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Clinical study

Effect of radiation therapy on overall survival following subtotal resection of adult pilocytic astrocytoma

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ABSTRACT

Objective: Pilocytic astrocytoma (PCA) is a low-grade glioma that primarily presents in children, but can also present in adulthood. Ideal primary treatment for PCA is gross total resection. However, for patients who are only able to undergo subtotal resection, the optimal course of post-operative therapy remains unclear. We investigated the association of patient characteristics and radiation therapy (RT) with overall survival specifically for adult PCA patients who underwent subtotal tumor resection.

Methods: Information on adult patients (age ≥18 years old) who underwent subtotal PCA resection between 2004 and 2016 was collected from the National Cancer Database (NCDB). A multivariate Cox proportional hazards model was utilized to determine factors associated with overall survival.

Results: A total of 451 patients were identified. The mean age of our patient cohort was 36.8 years old, and the majority of patients (83.4%) did not receive RT following subtotal PCA resection. Overall median survival was >93.8 months. On multivariate analysis, patients who were older at diagnosis (hazard ratio [HR] = 1.04, 95% confidence interval [CI] = 1.02–1.06, $p < 0.01$), black (HR = 2.35, CI = 1.05–5.23, $p = 0.037$), had a Charlson/Deyo comorbidity score ≥ 1 (HR = 2.27, CI = 1.00–5.14, $p = 0.049$), or received RT during their initial treatment (HR = 3.77, CI = 1.77–8.03, $p < 0.01$) had a significantly higher risk of death following subtotal PCA resection.

Conclusion: Post-operative RT was associated with a significantly higher risk of death among adults who underwent subtotal PCA resection. Our findings provide support for further inquiry into the efficacy of RT within this patient population.

1. Introduction

Pilocytic astrocytoma (PCA) is a World Health Organization (WHO) grade I glioma that comprises 5% of all gliomas. While the tumor is commonly seen in pediatric patients, it is also rarely diagnosed in adults [1]. Pediatric cases of PCA are generally viewed as having an excellent prognosis, but research has shown that adult PCA is associated with increased mortality compared to PCA in children, likely due to more aggressive tumor behavior [1–5]. For PCA in both children and adults, the ideal treatment is gross total resection. However, the optimal treatment strategy following subtotal resection (STR) remains controversial, and the role of adjuvant radiation therapy (RT) for these patients is currently unclear [2,6–11]. Specifically, it is undecided whether RT following STR of PCA is necessary or if observation constitutes adequate post-surgical management. Certain studies have shown that post-operative RT following PCA resection confers a survival benefit, while other studies have demonstrated no benefit or even decreased survival [2,7,8,12–14]. Given these conflicting findings, further investigation of the effects of RT in managing adult PCA may be helpful to better understand its impact upon patient outcomes. This is the first study to investigate the role of RT specifically among adults who have undergone STR of PCA within the National Cancer Database (NCDB) and aims to clarify the utility of post-operative RT for these patients.

2. Methods

The present study utilized patient data obtained from the NCDB, which is a joint project of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. This oncology data set is a nationwide, hospital-based, comprehensive clinical surveillance resource that receives information on approximately 70% of newly diagnosed cancers in the United States from more than 1450 hospitals annually [15]. The NCDB data is provided in a de-identified Participant User File (PUF) and is therefore

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exempt from Institutional Review Board approval. Additionally, the American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each CoC accredited hospital that allows for de-identified data analysis.

