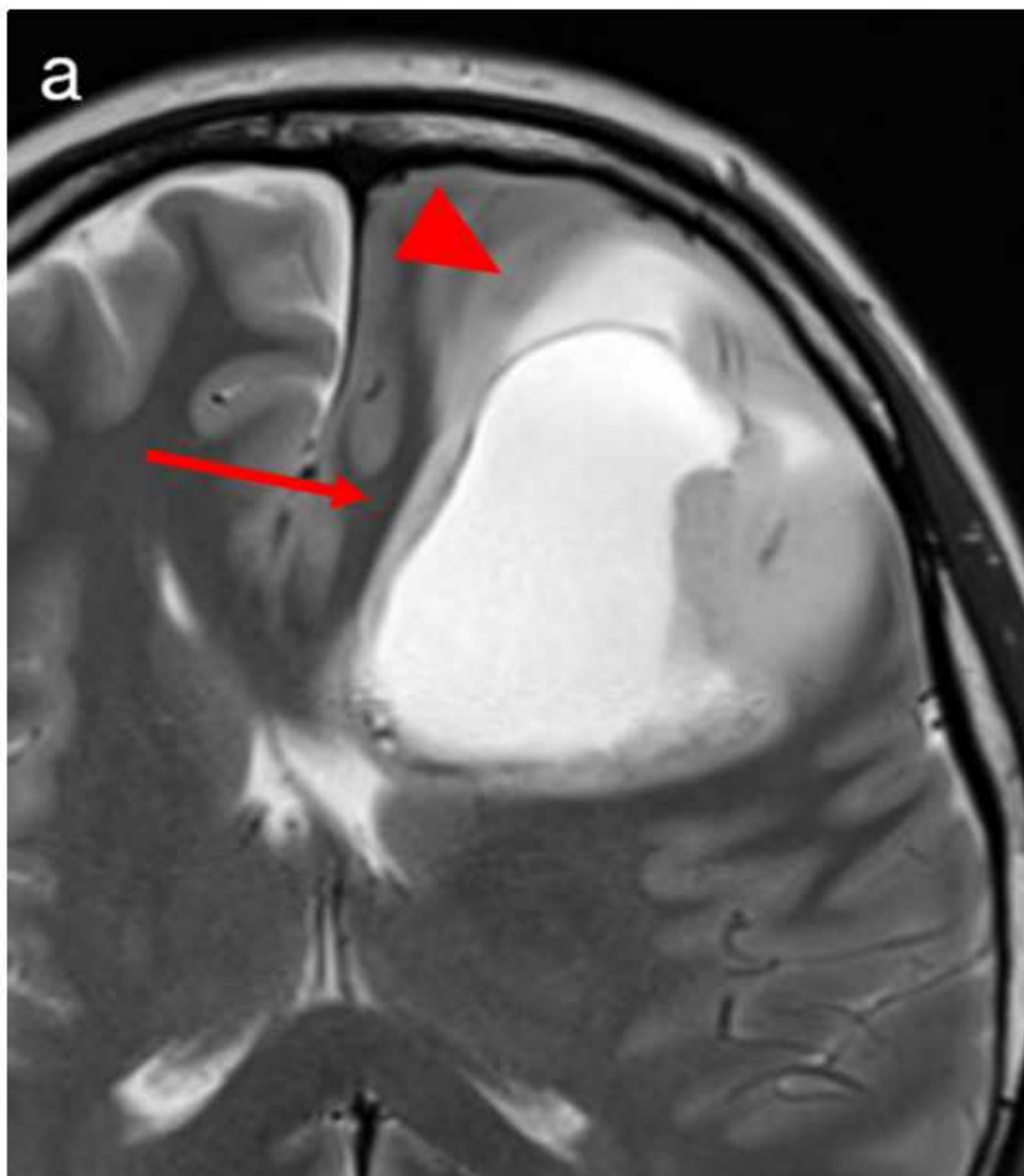


Fig.2b

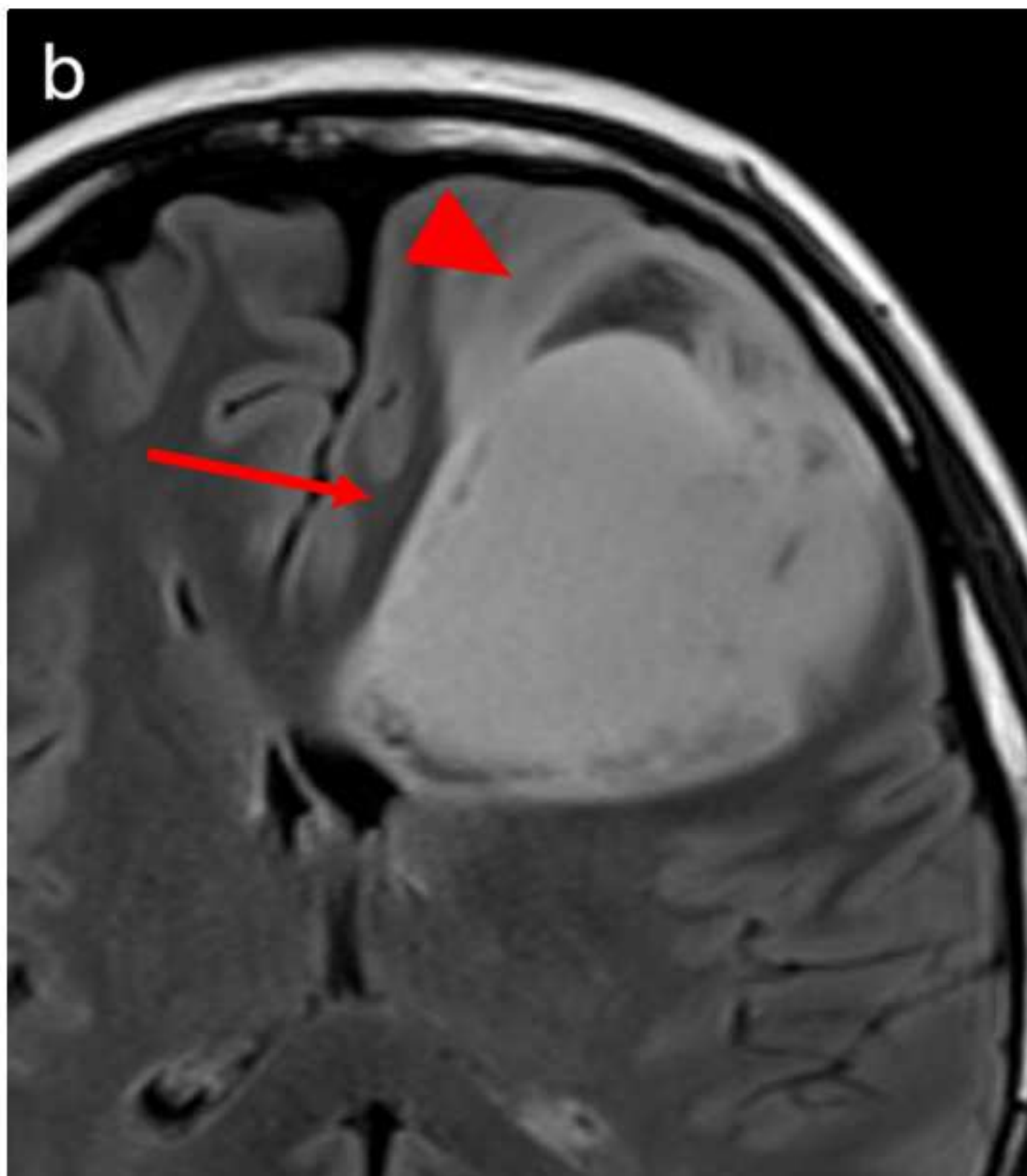


Fig.2c

