ORIGINAL RESEARCH

Clinical Characteristics of Childhood-Onset Craniopharyngioma

Lihua Tian, MD; Liyong Zhong, MD, PhD

ABSTRACT

Objective • Craniopharyngioma (CP) is an intracranial congenital epithelial tumor that can occur at any age. CP tumors are histologically benign (WHO grade I), and childhood-onset CP (CO-CP) patients have a high rate of survival. The major concern for CO-CP patients is delayed diagnosis. Delayed diagnosis can further lead to serious adverse consequences such as acute and chronic complications, thereby endangering the life of the patient. We evaluated the early-stage clinical characteristics of CO-CP patients to provide clues for making rapid and accurate diagnoses.

Methods • This was a retrospective, single-center study. We retrospectively reviewed all pediatric patients (<18 years of age) undergoing CP surgery between 2012 and 2019 at a single institution. Data including demographic data, clinical presentation, neuroendocrine dysfunction, and tumor imaging characteristics at diagnosis were analyzed.

Results • The average age of the 192 children in this study was 7.32±3.94 (0–16) years, 91.0% were diagnosed when under 14 years old, and 92.7% of patients had at least one clinical symptom, and 90.7% of tumors have a diameter greater than 2cm, and 95.9% of tumor consistency was mixed or cystic, and 89.0% of tumors found calcification. The patients with hydrocephalus had higher BMI values than those without hydrocephalus (P = .006), and the incidence of calcification of tumors significantly decreased with age (P = .027).

Conclusions • For pediatric patients with calcification, >2 cm, cystic or mixed intracranial mass lesions, CP tumors should be considered, and early neuroendocrine function evaluation and further surgical treatment should be performed to avoid delayed diagnosis. (*Altern Ther Health Med.* 2024;30(10):302-307).

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INTRODUCTION

Craniopharyngioma (CP) is a rare and histologically benign embryonic tumor that grows along the pathway of the embryonic craniopharyngeal tube. The latest research suggests that CP tumors are non-neuroepithelial tumors located in the epi-pia mater and epi-third ventricle.[1] The overall incidence of CP is 0.13 cases per 100 000 person-years.[2] CP includes two histologically distinct variants: adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). Genetic and molecular pathologic features support the distinct pathogeneses of ACP and PCP. The majority of ACP cases involve somatic mutations in CTNNB1, resulting in the expression of a degradation-resistant form of β-catenin and activation of the WNT/β-catenin pathway.[3,4] V600E point mutations in BRAF have been identified as a signature of most PCP tumors.[4,5] Moreover, mutations in CTNNB1 and BRAF V600E are mutually exclusive in ACP and PCP.[5] Surgical resection with/without radiotherapy is considered to be the first choice of treatment for CP. In some PCP patients, BRAF inhibitors can be used for treatment.[6] The main clinical symptoms of CP are similar to those of other intracranial tumors and include high intracranial pressure, visual field defects, endocrine dysfunction, and hypothalamic dysfunction.

CP can be found at any age, and the age distribution of CP is thought to be bimodal, with peaks corresponding to childhood-onset CP (CO-CP) at 5–14 years and adult-onset CP (AO-CP) at 50–74 years. Compared with AO-CP, the tumors of CO-CP patients tend to progress more slowly, hindering early detection.[7] Therefore, CO-CP patients have more serious long-term health conditions, many CO-CP patients suffer from challenging neurobehavioral, social, and emotional issues. [8]

Although our understanding of CP has increased greatly in the last 20 years, [3-5] however, few studies have focused on

the diagnostic stage of CP. Our study seeks to identify the relationship between internal factors of tumors and clinical data of patients, utilizing accurate evaluation of early diagnostic symptoms and preoperative computed tomography (CT) and magnetic resonance imaging (MRI) to obtain neuroimaging features of tumors,[9] in order to provide early clinical information for diagnosis and avoid delayed diagnosis.

Table 1. Distribution of the age at CO-CP diagnosis.