2.1. Patient identification and variables analyzed

The NCDB was queried for adult patients (age ≥18 years old) who underwent STR for histologically-confirmed PCA. Cases were identified using the ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) pathology code "9421" for pilocytic astrocytoma in combination with topography codes for site of origin (C710-720, C723, C728-C729). Tumor locations were classified as follows: cerebrum (C710-C714), ventricle (C715), cerebellum (C716), brain stem (C717), spinal cord (C720), optic nerve (C723), and "other" locations [including those not otherwise specified within the brain (C719) or nervous system (C279), and overlapping lesions (C718, C728)]. Locations defined as infratentorial included the cerebellum and brain stem; supratentorial tumors were defined as those in the cerebrum and ventricles. Due to their heterogeneity, "other" locations were not included in survival analyses. The extent of surgical resection is defined within the NCDB using the Facility Oncology Registry Data Standards (FORDS). In this study, codes 21 ("Subtotal resection of tumor, lesion or mass in brain") or 40 ("Partial resection of lobe of brain") were considered to be STR [16]. For all patients, we collected information on age at diagnosis, sex, race, ethnicity, median household income (stratified into three categories: ≤$34,999; $35,000–$45,999; or ≥$46,000), adjuvant RT, tumor location, tumor size (defined as the largest tumor diameter on imaging, typically based on contrast enhanced imaging), and Charlson/Deyo comorbidity score (0, 1, 2, or 3+, with higher scores corresponding to a greater number of comorbidities). Patients were categorized as either having received adjuvant RT or not having received adjuvant RT. The primary outcome of this study was overall survival, which was defined as death from any cause.

2.2. Statistical analysis

Statistical analyses were conducted using SAS version 9.4 (SAS Institute). Baseline characteristics were compared using Chi-squared and t tests. Survival analyses were performed in three phases. First, univariate analyses were performed using the Kaplan-Meier method to model overall survival for different patient factors such as age and tumor location. Next, bivariate analyses were performed using the log-rank test to assess whether overall survival was statistically significantly different between two variables. Lastly, a multivariate analysis was performed for the dependent variable of overall survival using a Cox proportional hazards model. Hazard ratios and 95% confidence intervals were also calculated. Values of $p < 0.05$ were considered significant and two-sided p-values were reported.

3. Results

3.1. Patient characteristics

A total of 1515 adult patients with histologically confirmed PCA underwent surgical resection between 2004 and 2016. Of those, 451 underwent STR. It is important to note that of these 451 patients, 8 were missing race data, 14 were missing median income data, 6 were missing RT data, and 98 were missing tumor size data. The mean and median ages of the overall patient cohort were 36.8 and 32.0 years, respectively (Table 1). The majority of patients in our cohort were male (51.0%), White (81.0%), and non-Hispanic (87.8%). Regarding median household income, 109 (24.9%) patients made <$35,000 annually, while 190 (43.5%) made ≥$46,000. The majority of patients (83.4%) did not receive RT following STR of PCA. Of the 74 patients that received RT, 63 (85.1%) received external beam radiotherapy, 5 (6.8%) received proton therapy, and 6 (8.1%) received stereotactic radiosurgery. The most common tumor location was in the cerebellum (23.7%) and mean tumor size across the patient cohort was 4.3±7.7 cm^3. Overall, 193 (42.8%) patients had infratentorial tumors and 143 (31.7%) patients had supratentorial tumors. The majority of patients (82.3%) had a Charlson/Deyo score of 0, indicating no comorbidities. On Chi-squared analysis, patients who did and did not receive RT had a significant difference in tumor location ($p = 0.027$) (Table 2). Notably, the proportion of patients with brainstem tumors receiving RT was 23.8%, which is considerably greater than the proportion of patients who received RT in the overall cohort (16.6%).

3.2. Survival analysis

Overall median survival was >93.8 months, as seen in Fig. 1. An exact estimate of median survival could not be determined because survival probability did not cross 0.5 during the study period. The Kaplan-Meier plot in Fig. 2 compares overall survival between patients who received RT following STR of PCA with patients who did not receive RT. Notably, the log-rank test demonstrated that patients who did not receive post-surgical RT had sig-

Table 1
Demographic and treatment characteristics of adult patients with pilocytic astrocytoma undergoing subtotal resection from 2004 to 2016.

Variables	All patients, N = 451
Age at diagnosis, years	
Mean (SD)	36.8 (15.8)
Median (IQR)	32.0 (23.0–46.0)
Gender, N (%)	
Male	230 (51.0)
Female	221 (49.0)
Race, N (%)	
White	359 (81.0)
Black	66 (14.9)
Asian	6 (1.4)
Other	12 (2.7)
Hispanic, N (%)	
Yes	55 (12.2)
No	396 (87.8)
Median Household Income, N (%)	
≤$34,999	109 (24.9)
$35,000–$45,999	138 (31.6)
≥$46,000	190 (43.5)
Tumor Location, N (%)	
Supratentorial	
Cerebrum/lobar	103 (22.8)
Ventricle	40 (8.9)
Infratentorial	
Cerebellum	107 (23.7)
Brainstem	86 (19.1)
Spinal cord	13 (2.9)
Optic nerve	10 (2.2)
Other (Overlapping or NOS)	92 (20.4)
Tumor Size, cm	
Mean (SD)	4.3 (7.7)
Charlson/Deyo Score, N (%)	
0	371 (82.3)
1	60 (13.3)
2	13 (2.9)
3+	7 (1.6)
Radiation Treatment, N (%)	
Yes	74 (16.6)
No	371 (83.4)

