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Short Communication / Kısa Rapor

The Association of Alpha-thalassemia X-Linked Intellectual Disability Mutation with Histopathological Grading in Isocitrate-Dehydrogenase-mutant Glioma

İzositrat Dehidrojenaz-mutant Gliomada Alfa-talasemi/Mental Retardasyon X'e Bağlı Mutasyonunun Histopatolojik Derecelendirmeyle İlişkisi

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Abstract

Gliomas are the most common malignancies of the central nervous system. Two molecular profiles involved in gliomagenesis are *isocitrate dehydrogenase* (*IDH*) and *alpha-thalassemia X-linked intellectual disability (ATRX).* Inactive mutations in the *ATRX* gene are associated with tumorigenesis via the alternative telomere lengthening pathway as well as with IDH and *tumor protein p53* mutation. The present study aims to determine the relationship between *ATRX* mutation and histopathological grading in *IDH*-mutant gliomas. This is a cross-sectional study using formalin-fixed paraffin-embedded blocks to examine the data of patients with an *IDH*-mutant glioma admitted to the Sardjito General Hospital between January 2017 and March 2022. The *IDH*-mutant status and *ATRX* mutation were determined via a polymerase chain reaction-sequencing examination and immunohistochemistry analysis. The association between *ATRX* mutation and histopathological grading was tested using the chi-square test. A total of 39 glioma samples from patients with *IDH*-mutant status were included in this study. Of these, 26 were obtained from men (66.67%). The age range of all patients was 20–66 years. A total of 19 samples (48.72%) showed immunopositivity to *ATRX*. The bivariate analysis revealed that *ATRX* mutation was not associated with histopathological grading ($P > 0.05$). The *ATRX* mutations were not associated with *IDH*-mutant glioma grading in the present study.

Keywords: Glioma, *alpha-thalassemia X-linked intellectual disability*, immunohistochemistry, grading, *isocitrate dehydrogenase* mutant

Öz

Gliomalar merkezi sinir sisteminin en sık görülen maligniteleridir. Gliomagenezde yer alan bazı moleküler profiler; *izositrat dehidrojenaz* (*IDH*) ve alfa talasemi/mental retardasyon *X'e* (*ATRX*) bağlıdır. *ATRX* genindeki aktif olmayan mutasyonlar, alternatif telomer uzatma yolu aracılığıyla tümör oluşumuyla ilişkilidir ve *IDH* ve *TP53* mutasyonuyla ilişkilidir. Bu çalışmada IDH-mutant gliomalarda *ATRX* mutasyonu ile histopatolojik derecelendirme arasındaki ilişkinin belirlenmesi amaçlandı. Bu, Ocak 2017'den Mart 2022'ye kadar Sardjito Genel Hastanesi'nden formalinde fikse edilmiş parafine gömülü dokular kullanılarak *IDH*-mutant olan gliomalı hastalarda yapılan kesitsel bir çalışmadır. *IDH*-mutant durumu ve ATRX mutasyonu sırasıyla, polimeraz zincirleme reaksiyonu dizileme incelemesi ve immünohistokimya analizi ile belirlendi. *ATRX* mutasyonu ile histopatolojik derecelendirme arasındaki ilişki ki-kare kullanılarak test edildi. Bu çalışmaya *IDH*-mutantları içeren 39 glioma örneği dahil edildi. Hastaların 26'sı (%66,67) erkek olup, tüm deneklerin yaş aralığı 20 ile 66 arasındaydı. *ATRX*'e karşı immünopozitiflik gösteren 19 örnek (%48,72) vardı. İki değişkenli analiz sonuçları *ATRX* mutasyonunun histopatolojik derecelendirmeyle ilişkili olmadığını ortaya çıkardı ($P > 0,05$). Bu çalışmada ATRX mutasyonları *IDH*-mutant glioma derecelendirmesi ile ilişkili bulunmadı.

Anahtar Kelimeler: Glioma, *alfa talasemi/menral retardasyon X'e bağlı*, immünohistokimya, derecelendirme, *izositrat dehidrojenaz* mutant

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Introduction

Glioma is a broad term describing neuroepithelial tumors originating from the glial or supporting cells of the central nervous system (CNS). Gliomas account for 24% of all primary CNS tumors and vary widely histologically, from benign astrocytoma tumors to extremely aggressive and fatal grade IV glioblastomas (1).