Age (y)	0+	1+	2+	3+	4+	5+	6+	7+	8+	9+	10+	11+	12+	13+	14+	15+	16+	17+
n	1	4	19	22	18	17	21	26	16	15	16	10	12	7	7	7	6	0
%	0.4	1.8	8.5	9.8	8.0	7.6	9.4	11.6	7.1	6.7	7.1	4.5	5.4	3.1	3.1	3.1	2.8	0
Cumulative Percentage (%)	0.4	2.2	10.7	20.5	28.5	36.1	45.5	57.1	64.2	70.9	78.0	82.5	87.9	91.0	94.1	97.2	100	-

Table 2. Numbers of male and female CO-CP patients by age.

Age (y)	0+	1+	2+	3+	4+	5+	6+	7+	8+	9+	10+	11+	12+	13+	14+	15+	16+	17+
Male (n)	1	1	10	13	10	9	10	14	12	7	8	2	7	4	4	4	4	0
Female (n)	0	3	9	9	8	8	11	12	4	8	8	8	5	3	3	3	2	0
$\chi 2$	11.272																	
P value	.792																	

METHODS

Ethical approval

This study was approved by the local ethics committee according to the Declaration of Helsinki (IRB of Beijing Tiantan Hospital, Capital Medical University, KY2022-024-01, 2022.3.16). All procedures involving human participants followed the ethical standards of the institutional and/or national research committee and complied with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Subjects

The clinical records of 192 CO-CP patients treated by CP surgical resection from May 2012 to June 2019 were reviewed. The medical records and imaging data of the patients at the diagnostic stage were analyzed retrospectively. The inclusion criteria were as follows: 1) age less than 18 years and 2) surgical resection with a histopathological diagnosis of CP. Of the 192 patient tumors, 188 (97.9%) were classified as ACP subtype, and 4 (2.1%) were classified as PCP subtype.

Methods

The following clinical data of CO-CP patients were retrospectively retrieved from medical records:

1) demographic data at diagnosis, including age, gender, weight, and height;
2) clinical symptoms at diagnosis, including visual impairment (e.g., loss of visual acuity and visual field defects), increased internal pressure (e.g., headache, nausea, and vomiting), growth retardation, polydipsia, and polyuria;
3) pituitarytarget gland axis dysfunction and hyperprolactinemia at diagnosis;
4) radiographic characteristics at diagnosis, including preoperative tumor MRI/CT indexes, including tumor diameter, tumor texture, tumor location, tumor calcification, and hydrocephalus.

The concepts involved in the article are explained as follows:

1. Growth retardation: height lower than the P3 percentile value of the "standardized curve of height of children and adolescents aged 0–18 in China".[10]
2. Polydipsia and polyuria: urine volume > 3 mL/kg/h or > 2000 mL/24 h, urine specific gravity decreased < 1.005, and water deprivation test for the diagnosis of central diabetes insipidus or lack of sense of thirst.[11]
3. Impaired pituitarytarget gland axis at diagnosis: 1) impaired pituitary-adrenal axis (IAA): It was indicated by cortisol and adrenocorticotropic-hormone (ACTH) levels are below the lower limit of the normal reference value (< 50 ng/mL at 8 AM) and and/or the rhythm of secretion disappears; 2) impaired pituitary-thyroid axis (ITA) : It was indicated by over two items (TT3, TT4, FT3, and FT4) being lower than the normal low limit along with normal thyroid-stimulating-hormone (TSH) or TSH below the normal low limit; 3) impaired pituitary-gonad axis (IGA): It was indicated by abnormal secondary sexual characteristics (irregular menstruation or stunted secondary sexual characteristics).[12]
4. Hyperprolactinemia (HPRL): It was indicated that serum prolactin (PRL) level was higher than normal (normal reference value: 0–25 mg/mL).
5. Preoperative tumor CT/MRI imaging indexes: 1) tumor diameter, 2) tumor texture, 3) tumor location (CP was classified into three types, intrasellar, suprasellar, and intrasellar-suprasellar, according to the Steno method), 4) hydrocephalus, and 5) calcification.