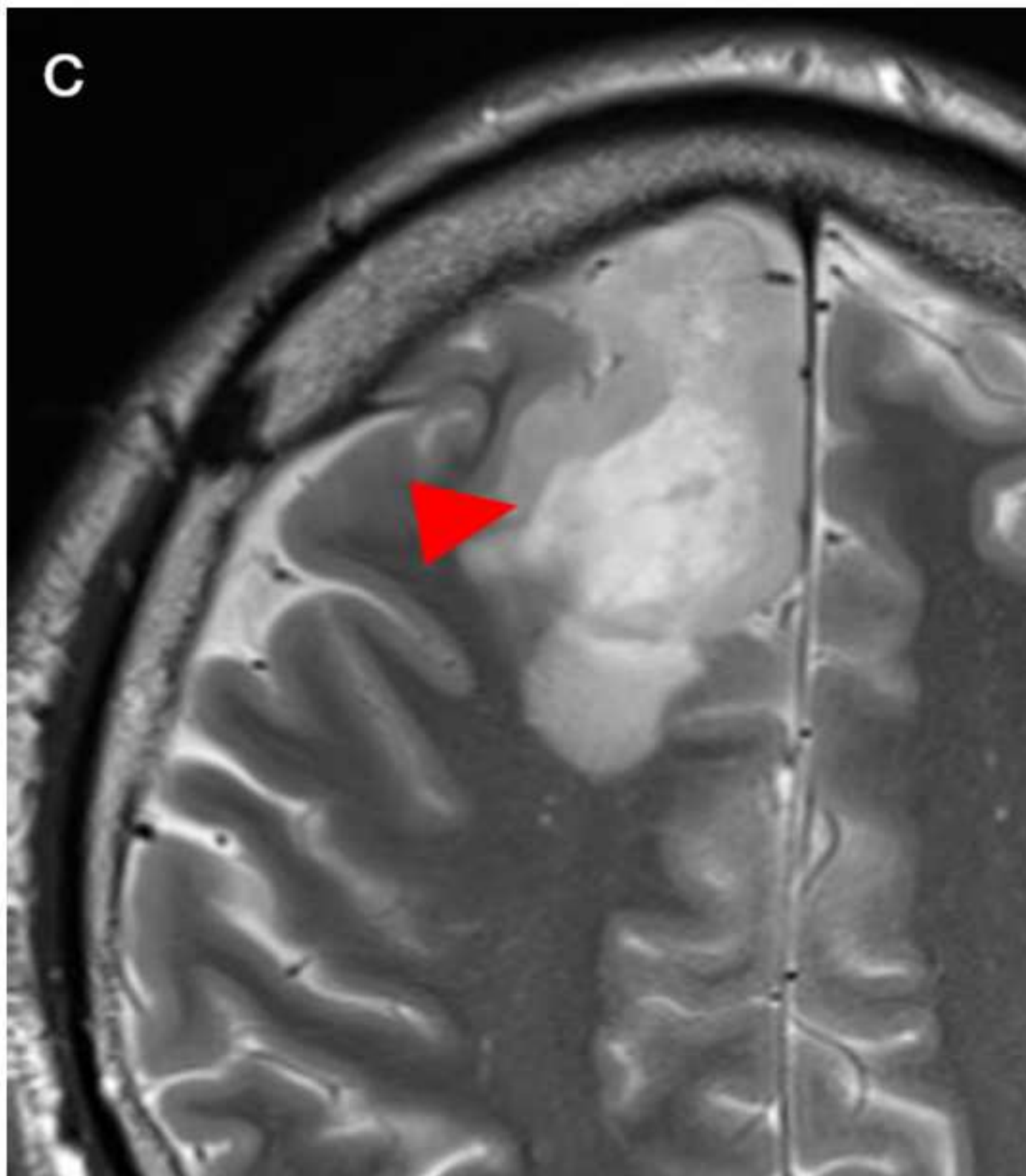


Fig.2d

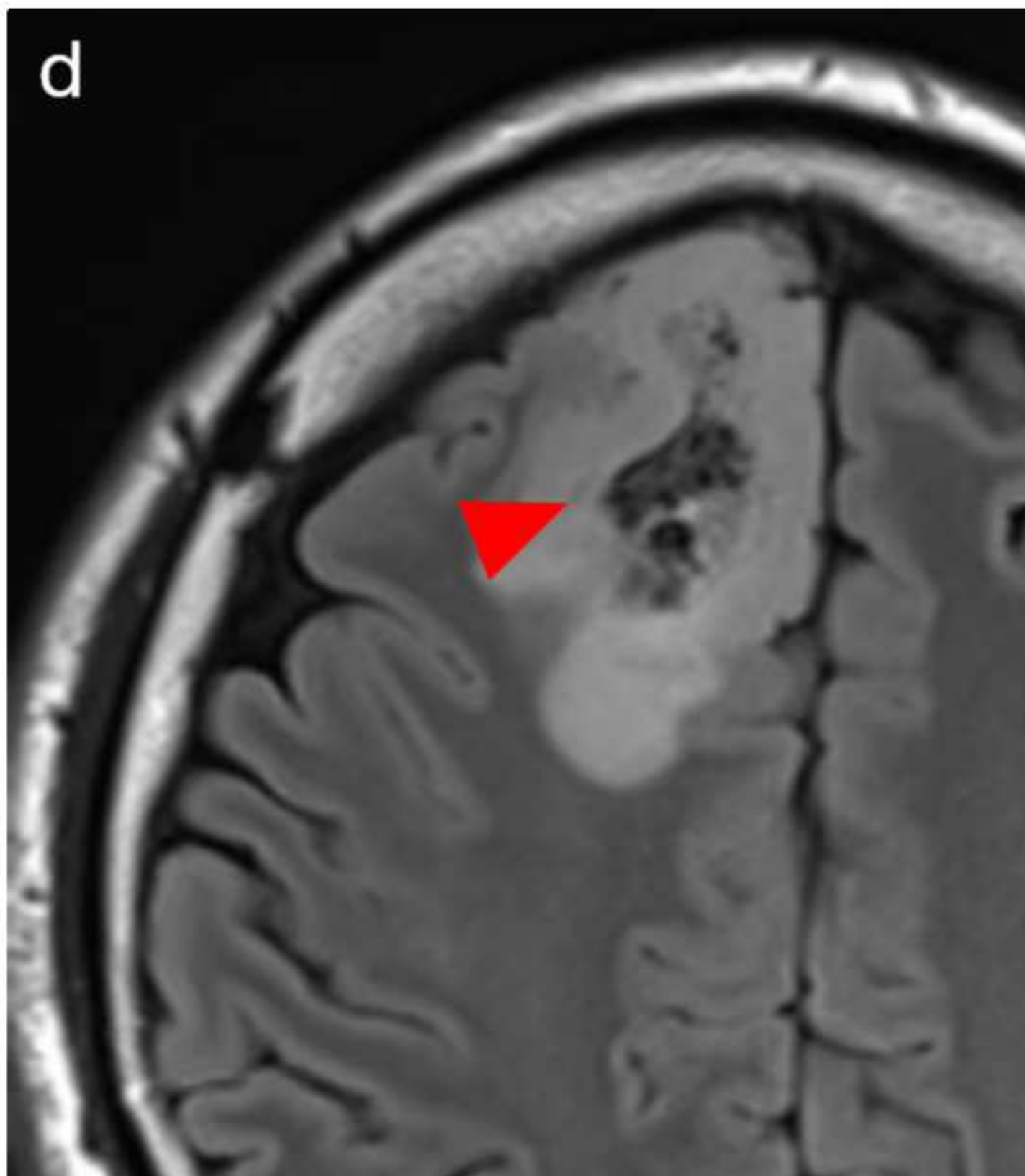


Fig.2e

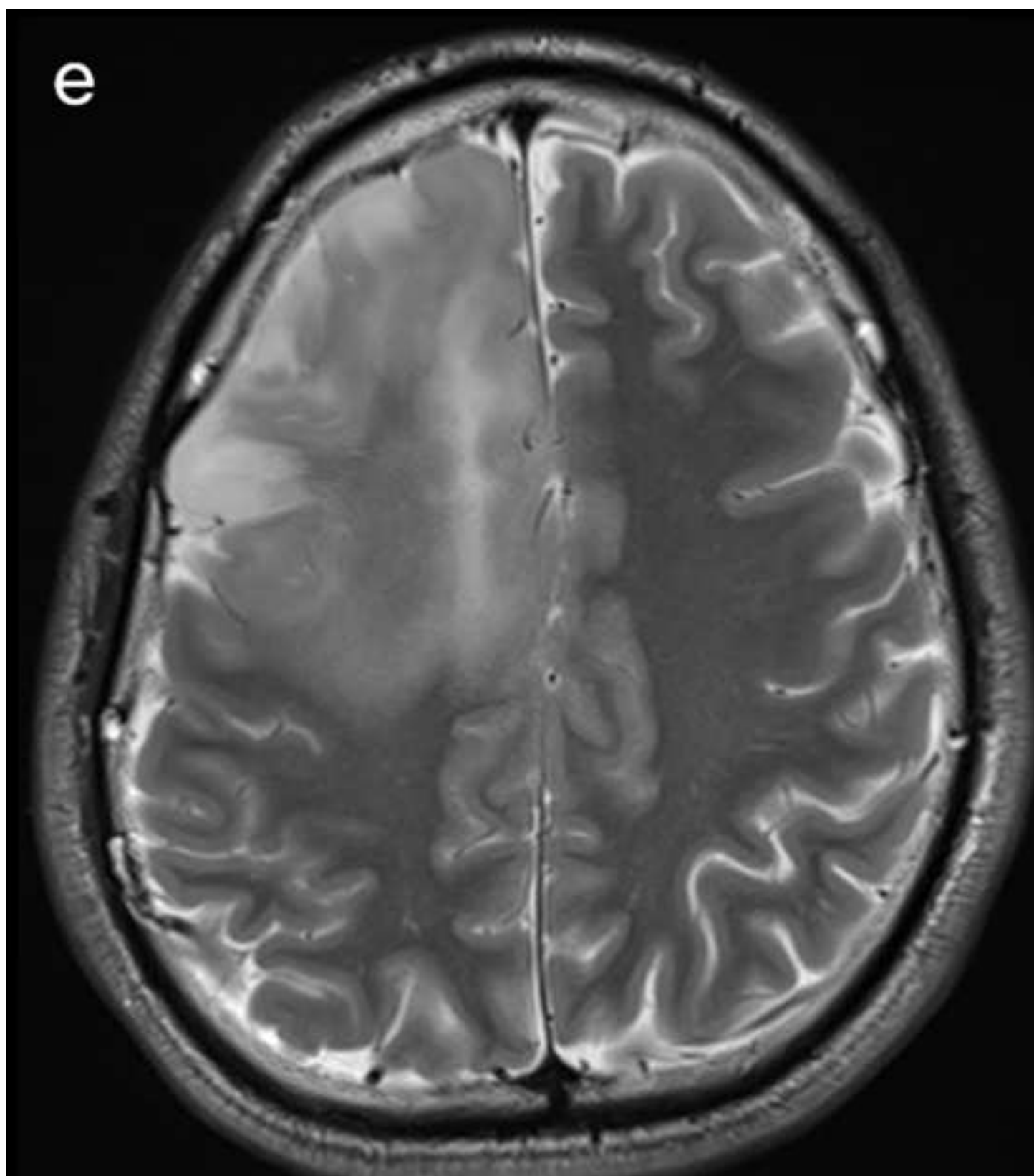


