Heliyon 9 (2023) e21204

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Pediatric gliosarcoma, a rare central nervous system tumor in children: Case report and literature review

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ARTICLE INFO

Keywords:
Gliosarcoma
Glioblastoma
Cerebral hemispheres
Pediatric
Surgery

ABSTRACT

Gliosarcoma is a rare and highly malignant central nervous system tumor that accounts for 1%–8% of glioblastomas; it usually occurs in middle-aged and older adults between 40 and 60 years of age and is rare in children. We report an 11-year-old boy with right frontal lobe gliosarcoma who underwent aggressive gross total resection and postoperative radiotherapy, experienced recurrence and subsequently underwent a second operation. To better understand the disease and explore treatment options, we briefly report this case and review the relevant literature.

1. Introduction

Gliosarcoma (GSM) is a rare and highly malignant central nervous system (CNS) tumor, defined as a grade 4 tumor in the WHO classification, an isocitrate dehydrogenase (IDH) wild-type glioblastoma (GBM) with an extremely poor prognosis. Compared to other GBMs, gliosarcoma has a shorter survival period and worse prognosis and is prone to invade the meninges and skull and develop extracranial metastases [1].Gliosarcoma was first documented in 1985 by Stroebe et al. [2]. It accounts for 1%–8% of glioblastomas and usually occurs in middle-aged and older patients; it rarely presents in children [2]. Gliosarcoma is commonly found in the frontal or temporal lobes of the brain and occasionally in the ventricles，however a small number of gliosarcoma are found in the posterior fossa [3,4]. Histologically, it demonstrates a biphasic pattern of glial and malignant mesenchymal, astrocytic and spindle cell elements [5].

In addition, there is a lack of a definitive treatment that significantly improves prognosis for this tumor, even with aggressive surgical treatment coupled with postoperative radiotherapy and chemotherapy.

To date, fewer than 50 cases of gliosarcoma in children have been reported [5]. We reviewed in detail the literature describing this highly aggressive tumor(Table 1).

2. Case presentation

An 11-year-old boy was admitted to our center with complaints of headache and dizziness for 3 days. Subsequent MRI of the brain

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https://doi.org/10.1016/j.heliyon.2023.e21204
Received 24 June 2023; Received in revised form 18 October 2023; Accepted 18 October 2023
Available online 22 October 2023

showed an occupying lesion in the right frontal lobe, isointense on both T1-and T2-weighted MRI with peripheral edema and a leftward midline shift, and fluid-attenuated inversion-recovery (FLAIR) images showed more defined edema and fluid cavities within the mass. In addition, the mass showed heterogeneous ring or wreath-like enhancement on enhanced MRI, all of which are consistent with the imaging features of high-grade glioma(Fig. 1A–F).The patient underwent right frontal occupancy resection in the supine position. During surgery, the skull was opened using a pterygoid approach, revealing the tumor, which was grayish-brown, avascular, and mucinous. We performed segmental resection of the tumor. Postoperative MRI showed complete resection of the tumor with reduced midline shift and disappearance of the edematous area(Fig. 1G-L). Postoperative pathology indicated a gliosarcoma, WHO grade IV; glioblastoma area: giant nucleus with visible distinct nuclear divisions; sarcoma area: spindle-shaped portion; spindle-shaped cell bundle as sarcoma with interspersed glioblastoma components(Fig. 2A–C). Genetic testing revealed telomerase reverse transcriptase (TERT) C228T and TP53 p.V274F point mutations, IDH1 negativity, EGFR negativity, and chromosome 10 deletion(Table 2). After gross total resection, the patient received aggressive pharmacological treatment, after which he received radiotherapy and concurrent chemotherapy (temozolomide, pemetrexed, Avastin, etc.) at the oncology hospital.

Unfortunately, at an MRI review on the eighth month after tumor removal, the tumor recurred. This time, the tumor was larger than before, as seen in Fig. 3A–F. We performed a second total tumor resection, which was more difficult than the first surgery, as there was greater hematopoiesis, and the tumor had invaded the base of the anterior cranial fossa with extensive bone destruction. Postoperative CT showed that the tumor was completely removed. Less than a week later, the child presented with hydrocephalus, which we treated with placement of another V–P shunt(Fig. 3G–H). However, after three surgeries and aggressive drug therapy, the patient died in the ninth month after the first surgery.