Molecular biology studies have provided new insights into diffuse glioma carcinogenesis and progression, prompting neurologists to rethink the biology of diffuse gliomas. Therefore, in 2016, the World Health Organization (WHO) updated the classification of diffuse gliomas, using a new classification that integrates traditional histological and novel molecular biological features to provide a consistent prognosis.

Mutations in *the isocitrate dehydrogenase (IDH)* gene are estimated to occur in 70%–90% of low-grade diffuse gliomas, specifically in astrocytomas and oligodendrogliomas, and affect the epigenetic regulation of the genome. They are also strongly associated with tumorigenesis and prognosis (2). Inactivating mutations of the *alpha-thalassemia X-linked intellectual disability (ATRX)* gene corresponds with the alternative telomere lengthening (ALT) phenotype and are strongly associated with *IDH* and *tumor protein p53 (TP53)* mutation; however, they are commonly exclusive with 1p19q-codeletion (3).

The *ATRX* protein is an essential component of the chromatin remodeling complex that functions at the telomere level. The *ATRX* gene encodes the protein at Xq13 (4). The loss of *ATRX* causes telomere instability and elongation, resulting in genetic instability (3). Mutations in the gene abolish nuclear protein expression in tumor cells but retain expression in non-tumor cells (endothelial and pre-existing glial cells), thus serving as a positive internal control. In glioblastoma, the expression of *ATRX* is different. Low *ATRX* expression was observed more frequently in primary glioblastoma and anaplastic glioma than in grade II glioma, suggesting it is a malignancy marker (2).

A study was conducted on the association of *ATRX* mutation with the histopathological classification of glioma (4). However, most reports are correlative rather than mechanical (4,5,6). The present study aimed to evaluate the association of *ATRX* mutation with the histopathologic grading of patients with *IDH*-mutant glioma.

Materials and Methods

The present study assumes a cross-sectional approach to assessing the association of variable-dependent *ATRX* mutation and other variables, including age, sex, and lobe involvement, with histopathological grading in patients with *IDH*-mutant glioma. Ethical eligibility approval was obtained from the Faculty of Medicine Ethics Committee, Gadjah Mada University (number KE/FK/0540/EC 2022).

The study sample comprised patients diagnosed with glioma (astrocytomas and oligodendrogliomas) between January 2017 and March 2022 at Sardjito General Hospital, Yogyakarta, Indonesia. All patients signed an informed consent form before participating in the study. Two independent pathologists reviewed and reclassified histopathology samples and clinical data based on the 2021 WHO classification of CNS tumors. Clinical data on age, sex, and tumor location were collected from the patient's medical records.

The *IDH* mutation status was determined using a polymerase chain reaction-sequencing method, allowing the detection of *IDH1* or *IDH2* mutations, as described previously (7). A total of 39 patients with *IDH*-mutant glioma were included in the study.

The *ATRX* mutations were evaluated using an immunohistochemical examination. Tissue sections with a thickness of 3 µm were obtained from formalin-fixed paraffin-embedded (FFPE) blocks from all samples and stained with anti-*ATRX* polyclonal antibodies (Sigma Aldrich HPA001906). Immunoreactive cells were visualized using diaminobenzidine chromogen. The immunohistochemistry staining results were assessed by two observers using an Olympus CX23 microscope. The positive controls for *ATRX* were normal brain cells and endothelial cells. The area of necrosis and many inflammatory cells were not assessed. The immunohistochemistry results were evaluated using an eyeballing technique with a cut-point value of 10%. Gliomas with an *ATRX* gene mutation were defined when immunohistochemistry examination showed a negative nuclear expression of <10% in tumor cells.

Statistical Analysis

The data obtained were evaluated using the Kappa test. Analysis of the association between the results of the *ATRX* immunohistochemistry examination and histopathological grade was performed using the chi-square test via a computerized statistical test because of the two category-scale variables. Existing data were presented in the form of text and tables. A P value of <0.05 was considered statistically significant.