Fig.2f

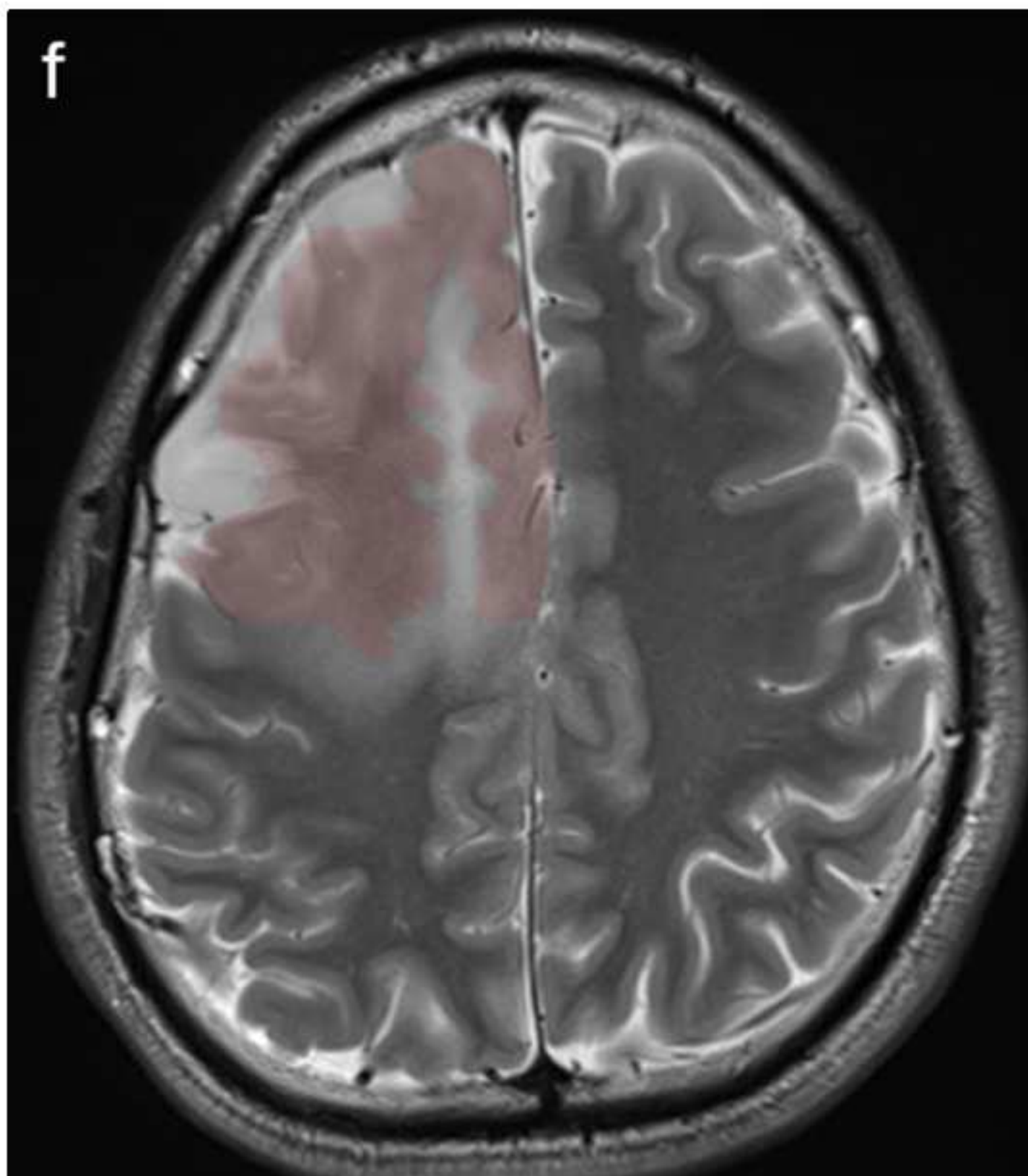


Fig.3a

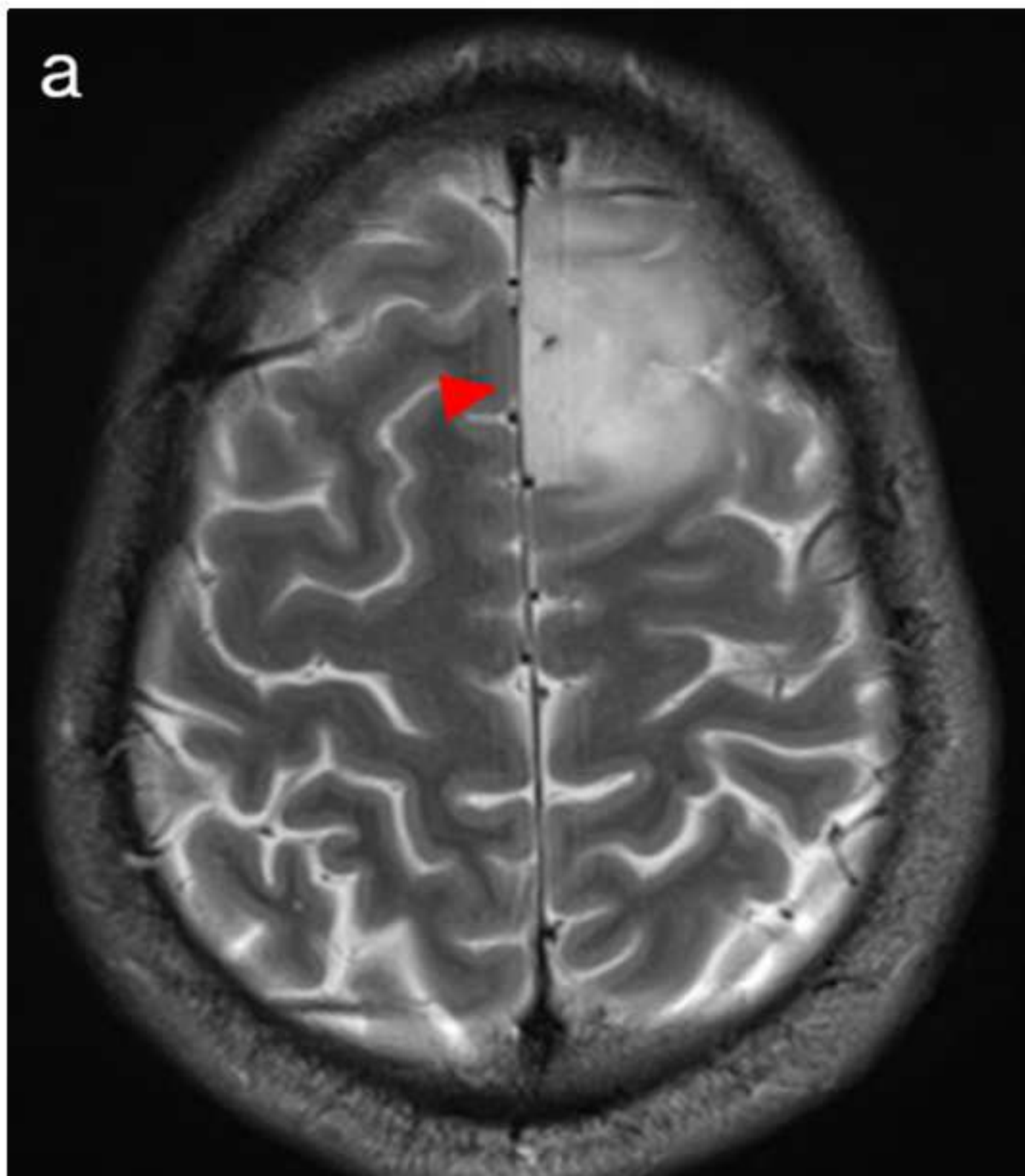