3. Discussion

3.1. Predisposing

Pediatric gliosarcoma is a highly aggressive tumor of the central nervous system that is rarer than adult gliosarcoma. The mean age of onset of pediatric gliosarcoma is 13 years, with a median of 16 years [5]. The incidence of GSM is not high, and large-scale studies are still lacking.

3.2. Histology

Histopathologically, gliosarcoma is characterized by a biphasic pattern of glial and sarcomatous interstitial cells; the glial component is mainly typical GBM cells, and the sarcomatous component is mainly malignant fibrous histiocytes [5]. A related study suggested that the monoclonal origin of gliosarcoma, the sarcomatous component, originates from the aberrant mesenchymal differentiation of malignant glial cells during tumor progression [21]. Sarcomatous areas are reticulated and glial fibrillary acidic protein (GFAP) negative, while the glial components are reticuloid deficient and GFAP positive. Moreover, glial cells and cells with a sarcomatous appearance within the same tumor share the same genetic aberrations [21,33,34]. On histological examination, when the typical biphasic nature develops well, a diagnosis of gliosarcoma can be made easily. Some cases may show other types of mesenchymal differentiation, such as bone and cartilage formation, smooth and striated muscle differentiation, lipomatous differentiation and primitive neural differentiation. The presence of gemistocytic and rhabdoid cells may lead to erroneous diagnoses of gemistocytic astrocytoma and atypical teratoid/rhabdoid tumors in the pediatric age group [5].

3.3. Genetics

From the previous literature, the most common chromosomal mutation in gliosarcoma is copy number loss, accounting for 57 % of the total copy number change, far exceeding the increase in copy number (26.2 %), amplification, and heterozygous loss events. Chromosomes 9 and 10 show the highest number of losses, while the majority of copy number gains are seen on chromosome 7 [35,36]. In previous genomic assay reports, epidermal growth factor receptor (EGFR), phosphatase and tension protein homolog (PTEN) and TP53 were the most reported candidate genes; however, mutations in EGFR are also uncommon in GSM [37,38]. In GSM, TP53 mutations are more common (70 %) and show a positive correlation with the shorter survival time and epithelial mesenchymal transition (EMT) process of the sarcomatous components of GSM patients [39].Although we have identified potential biomarker genes for the occurrence of GSM, the typical underlying mechanisms remain unclear.

3.4. Management

Meis et al. established criteria for the diagnosis of gliosarcoma on the basis of histological features: the tumor should be bimorphic, composed of two morphologically distinct populations of malignant cells; one component should be glial in nature with necrotic areas and must fulfil criteria adopted for defining glioblastoma, and the other component should be sarcomatous, resembling spindle cell sarcoma, and must fill one medium-power field under a 10× objective with a 10× eyepiece [40].Previous literature has reported the importance of general total resection in obtaining a relatively good prognosis [5].However, other studies have shown that despite the use of general resection and aggressive chemoradiation, the prognosis remains unsatisfactory or even poor [14,19,24]. The median survival period after aggressive treatment is only a few months [24,14]. In a previous case report, researchers suggested that temozolomide (TMZ) showed good tolerance in the treatment of gliosarcoma in children, with two-year progression-free survival and

Table 1
Summary of cases of pediatric gliosarcoma published previously by literature search.