SD, standard deviation; IQR, interquartile range; NOS, not otherwise specified.

Table 2
Demographics and treatment characteristics for patients who did and did not receive post-operative radiotherapy.

Variables	Received Radiotherapy, N = 74	Did Not Receive Radiotherapy, N = 371	p value
Age at diagnosis, years			0.107
Mean (SD)	39.8 (16.8)	36.3 (15.6)	
Median (IQR)	40.5 (24.0-51.0)	32.0 (23.0-46.0)	
Gender, N			0.626
Male	36	192	
Female	38	179	
Race, N[a]			N/A
White	55	299	
Black	15	50	
Asian	1	5	
Other	2	10	
Hispanic, N			0.440
Yes	7	47	
No	67	324	
Median Household Income, N			0.113
≤$34,999	12	95	
$35,000–$45,999	29	108	
≥$46,000	30	157	
Tumor Location, N[b]			**0.027**
Supratentorial	14	125	
Cerebellum	16	91	
Brainstem	20	64	
Spinal cord	4	9	
Optic Nerve	3	7	
Other (Overlapping or NOS)	17	75	
Tumor Size, cm			
Mean (SD)	3.4 (1.6)	4.4 (8.5)	0.057
Charlson/Deyo Score, N			
0	61	305	0.964
≥1	13	66	

SD, standard deviation; IQR, interquartile range; NOS, not otherwise specified.
[a] Sample sizes do not meet Chi-Squared test sample size assumptions.
[b] Spinal Cord, Optic Nerve, and Other analyzed as a single category to meet Chi-Squared test sample size assumptions.

nificantly improved overall survival compared to patients who did receive RT ($p < 0.0001$). Additionally, patients with PCA tumors in a supratentorial location also had significantly improved survival

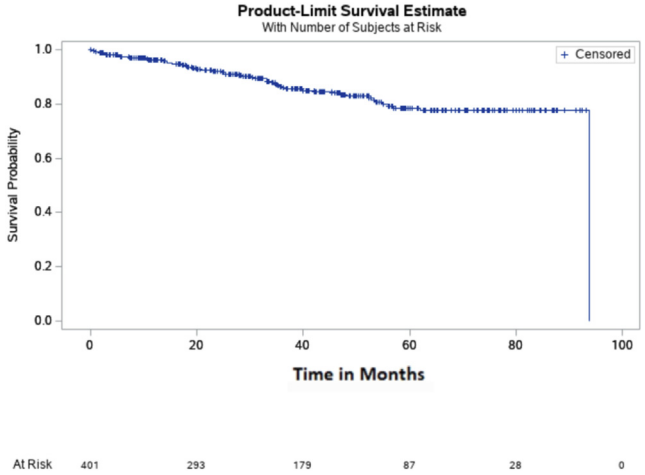

Fig. 1. Kaplan–Meier survival curve for adult patients with pilocytic astrocytoma who underwent subtotal resection.

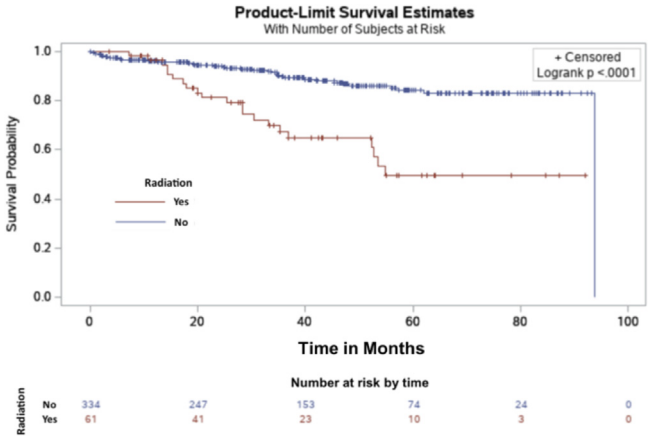

Fig. 2. Kaplan–Meier survival curves comparing overall survival for adult patients who received radiation treatment versus those who did not receive radiation treatment following subtotal pilocytic astrocytoma resection.

compared to patients who did not have supratentorial tumors ($p = 0.0155$) in bivariate analysis, as displayed in Fig. 3.