Results

The present study involved patients with *IDH*-mutant glioma from Sardjito General Hospital, Yogyakarta. Clinically, the recruited patients experienced headaches (56%), seizures (21%), and other neurological deficits (32%). The radiologic results showed brain tumors located in the frontal lobe (46%), parietal lobe (38%), temporal lobe (28%), and brainstem (5%), with single lobe involvement in 59% of cases and multilobe involvement in 41% of cases. Histopathologically, most tumors were diagnosed as astrocytoma (74%), followed by oligodendroglioma (26%) Table 1. Most participants were men (66.67%) aged 20–66 years, with a mean age of 41.07. The complete characteristics of the participants are shown in Table 2.

The immunohistochemistry results in this study were assessed by two observers (pathologists); the coefficient value of Cohen's Kappa for suitability between observers was 0.84. Representative images of the immunohistochemistry results are shown in Figure 1.

Bivariate analysis was conducted on independent variables of the *ATRX* mutation status assessed through immunohistochemistry examination and dependent variables, such as sex, age, and histopathological morphology. The chi-square test was performed to evaluate the association of each variable with the dependent variable histopathologic grading (Table 3).

The bivariate analysis showed no statistical association between patients' sex, age, tumor location, *ATRX* mutation, and histopathological grading ($P > 0.05$).

Table 1. Clinical features, radiological imaging, and histopathological diagnosis of patients with isocitrate dehydrogenase-mutant glioma.

No	Sample ID	Clinical features	Radiology (head computed tomography scan)	Diagnosis
1	FG-05	Seizure	Tumor of the frontal and parietal lobes	Oligodendroglioma, WHO grade 2
2	FG-09	One-sided body pain	Tumor of the parietal lobe with perifocal edema, midline shift to the right side	Astrocytoma, WHO grade 4
3	FG-25	Headache	Tumor of the frontal and parietal lobes	Diffuse astrocytoma, WHO grade 2
4	FG-27	Headache	Tumor of the parietal lobe with rim enhancement	Diffuse astrocytoma, WHO grade 2
5	FG-34	Impaired consciousness	Solid tumor and cyst of the left frontal lobe, midline shift to the right side	Astrocytoma, WHO grade 4 NOS
6	FG-36	Headache, seizure	Tumor of the brainstem	Oligodendroglioma, WHO grade 2
7	FG -55	Headache	Tumor of the left fronto temporoparietalis lobe	Oligodendroglioma, WHO grade 2
8	FG-59	Headache	Tumor of the right frontalis lobe suspected oligodendroglioma with micro bleeding and calcification	Anaplastic oligodendroglioma, WHO grade 3
9	FG-71	Impaired consciousness	Suspected recurrent astrocytoma of the left temporoparietal lobe	Astrocytoma, WHO grade 4
10	FG-73	Headache	Tumor of the frontoparietal lobe dextra with intratumoral hematoma, suspected who grade 4 astrocytoma narrowing the lateral ventricle dextra	Astrocytoma, WHO grade 4
11	FG-76	Headache	Inhomogeneous mass in the frontal lobe sinistra causing a midline shift to the sinistra and compressing the lateral ventricle of the sinistra, leading to a picture of who grade 4 astrocytoma	Astrocytoma, WHO grade 4
12	FG-78	Speech disorder	Tumor of the left fronto temporoparietalis lobe	Anaplastic astrocytoma, WHO grade 3
13	FG-86	Headache	Tumor of the frontal lobe	Oligodendroglioma, WHO grade 2
14	FG-99	Impaired consciousness	Susp intracerebral and intratumoral hemorrhage (astrocytoma)	Diffuse astrocytoma, WHO grade 2
15	FG-105	Impaired consciousness	WHO grade 4 astrocytoma in the right temporal lobe causing herniation	Diffuse astrocytoma, WHO grade 2
16	FG-107	Headache	High-grade astrocytoma in the parietal lobe sinistra causing herniation	Anaplastic oligodendroglioma, WHO grade 3
17	FG-108	Headache	Hypervascular solid lesions in the tentorium sinistra superomedial aspect, amorphous form, indecisive border, irregular edges	Astrocytoma, WHO grade 4
18	FG-109	Impaired consciousness, seizure	Inhomogeneous masses in the left temporal lobe, accompanied by intratumoral hemorrhage extending to the bilateral lateral intraventricular, causing narrowing of the left lateral ventricle and midline shifting to the right	Anaplastic astrocytoma, WHO grade 3
19	FG-110	Headache	Intraaxial mass in the left temporoparietal, accompanied by broad perifocal edema, narrowing the left lateral ventricle and shifting the midline to the right, causing subfalcine herniation with intratumoral bleeding, suspected WHO grade 4 astrocytoma	Astrocytoma, WHO grade 4
20	FG-112	Headache	Mass in the parietal lobe of the dextra with intratumoral bleeding, accompanied by perifocal edema constricting the lateral ventricle dextra, causing midline shifting toward the sinistra by 0.7 cm, suspected astrocytoma	Anaplastic astrocytoma, WHO grade 3
21	FG-115	Headache	Low-grade astrocytoma of the frontal dextra	Oligodendroglioma, WHO grade 2
22	FG-116	Impaired consciousness	Low-grade astrocytoma of the left frontal lobe	Diffuse astrocytoma, WHO grade 2
23	FG-117	Seizure	Low-grade astrocytoma of the left temporal lobe	Diffuse astrocytoma, WHO grade 2