Statistical analyses

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS 25.0 IBM, Chicago, IL, USA). Evaluations were based on the number of patients with available data. Students' ttest was used to compare the BMI values of CO-CP patients with and without hydrocephalus, and chisquare test were used to compare the numbers of male and female CO-CP patients by age and the occurrence of tumor calcification by age. Results were considered to be statistically significant at $P < .05$.

RESULTS

Part 1 Characteristics of CO-OP at diagnosis

Distribution of age at first diagnosis. The average age of the 192 CO-CP patients was 7.32±3.94 (0–16) years. The distribution of age at first diagnosis centered around 2–10 years, with 91.0% of the CO-CP patients diagnosed at under 14 years old and none diagnosed at 17 years or older (Table 1).

Gender distribution of patients. The study population included 120 males (53.5%) and 104 females (46.5%), resulting in a male-to-female ratio of 1.15:1. The gender distribution was similar in all age groups ($\chi^2 = 11.272$, $P = .792$; Table 2).

Presenting symptoms at diagnosis. The most common symptoms in the 192 cases of CO-CP included high intracranial pressure (e.g., headache/nausea/vomiting and visual disturbances), growth retardation, polyuria, and polydipsia, which occurred in 59.9%, 55.7%, 32.8%, and 20.3% of the patients, respectively. The distribution of presenting symptoms was similar among all age groups and genders (Table 3).

Of the 192 patients, 178 (92.7%) had at least one clinical symptom, 9 (4.6%) had all four of the above clinical symptoms, 26 (13.5%) had three, 67 (34.9%) had two, 75 (39.0%) had one, and 14 (7.3%) had no clinical symptoms (Table 3).

Endocrinological status at diagnosis. All patients in this study were preadolescents with immature pituitary-gonadal function; thus, the gonadal axis was not evaluated. The patients did not complete insulin tolerance tests, and the serum insulin-like growth factor (IGF-I) concentrations were not measured. Thus, the growth hormone (GH)-IGF-1 axis was not evaluated. Endocrinological status was evaluated at diagnosis based on TSH, ACTH, and PRL.

Of the 192 patients, 80 (41.7%) had at least one impaired pituitarytarget gland axis; 12 (6.3%) were IAA, 34 (17.7%) were ITA, and 33 (17.2%) were HPRL. The impaired pituitarytarget gland axis at diagnosis was similar among all age groups and genders (Table 3).

Body mass index (BMI) at diagnosis. Of the 192 patients, the average BMI was 18.09±4.37 (9.92–33.30) kg/m^2. Based on the BMI and age-growth charts, the patients were classified as obese (51 of 192 patients, 26.6%), overweight (24, 12.5%), underweight (63, 32.8%), or normal (54, 28.1%; Table 3).

Neuroimaging characteristics at diagnosis. The neuroimaging characteristics evaluated at diagnosis included tumor size (mm), consistency, localization, and hydrocephalus. CT and MRI were available in our institution. Localization, the maximum diameter of the mass, consistency of the mass, and hydrocephalus were assessed based on cranial MRI at diagnosis. Hydrocephalus was defined as progressive ventricular enlargement. CT assessed the presence of calcification in all cases. Tumor size was estimated by measuring the maximum anteroposterior, vertical, and horizontal diameters. The mean initial tumor diameter among the 192 patients was 38.0 mm (IQR, 30.0–46.0 mm). No tumor was smaller than 10 mm, and 174 patients (90.7%) had tumors exceeding 2 cm in size. The consistency of the tumor was categorized as cystic (61 patients, 31.8%), solid (8 patients, 4.1%), or mixed (123 patients, 64.1%). Lesions were topographically defined as intrasellar, suprasellar, or both intra- and suprasellar according to their relationship with the diaphragm sellae. Intrasellar and supradiaphragmatic tumors accounted for 13 cases (6.7%) and 82 cases (42.7%), respectively, and the remaining 97 cases (50.5%) showed intro/extra-ventricular extension. Calcification was found in 171 (89.0%) of patients. Hydrocephalus was found in 55 (28.6%) of patients (Table 3).