After calculating adjusted hazards ratios (Table 3), our multivariate Cox proportional hazards model demonstrated that patients who were older at diagnosis (hazard ratio [HR] = 1.04, 95% confidence interval [CI] = 1.02–1.06, $p < 0.01$), black (HR = 2.35, CI = 1.05–5.23, $p = 0.037$), had a Charlson/Deyo score ≥ 1 (HR = 2.27, CI = 1.00–5.14, $p = 0.049$), or received RT during their initial treatment (HR = 3.77, CI = 1.77–8.03, $p < 0.01$) had a significantly higher risk of death following STR of PCA. No patients with a race of "Other" with complete data reached the pre-specified event (death); thus, we were unable to determine the effect of "Other" race on survival.

4. Discussion

PCA is a low-grade glioma that is rarer and more aggressive in adult patients compared to children. While gross total resection is the optimal initial management strategy for adult PCA, only STR is achievable for a number of patients; more information is needed regarding the factors that may affect outcomes for these patients. Thus, we performed the first national database analysis specifically investigating outcomes for adult PCA patients who

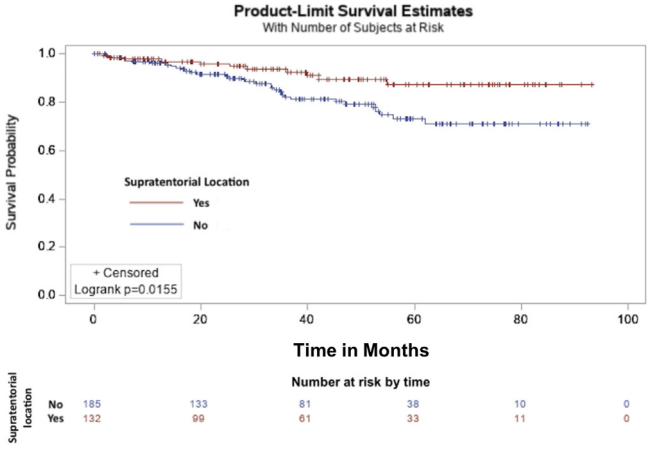

Fig. 3. Kaplan–Meier survival curves comparing overall survival between adult patients with supratentorial versus non-supratentorial pilocytic astrocytomas.

Table 3
Adjusted hazard ratios identifying factors associated with overall survival (N = 235).

Variable (reference)	HR (95% CI)	P value
Greater Age at Diagnosis[a]	1.04 (1.02–1.06)	**<0.01**
Race (Reference: White)		
Black	2.35 (1.05–5.23)	**0.037**
Asian	1.65 (0.22–12.67)	0.63
Other	–	–
Median Household Income (Reference: ≤$34,999)		
$35,000–$45,999	2.52 (0.98–6.50)	0.056
>$46,000	0.67 (0.23–1.91)	0.45
Greater Tumor Size[a]	1.00 (0.99–1.01)	0.98
Radiation During Initial Treatment (Reference: No)		
Yes	3.77 (1.77–8.03)	**<0.01**
Charlson/Deyo Score (Reference: 0)		
≥1	2.27 (1.00–5.14)	**0.049**
Supratentorial Location (Reference: No)		
Yes	0.60 (0.27–1.32)	0.20

[a] Analyzed as a continuous variable.

underwent STR to better understand the association of patient characteristics and treatment regimens with survival.

Our study identified that patient race was significantly associated with survival for adult PCA patients undergoing STR. Namely, black race was significantly associated with poorer survival on multivariate analysis. This finding is consistent with a prior study that investigated the association of race with survival for primary malignant brain tumors [17]. This prior study determined that race was not significantly associated with survival for the whole entire on univariate analysis, but black race was significantly associated with poorer survival for patients who underwent STR. These results may point toward racial disparities in access to and delivery of care, a finding that is prevalent throughout the oncology literature [18–20].