Table 1. Continued

No	Sample ID	Clinical features	Radiology (head computed tomography scan)	Diagnosis
24	FG-125	Headache	Low-grade astrocytoma of the left frontoparietal lobe	Diffuse astrocytoma, WHO grade 2
25	FG-129	Headache	Intraaxial masses in the left frontoparietal with intratumoral micro-bleeding infiltrating into the contralateral and lepto-meninge, passing through the corpus callosum, suspected WHO grade 4 astrocytoma with perifocal edema	Oligodendroglioma, WHO grade 2+D28
	FG-135	Headache	Intraaxial mass in the frontoparietal sinistra lobe with multiple calcifications, constricting the left lateral ventricle, causing midline shifting accompanied by perifocal edema, leading to oligodendroglioma	Anaplastic oligodendroglioma, WHO grade 3
26	FG-136	Seizure	Suspected anaplastic astrocytoma of the frontal lobe sinistra, causing subfalcine herniation in the direction of the dextra by as much as 2.03 cm	Anaplastic oligodendroglioma, WHO grade 3
27	FG-141	Headache	Multiple lesions in the right frontal lobe, with an amorphous shape, firm boundaries, regular edges, and perifocal edema	Astrocytoma, WHO grade 4
28	FG-142	Headache	Low-grade astrocytoma of the right frontal lobe	Diffuse astrocytoma, WHO grade 2
29	FG-153	Headache, seizure	The cystic lesion in the right frontal lobe with perifocal edema, causing a midline deviation toward the left by 1 cm, suspected astrocytoma	Diffuse astrocytoma, WHO grade 2
30	FG-155	Headache	Inhomogeneous mass in the left frontoparietal lobe, surrounded by perifocal edema, narrowing the bilateral ventricular system, especially the left and third and subfalcine herniation, suspected WHO grade 4 astrocytoma	Giant cell astrocytoma, WHO grade 4
31	FG-160	Seizure	Mass in the left parietal lobe suspected high-grade astrocytoma	Astrocytoma, WHO grade 4
32	FG-166	Seizure, increased intracranial pressure	Intraaxial lesion in the left parietal lobe, with calcification and areas of intralesional necrosis, suspected oligodendroglioma with perifocal edema causing subfalcine herniation and narrowing of the left lateral ventricle	Anaplastic oligodendroglioma, WHO grade 3
33	FG-170	Increased intracranial pressure syndrome	Suspect diffuse astrocytoma, WHO grade 2, in the right frontotemporal lobe, compressing and narrowing the anterior and posterior horns of the right lateral ventricle, causing a shift of the midline toward the left	Diffuse astrocytoma, WHO grade 2
34	FG-173	Hydrocephalus, headache	Intraaxial lesion in the right frontoparietal lobe, with surrounding perifocal edema and intratumoral hemorrhage with intralesional calcifications, suspected high-grade oligodendroglioma dd/ astrocytoma, WHO grade 4	Giant cell astrocytoma, WHO grade 4
35	FG-177	Visual impairment	Intraaxial mass in the right parieto-temporooccipital lobe, surrounded by extensive perifocal edema, suggesting a WHO grade 4 astrocytoma constricting the right lateral ventricle, causing a left midline shift	Astrocytoma, WHO grade 4
36	FG-203	Left body weakness	Low-grade astrocytoma of the frontal dextra	Diffuse astrocytoma, WHO grade 2
37	FG-205	Difficulty walking	Pathological lesion in the left frontal lobe, amorphous shape, indistinct borders, irregular edges	Diffuse astrocytoma, WHO grade 2
38	FG 213	Headache	Multiple cystic lesions in the left frontal and right temporal lobes constricting the lateral ventricles bilaterally, the third ventricle and causing pathological mid-line shifting toward the right in the left frontal lobe, amorphous shape, unclear boundaries, irregular edges	Gemistocytic astrocytoma, WHO grade 2