S. No	Ref	Year of publication	Numer of cases	Age (years)	Gender (Male/ Female)	Location	Extent of resection (Total/partial)	Post-resection radio/ chemotherapy	Follow up
1	Goldstein et al. [6]	1981	1	0	Female	Left cerebral hemisphere (diffuse widespread involvement)	-	-	–
2	McKeewer et al. [7]	1984	1	18	Female	Occipital lobe	Subtotal	Radiotherapy	Died 12 months after resection
3	Bukhari et al. [8]	2020	1	12	Male	Occipital lobe	Subtotal	–	Recurrence 2 years after resection. Re-resection done, then lost to follow up
4	Jeng & Reynolds [9]	2020	1	12	Male	Right frontal lobe	Partial	Radio & chemotherapy	Recurred 8 months after resection. Alive *
5	Dutta et al. [10]	2018	1	8	–	Parieto-occipital lobe	Subtotal	Radio & chemotherap	Tumor recurred. Repeat surgery. Died
6	Yao et al. [11]	2017	1	6	Female	Cervical spine (C1–C6)	–	Radiotherap	Metastatic dissemination
7	Granados et al. [12]	2017	1	5	Female	Pineal	–	Radio & chemotherapy	Died 6 months after resection
8	Meena et al. [2]	2016	1	12	Female	Right parieto-occipital lobe	Total	Radiotherapy	–
9	Mallick et al. [13]	2015	5	7	Female	–	Total	Radiotherapy, Temozolomide	Progressed 13 months after resection
				–	Male	–	Subtotal	–	Lost to follow up Alive at 3.5 years after resection
				–	Female	–	Total	Radiotherapy, Temozolomide	
				–	Female	–	Total	Radiotherapy, Temozolomide	Alive at 2 years after resection
				19	Female		Total	Radiotherapy, Temozolomide	Progressed 43 months after resection
10	Savant et al. [14]	2015	1	5	Female	Left parieto-occipital lobe	Total	Chemotherapy	Died 9 months after resection
11	Burzyuski et al. [15]	2014	1	9	Male	Pons	Subtota	Chemotherapy	Alive at > 13 years*
12	Martin et al. [16]	2014	1	11	Male	–	Near total	Radio & chemotherapy	Alive at 34 months after resection
13	Ravisanker et al. [17]	2012	1	11	Male	Right temporo-parietal cortex	Total	Radiotherapy, Temozolomide	Alive
14	Neelima et al. [18]	2012	1	11	Male	Thalamus	Near total	–	–
15	Karremann et al. [19]	2010	4	8	Female	Right temporal lobe	Total	Radiotherapy	Died 6 months after resection
				10	Male	Right temporal lobe & lateral ventricle	Total	Radiotherapy	Died 18 months after resection
				6	Male	Right fronto-parietal lobes, corpus callosum	Partial	Radiotherapy	Died 4 months after resection
				9	Male	Right mesencephalon	Partial	Radiotherapy	Alive at 14 months after resection
16	Hocwald et al. [20]	2009	1	0 (congenital)	Male	Left anterior cerebral hemisphere	None	Not given	The anterior fontanelle is protruding. Unresponsive at birth. Intensive care was withdrawn after counseling Parents. Babies die at 1 day of age
17	Salvati et al. [21]	2006	3	15	Female	Right temporal lobe	Total	Not given	Died 5 months after resection

(*continued on next page*)

Table 1 (*continued*)

S. No	Ref	Year of publication	Numer of cases	Age (years)	Gender (Male/ Female)	Location	Extent of resection (Total/partial)	Post-resection radio/ chemotherapy	Follow up
				13	Female	Midline tumor-parieto-occipital lobes reaching corpus callosum	Subtotal	Radiotherapy	Alive at 9 months after resection
				16	Male	Parasagittal frontal	Total	Radiotherapy	Alive at 24 months after resection (Hemangioblastoma 10 years ago, radiation given)
18	Deb et al. [22]	2006	1	18	Male	Right frontal lobe	Decompression	Irradiation given for giant cell glioblastoma (transfor mation to gliosarcoma)	Alive at 1 month after decompression
19	Malde et al. [23]	2004	1	21	Female	Left frontal lobe	Total	Radiotherapy	Alive at 6 months after resection (Medulloblastoma eight years before, radiation)
20	Okami et al. [24]	2002	1	2	Male	Left frontal lobe	Total	Radiotherapy	Died 3 months after resection (relapsed in one month)
21	Rizk et al. [25]	2000	1	0		Left temporo-parieto-occipital lobes	Total	Not given	Perioperative death
22	Kepes et al. [26]	1996	1	19	Female	Left parieto-occipital lobe	–	Not given	Died 7 months after resection (had recurrent ependymoma, WHO grade II 29 months ago; irradiated)
23	Lach et al. [27]	1996	1	18	Male	Right frontal lobe	Partial	Not given	Died 5 months after resection (had diffuse astrocytoma, WHO grade II 10 years ago)
24	Kaschten et al. [28]	1995	1	13	Male	Right temporo-parieto-occipital lobes	Total	Radiotherapy	Died 13 months after resection
25	Ono et al. [29]	1990	1	0	Female	Left temporo-parietal lobes & basal ganglia	Total	Radiotherapy	Alive at 34 months after resection
26	Radkowski et al. [30]	1988	1	0	Male	Right temporal lobe	–	–	Alive at 21 months after resection
27	Takaue et al. [31]	1986	1	11	Male	Right fronto-parietal lobes	Total	Radiotherapy	Alive at 25 months after resection (had Hodgkin lymphoma seen years ago
28	Lee et al. [32]	1985	2	12	Male	Right frontal lobe	Total	Radiotherapy (had Hodgkin lymphoma seven years ago)	Alive at 16 months after resection
				14	Female	Both frontal lobes & corpus callosum	Partial	Partial	Died 3 months after resection