While two prior national database studies have been performed assessing outcomes among all pilocytic astrocytomas, neither identified race as a significant prognostic indicator for survival. A 2012 study by Johnson and colleagues examining survival among 3066 adult PCA patients from the Surveillance, Epidemiology, and End Results (SEER) database determined that younger age, greater extent of tumor resection, and lack of RT were significantly associated with improved survival [2]. Similarly, a study investigating the NCDB by Lee et al. examining survival for 3057 adult PCA patients determined that older age, lower income, higher Charlson/Deyo score, larger tumor size, and external beam RT were associated with inferior survival [21]. However, neither study stratified patients by extent of surgical resection in their analyses, nor identified race as a significant prognostic indicator for survival. Thus, the current study highlights the importance of performing subgroup analyses for clinically important cohorts, such as patients undergoing STR, to determine factors within that group that may be important to predicting overall patient prognosis.

Notably, tumor location was significantly associated with survival in bivariate analysis, but it was not significantly associated with survival in multivariate analysis. Our results align with the findings of both Lee et al. and Johnson et al., who also performed national database studies that determined tumor location was not a significant prognostic indicator when taking into account other known prognostic factors on multivariate analysis [2,21]. However, other studies in the pediatric literature suggest that location may be related to both the biology of PCAs and prognosis. One study of 86 pediatric PCA patients noted that the transcriptional profiles of tumors were associated with specific locations, even when controlling for other factors including radiological appearance of the tumor [22]. However, these transcriptional differences were not found to be associated with the clinical course of disease. Another study in pediatric patients concluded that early RT improved overall survival over delayed RT specifically for patients who had tumors in the midbrain or thalamus [23]. Though assessing tumor location can aid in pre-operative planning and determining surgical risk, further investigation is needed to determine the association of tumor location with survival outcomes, especially in adult PCAs.

Our results also demonstrated that patients who received RT following STR of PCA had a significantly higher risk of death compared to their counterparts who did not receive RT as part of their first course of treatment. As discussed by Johnson et al. and Lee et al., surgeons may selectively recommend RT following resection for patients with certain clinical characteristics such as multiple medical comorbidities or for patients with pathologic factors indicating increased tumor aggressiveness, which may lead to an apparent decreased overall survival in this cohort of patients already expected to have poorer outcomes [2,21]. Our study design attempted to control for some of these factors by inclusion of the Charles/Deyo comorbidity score in our multivariate analysis, though we did not have a proxy for gauging tumor aggressiveness. Additionally, patients with tumors located in regions that are difficult to approach surgically, such as the brainstem, may have poorer prognosis due to more limited extents of resection and may also be more likely to receive RT [24,25]. Again, we attempted to control for this by including tumor location in our multivariate survival model. Nevertheless, our findings demonstrate that patients who undergo STR and who are identified as needing upfront RT have significantly poorer survival than their counterparts not receiving upfront RT.

Though physicians may recommend RT following surgical resection of a PCA, there is still limited consensus on the efficacy of RT in the management of adult PCAs within the literature. One study determined that post-operative adjuvant external beam RT of 5000 centigray in 25 fractions in adult patients with PCA caused a statistically significant improvement in progression-free survival over salvage RT later in the disease course, but overall survival was not significantly different between the two groups. The authors state that the similarities in overall survival are likely explained by the indolent course of disease, even with progression [12]. A series of 43 spinal cord PCA patients by Minehan et. al. also found that post-operative RT did not improve overall survival for patients when compared to those not receiving RT ($p = 0.14$) [14]. In analyzing the results of a prospective clinical trial conducted between 1986 and 1994, Brown et al. concluded that external beam RT following surgical resection of adult PCA is unnecessary due to a favorable prognosis observed within their patient cohort following surgery with no adjuvant therapy [24]. It is important to note that this study only followed 20 patients, so the generalizability of the

results may be limited. Brown and colleagues also noted, however, that the role of RT in the treatment of PCA remains poorly defined, and that it might be effective in patients whose tumors' continued growth has the potential to produce serious neurological symptoms. Finally, initial studies suggest that SRS may provide benefit as salvage therapy in adult PCA patients, warranting further investigation regarding its potential application as adjuvant therapy for those who undergo subtotal resection [5]. Importantly, the survival benefit of adjuvant RT versus observation alone has not been quantified in a large prospective study. Thus, more information regarding the efficacy of RT for these patients is needed to establish definitive guidelines regarding the use of RT in adult PCA patients.