WHO: World Health Organization, NOS: Not otherwise specified

Table 2. Characteristics of the research participants			
Variable	**Frequency**	**Percentage**	**Mean**
Sex			
Male	26	66.67%	
Female	13	33.33%	
Age (years)			
≥50	11	28.21%	41.07
<50	28	71.79%	
Involved lobe			
Frontal	18	46.15%	
Temporal	11	28.20%	
Parietal	15	38.46%	
Brainstem	2	7.69%	
Histopathological grading			
Grade 2	17	43.58%	
Diffuse astrocytoma, *IDH*-mutant	13	33.33%	
Oligodendroglioma, *IDH*-mutant	3	7.69%	
Gemistocytic astrocytoma, *IDH*-mutant	1	2.56%	
Grade 3	10	25.64%	
Anaplastic astrocytoma, *IDH*-mutant	6	15.38%	
Anaplastic oligodendroglioma, *IDH*-mutant	4	10.26%	
Grade 4	12	30.77%	
Astrocytoma, *IDH*-mutant	12	30.77%	
***ATRX* expression**			
ATRX loss	15	38.46%	
ATRX retained	24	61.53%	

IDH: Isocitrate dehydrogenase, ATRX: Alpha-thalassemia X-linked intellectual disability

Table 3. Bivariate analysis of the association of sex, age, involved lobe, histomorphology, and *ATRX* expression with histopathological grading			
Variable	**Low-grade**	**High-grade**	***P* value**
Sex, n (%)			
Male	10 (25.64%)	16 (41.02%)	0.25
Female	7 (17.94%)	6 (15.38%)	
Age (years), n (%)			
≥50	2 (5.12%)	6 (15.38%)	0.60
<50	15 (38.46%)	16 (41.02%)	
Involved lobe, n (%)			
Frontal	7 (17.94%)	14 (35.89%)	0.29
Temporal	7 (17.94%)	11 (28.20%)	0.80
Parietal	6 (15.38%)	14 (35.89%)	0.15
Brainstem	2 (5.12%)	0 (0%)	0.08
Histomorphology, n (%)			
Astrocytoma	11 (28%)	18 (46.15%)	0.38
Oligodendroglioma	5 (12.82%)	5 (12.82%)	
***ATRX* expression, n (%)**			
ATRX loss	5 (12.82%)	11 (28.20%)	0.30
ATRX retained	11 (28.20%)	12 (30.76%)	