overall survival rates of 44.2 % and 62.9 %, respectively [13].Tumor-treating field (TTField) therapy is a novel treatment technique that has been used in the treatment of GBM with good results [41].

3.5. Limitations

However, there are some limitations in this report. First, the number of cases included in the report is relatively small. Therefore, the statistical significance of the data is still worth discussing. Second, the case had no obvious positive signs. Finally, the prognosis for GSM is extremely poor despite the existence of relatively sophisticated treatments.

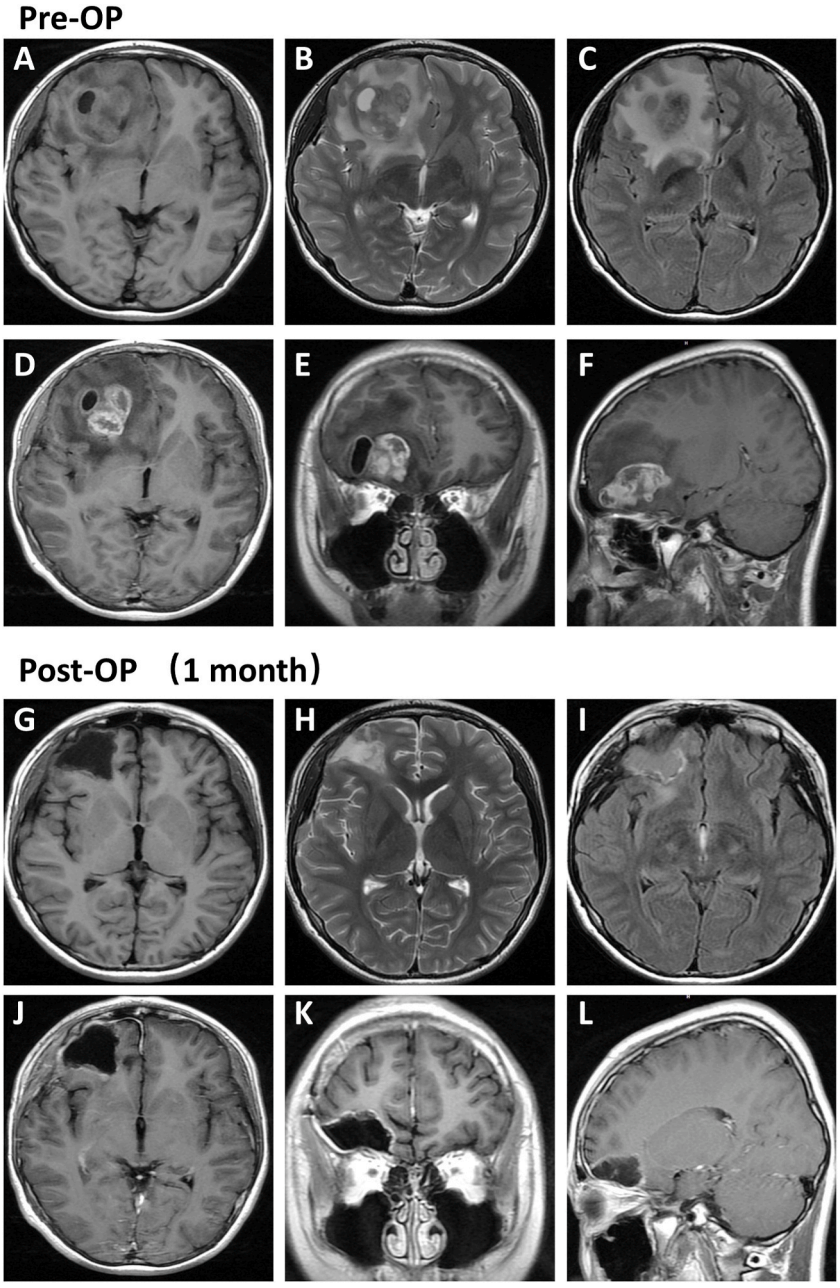