Given the relatively long survival of PCA patients and their relatively young age at diagnosis, it is also important to carefully consider the risks of RT. Though data remains conflicting, some studies have concluded that patients who undergo RT for low grade gliomas may have a decline in cognitive function [25–27]. One study by Klein et al. found that early RT with external beam radiotherapy with fraction doses of >2 Gray for low grade glioma patients may be associated with reduced performance on memory related outcomes at a mean of 6 years after diagnosis [25]. A later study by the same group found that attention was significantly worse in low grade glioma patients treated with RT when compared to those who did not have RT at a mean follow-up of 12 years, even with external beam radiotherapy with fraction doses of <2 Gray [26]. While these studies investigated low grade gliomas as a whole and are not specific to PCA, they demonstrate that there may be cognitive functioning risks to radiotherapy for adult PCA patients. In addition to these risks, there is also a theoretical risk of developing malignant transformation of the tumor due to RT [28–30]. A study by Parsa and Girvad investigating 24 cases of WHO grade I pilocytic astrocytoma in children $\leq$18 years old found that malignant transformation had only occurred in patients who were treated with RT, with the investigators concluding that such transformation was not likely to have occurred spontaneously [31]. A 2009 study by Ellis et al. examining a cohort of 20 adult PCA patients found that RT was not significantly associated with increased rates of malignant transformation [4]. However, the authors noted that their small sample size may have limited the generalizability of their findings. Overall, the potential adverse effects of RT must be considered when determining the optimal treatment course for PCA patients.

Further studies are greatly needed to better characterize both the survival benefit and possible deleterious effects of RT for adult PCA patients. In addition, these studies may identify factors that would allow clinicians to better determine which patients are most likely to attain survival benefit and which patients are most prone to adverse effects from RT. Such findings would provide valuable insight when deciding 1) whether RT is indicated and 2) the optimal timing of RT (e.g. adjuvant vs. salvage) for each patient. For example, one study investigating risk stratification for RT in pediatric low grade glioma patients found that patients with tumors in the midbrain or thalamus appeared to experience improved overall survival with early RT compared to RT after at least one line of chemotherapy, even when adjusting for histology [23]. Application of similar stratification strategies in the adult population may allow for an improved ability to deliver more optimal care.

4.1. Limitations

There are a number of limitations to our study. Given the retrospective nature of our experimental design, we were unable to establish causal relationships between the variables we analyzed, and our results regarding the significant association between race and RT with survival require validation from prospective studies in adults with PCA. Furthermore, any absence or irregularity of information (such as lack of information on cause of death, radiographic findings, residual tumor size, neurological deficits, proximity to eloquent areas, rate of tumor growth, and tumor molecular characteristics) within the NCDB could affect our conclusions. Karnofsky Performance Score was only available for 29 (6.4%) patients, and thus could not be included in survival analyses. Despite these limitations, our study is the first to examine outcomes specifically following STR among a large, national cohort of adult PCA patients. Thus, our results highlight the necessity for further investigation into the effects of RT on adult PCAs to develop optimal post-surgical treatment strategies for this patient population.

5. Conclusions

Our study investigated survival outcomes for 451 adult PCA patients who underwent STR to identify factors that may be related to prognosis. We found that older patient age, black race, , a Charlson/Deyo score $\geq$1, and post-operative RT were all associated with a significantly higher risk of death among adults who underwent STR on multivariate analysis. Our findings provide a rationale for further investigation into the use of RT within this patient population, as well as a re-evaluation of optimal post-surgical management strategies when gross total resection of PCA is not possible. Further research into the specific pathophysiologic mechanisms and genomic nature of adult PCA may be helpful in future efforts to personalize treatment approaches, improve patient outcomes, and better predict long-term prognosis.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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