ATRX: Alpha-thalassemia X-linked intellectual disability

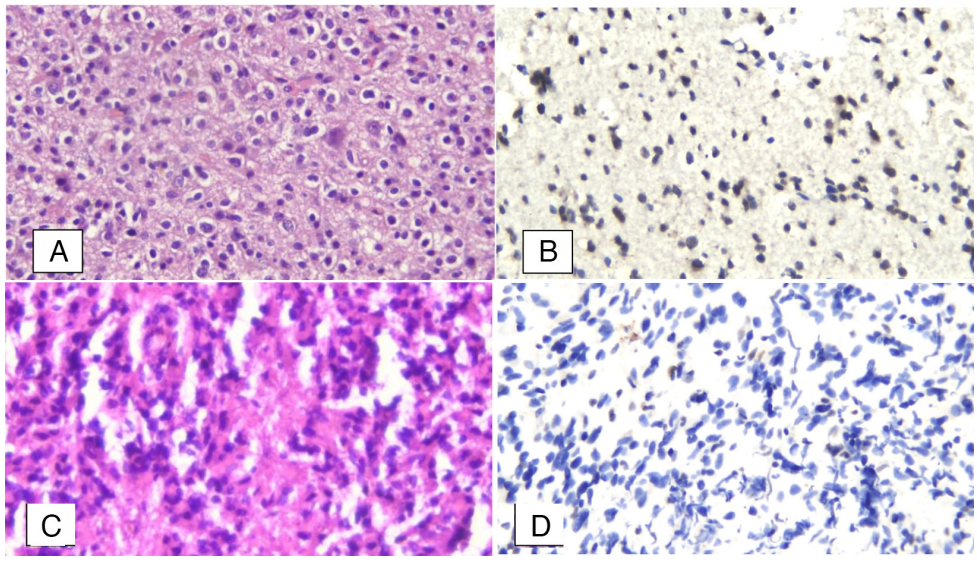

Figure 1. Results of *ATRX* immunohistochemistry examination. (A) *IDH*-mutant oligodendroglioma, WHO grade 2. (B) *ATRX* retained as >10% of tumor cell nuclei were positively stained (brown color). (C) Grade IV *IDH*-mutant astrocytoma. (D) *ATRX* loss due to cell nuclei not being positively stained (blue color; 400x magnification)

ATRX: Alpha-thalassemia X-linked intellectual disability, IDH: isocitrate dehydrogenase, WHO: World Health Organization

Discussion

The present study used 39 FFPE specimens from patients with *IDH*-mutation glioma ranging from grade 2 to 4. *IDH*-mutant glioma samples were used because approximately 75%–90% of *ATRX* mutations were found in *IDH*-mutant gliomas (8).

In the present study, the bivariate analysis of the association of *ATRX* mutation with histopathological grading showed no significant association ($P > 0.05$). This finding is inconsistent with previous studies, which found that *ATRX* mutation was associated with glioma grading and was commonly found in low-grade gliomas (4,5,6). This was because the mutation of *ATRX* and *IDH* occurred in the early stages of gliomagenesis (9). The incompatibility of the results with previous studies may be caused by the poor distribution of patients in the present study, which was dominated by patients with high-grade (grade 3 and 4) gliomas (n = 22).

Although *ATRX* mutations are more commonly found alongside *IDH* mutations occurring at the beginning of gliomagenesis, they are also found in patients with high-grade glioma, grade 3 covering astrocytoma, and secondary glioblastoma (grade 4 astrocytoma). Research has uncovered a significant correlation between canonical *IDH* mutations and *ATRX* mutation, allowing neuropathologists to discriminate between astrocytic and oligodendrocytic tumors (10).

In gliomas with *IDH1/2* mutations, *TP53* mutations are associated with *ATRX* changes. Most grade II/III gliomas with *ATRX* loss had *IDH1/2* mutations; furthermore, *TP53* mutation and p53 overexpression were significantly correlated with *ATRX* loss. According to a report revealing the relationship between *ATRX, IDH1/2*, and *TP53* mutations (3), *ATRX* changes are likely required alongside *TP53* mutations in *IDH1/2*-mutant astrocytomas (astrocytic lineage) to increase oncogenesis in adult gliomas.

This study is a single-institution study based in a referral hospital; thus, the sample has relatively low heterogeny. Further research involving patients without an *IDH* mutation status in various levels of health facilities is necessary.

Conclusion

There was no association between *ATRX* mutation, sex, age, involved lobes, or histopathological morphology with histopathological grading in patients with *IDH*-mutant glioma from the Sardjito General Hospital, Yogyakarta. *ATRX* mutations occur not only in low-grade gliomas but also in high-grade gliomas, which are secondary to low-grade gliomas. Although the mechanism of how *ATRX* mutations induce *ALT* is still unclear, it is believed that *ATRX* deficiency alone is insufficient for *ALT* induction. *ATRX* gene mutations are often found alongside *IDH* and *TP53* mutations in gliomagenesis. *ATRX*, *TP53*, and *IDH* combined mutations stimulate neoplastic growth in astrocytomas.

Ethics

Ethics Committee Approval: Ethical eligibility approval was obtained from the Faculty of Medicine Ethics Committee, Gadjah Mada University (number KE/FK/0540/EC 2022).

Informed Consent: Informed consent was taken from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.G.M., R.A.H., R.C., Concept: E.K.D., R.G.M., R.A.H., Design: E.K.D., R.G.M., Data Collection or Processing: E.K.D., R.C., A.S.A., Analysis or Interpretation: E.K.D., A.S.A., Literature Search: E.K.D., A.S.A., Writing: E.K.D., A.S.A., Y.P.K.

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