Table 3. Patient characteristics at CO-CP diagnosis.

Baseline characteristic	n	%
Symptoms	192	
High intracranial pressure	115	59.9
Visual disturbances	107	55.7
Growth retardation	63	32.8
Polyuria and polydipsia	39	20.3
The endocrinological status at diagnosed	192	
TSH loss	12	6.3
ACTH loss	34	17.7
PRL rise	33	17.2
BMI	192	
Obese	51	26.6
Overweight	24	12.5
Normal	54	28.1
Underweight	63	32.8
Tumor size (mm)	192	
≥ 50	25	13.0
40–49.9	38	19.8
30–39.9	63	32.8
20–29.9	48	25.0
10–19.9	18	9.3
< 10	0	0
Consistency	192	
Cystic	61	31.8
Solid	8	4.1
Mixed	123	64.1
Localization	192	
Intrasellar	13	6.7
Intra-/suprasellar	97	50.5
Suprasellar	82	42.7
Presence of hydrocephalus	55	28.6
Presence of calcification	171	89.0

Table 4. Comparison of the BMI values of CO-CP patients with and without hydrocephalus (*t* test).

	CO-CP patients with hydrocephalus	CO-CP patients without hydrocephalus
BMI	19.50±5.30	17.52±3.80
F	7.717	
P value	.006	

Table 5. Occurrence of tumor calcification by age.

Age(y)	0+	1+	2+	3+	4+	5+	6+	7+	8+	9+	10+	11+	12+	13+	14+	15+	16+	17+
Sample, n	1	3	17	16	16	15	17	22	16	11	14	9	10	6	6	7	6	0
Calcification, n (%)	1 (100)	3 (100)	17 (100)	16 (100)	15 (94)	12 (80)	13 (76)	21 (95)	16 (100)	9 (82)	13 (93)	8 (88)	9 (90)	4 (67)	4 (67)	5 (71)	3 (50)	0
$\chi 2$	28.631																	
P value	.027																	

Part 2 Relationships among the various indexes

BMI. Kendall's tau-b correlation was used to evaluate the relationships between BMI and age, gender, endocrinological status, and tumor characteristics. No correlations were found between BMI and age, gender, ACTH, TSH, PRL, tumor size, and calcification ($P > .05$). A poor correlation was observed between BMI and hydrocephalus (Kendall's tau-b = 0.192, $P = .004$). An independent-sample t-test indicated a difference between the BMIs of patients with and without hydrocephalus; patients with hydrocephalus had higher BMI values ($P = .006$; Table 4).

Age. The tumor size, consistency, localization, and hydrocephalus were similar among all age groups. The presence of tumor calcification differed between age groups, with the incidence of calcification decreasing significantly with increasing age ($P = .027$; Table 5).

DISCUSSION

Significant complications related to the tumor and its mass may occur during the diagnostic stage of CO-CP, including visual loss, neurological and behavioral deficits,

endocrinopathies, cerebral vascular disease, hypothalamic dysfunction, and hypothalamic obesity. These complications can significantly impair the patient's quality of life, resulting in challenging neurobehavioral, social, and emotional issues in CO-CP patients, 53% of CO-CP patients were overweight or obese， and there was a significant trend towards obesity over time. Hypothalamic obesity is associated with increased mortality. [13]

CP tumors grow slowly, and their location enables them to be large at the time of diagnosis. Because CP tumors originate adjacent to delicate structures, they often exert substantial mass effects on critical structures, including the hypothalamus, optic pathway, the vessels in the circle of Willis, and the third ventricle. The initial symptoms of CO-CP are frequently unspecific, and the infiltrative behavior of the lesion may hamper its early diagnosis, resulting in relatively late diagnoses.[14] Thus, it is paramount to understand the clinical manifestations at the diagnostic stage.