Fig. 1. Preoperative MRI: (A) axial T1 image; (B), axial T2 image; (C), axial T2-FLAIR image; (D), axial T1-weighted image with gadolinium contrast; (E) coronal T1-weighted image with gadolinium contrast; (F) sagittal T1-weighted image with gadolinium contrast. Postoperative MRI: (G) axial T1 image; (H) axial T2 image; (I) axial T2-FLAIR image; (G) axial T1-weighted image with gadolinium contrast; (K) coronal T1-weighted image with gadolinium contrast; (L) sagittal T1-weighted image with gadolinium contrast.

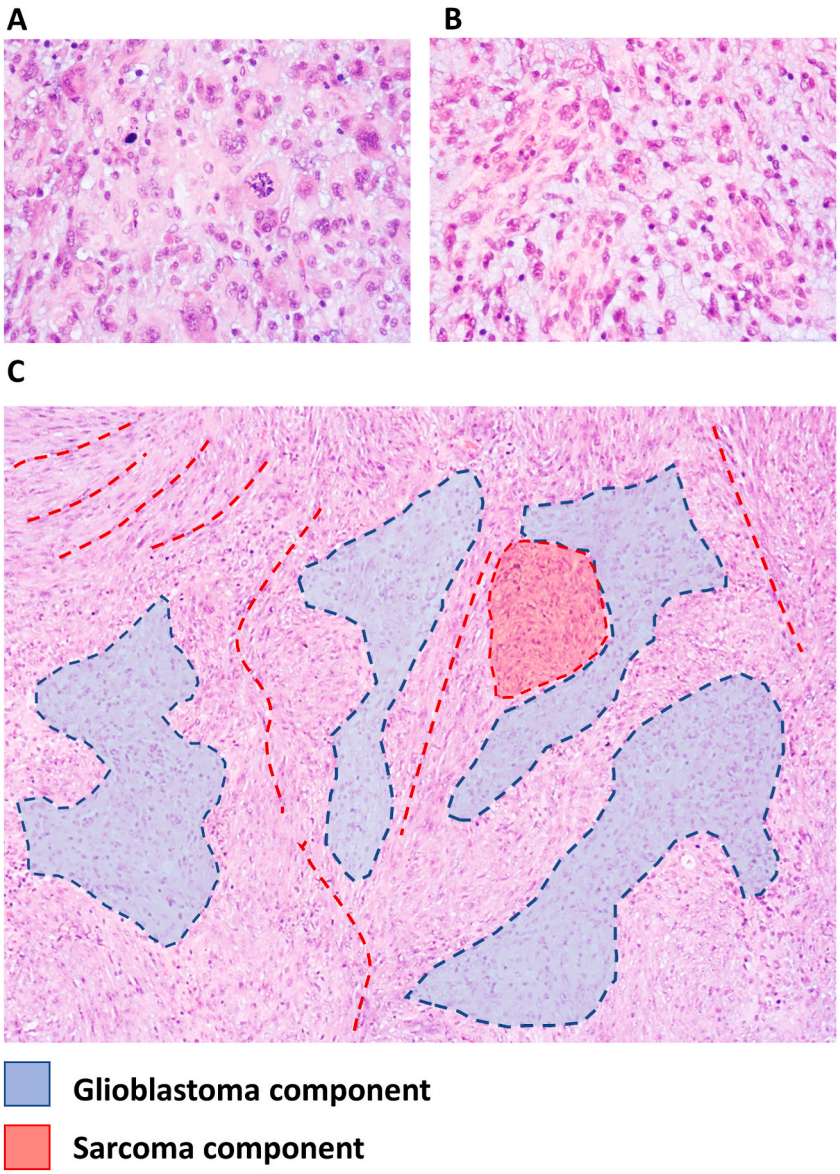

Fig. 2. Postoperative pathology: (A) Glioblastoma area; (B) Sarcoma area(C) The spindle cell bundle is a sarcoma with interspersed glioblastoma components.