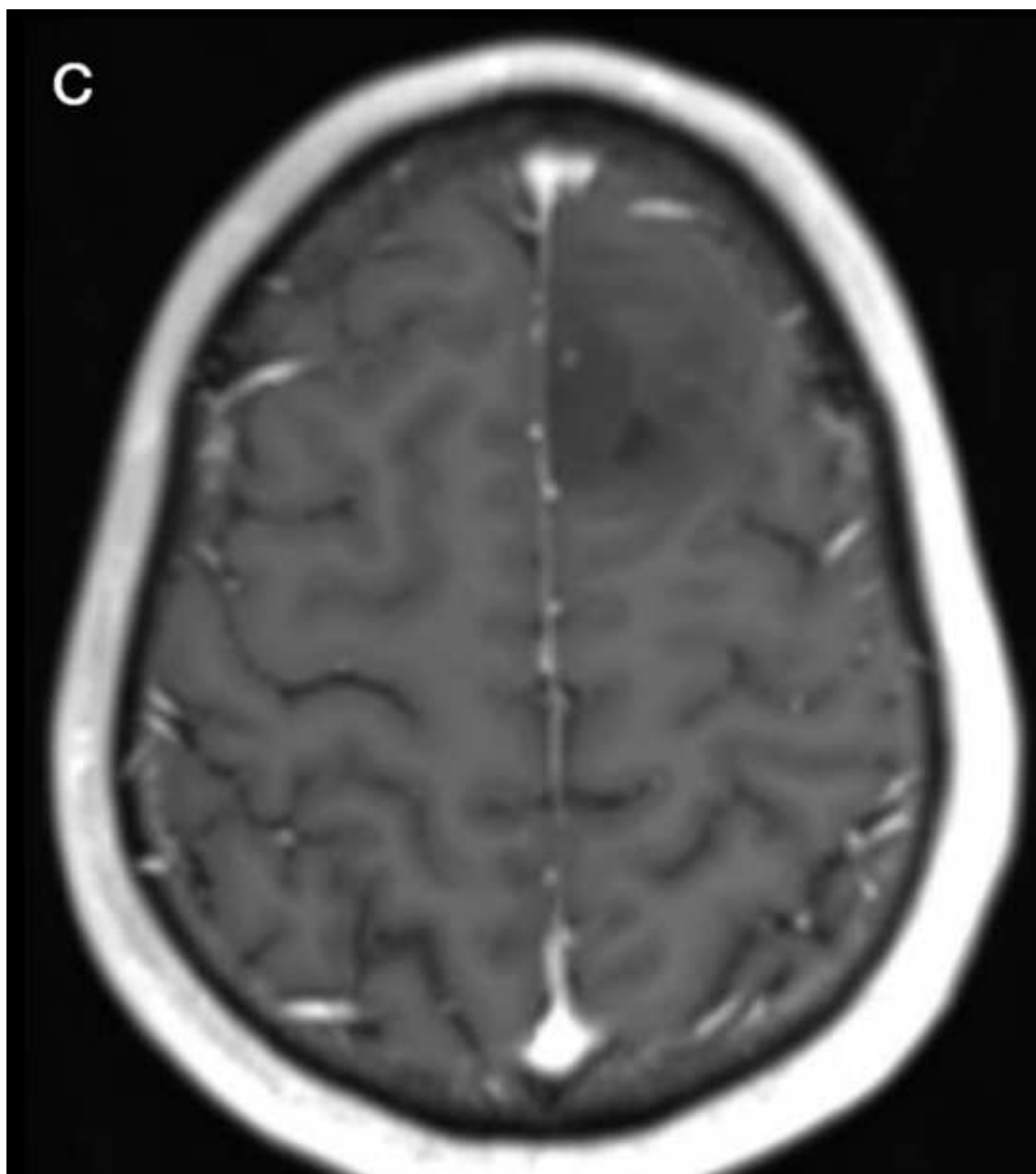


Fig.3b



Fig.3c



Contributions

- Conceptualization: SI, AS.
- Data curation: SI, AY, YMa
- Formal analysis: SI, AS, SOk, SN, SOt
- Funding acquisition: AS, YF, SO
- Investigation: SI, AS, YMi, YMa, YT
- Methodology: SI, AS, YM, YT.
- Project Adminstration: AS, YA, YN
- Resources: AY, YF, YN.
- Software: SI, AS
- Supervision: YMi, YMa, YT, YN
- Visulaization: SI, AS
- Writing-original draft preparation: SI, AS.
- Writing-review and editing: SI, AS, YA, YMi, YMa,YF, YT, SOk, SN, SOt, YN.
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