4. Conclusion

GSM is a rare disease, even more so in children. Pediatric GSM is clinically and morphologically consistent with adult gliosarcoma; however, molecular pathology and radiological differences remain to be noted. The prognosis of patients with GSM remains grim despite the variety of advanced diagnostic and therapeutic approaches. More case reports of GSM should be conducted, which would allow a clearer diagnosis and improved treatment methods and prognoses.

Table 2
Genetic testing of case.

IDH-1	TERT	BRAF	TP53	EGFR	Chromosome7	Chromosome10
-	+	-	+	-	-	-

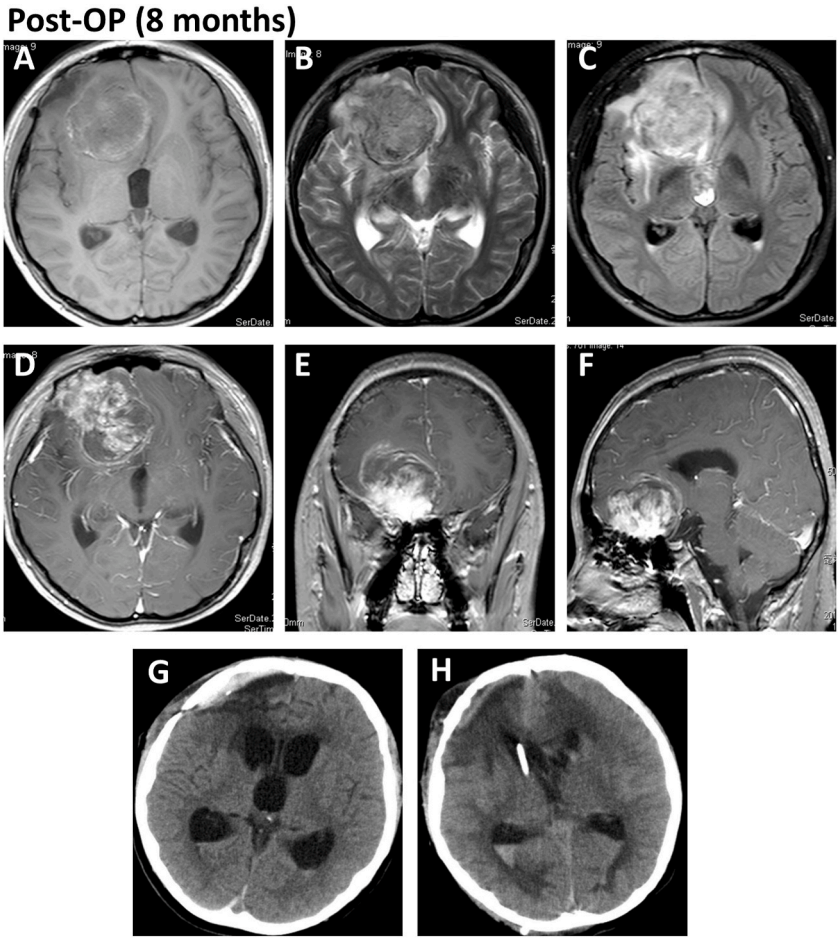

Fig. 3. Eight-month postoperative MRI: (A) axial T1 image; (B) axial T2 image; (C) axial T2-FLAIR image; (D) axial T1-weighted image with gadolinium contrast; (E) coronal T1-weighted image with gadolinium contrast; (F) sagittal T1-weighted image with gadolinium contrast; (G) second postoperative CT; (H) post–V-P bypass CT.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Funding

This work was supported by the Natural Science Foundation of Shandong Province (grant number: ZR2021MH228).

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jinyan Chen: Writing – review & editing, Writing – original draft. **Dong He:** Data curation. **Gengyin Guo:** Formal analysis. **Keke Zhang:** Formal analysis. **Wenliang Sheng:** Formal analysis. **Zhen Zhang:** Visualization, Supervision, Resources, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that

could be construed as a potential conflict of interest.

Acknowledgements

Not applicable.

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