CP is a continuous and chronic pathophysiological process, and its clinical phenotype has significant heterogeneity. In this study, we assessed clinical characteristics at the time of diagnosis.

Age

CP tumors may be detected at any age. The American study published in 1998,[2] it described the epidemiology of CP, approximately 96 cases in children from 0 to 14 years of age in the United States. In a Finnish study of CP patients diagnosed from 1951 to 1982, the distribution of age at onset peaked at 11–20 years.[15] In a study conducted in Denmark from 1985–2004,[16] the main groups of age at onset were 5–9 and 40–44 years. In a 2005 study conducted in the UK,[17] was the peak age at onset of CP, which was 15–20 years. In a Swedish study published in 2015,[18] the mean age at onset for children was 10±4.6 years.

Although our study was a single-center study, the participants came from all over the country. The study subjects were children aged 0–18 years. The peak age of CO-CP onset was 2–10 years, and 90.7% of the patients were under 14 years old at onset. The difference between the peak ages of CO-CP onset in this study and in past studies may be related to the different countries, study periods, number of patients, and age groups.

Gender

The results of our study agree with past works indicating that the morbidity of CO-CP is similar between males and females, regardless of the number of patients and study period.[2,15,18-23] We also found similar gender distributions among all age groups, and the characteristics at CO-CP diagnosis were not associated with gender.

Presenting symptoms at diagnosis

The clinical manifestations of CO-CP patients generally reflect the slow growth and location of CP tumors. These tumors frequently affect the hypothalamus, pituitary region, and optic chiasm. The diagnosis of CP is often made late, sometimes years after the initial appearance of symptoms.[24] Delayed growth, which is a common early symptom in many pediatric patients, becomes apparent long before diagnosis.[25] Visual impairment and headaches are the two most common manifestations of elevated intracranial pressure in CO-CP patients.[26-28] In our study, symptoms of high intracranial pressure, including headache/nausea/vomiting, were the most common disease manifestations.

The presentation of CO-OP varies by patient age, with young children (<10 years) manifesting with general symptoms of increased intracranial pressure and hydrocephalus and adolescents and young adults (10–18 years) presenting with visual deficits and hypopituitarism.[29,30] In our study, the presenting symptoms at diagnosis were similar for all age groups and genders. The discrepancy in comparison with past studies may be related to symptom heterogeneity.

A German study published in 2015[31] indicated that the initial symptoms were not found in the records of 16% of patients. In our current study, 14 patients (7.3%) showed no clinical symptoms, while 178 (92.7%) had at least one clinical symptom. This result differs from previous findings, which may be related to the development of modern medicine and improvement in quality of life, which has improved the early detection of CP.

Endocrinological status at diagnosis

Pituitary hormone deficiencies are frequent disease- and/or treatment-related morbidities in CP.[32] In many cases, the volume effect of the tumor results in panhypopituitarism.[33,34] A review published in 2008[24] indicated that 40%–87% of children present with at least one deficient hypothalamic-pituitary axis at the time of CP diagnosis, in a German study published in 2015,[31] 44% of CP patients presented with endocrine deficits at the time of diagnosis, whereas no endocrine deficits were initially noted in 56% of patients.

In our study, the endocrinological status (TSH, ACTH, and PRL) was evaluated at diagnosis. Among the 192 patients, 80 (41.7%) patients had at least one abnormal pituitary hormone level, and 122 (58.3%) had no abnormal hormone levels. Abnormal ACTH, TSH, and PRL were found in 12 (6.3%), 34 (17.7%), and 33 (17.2%) patients, respectively, with similar rates of each observed among all age groups and genders.

The preoperative identification of endocrine deficiency in CO-CP patients informs the possibility of intracranial turmors, and replacement hormone therapy optimizes patient safety for surgery.[35] In a previous study,[23] FSH/LH and GH were the most common abnormal hormones (56% and 53% of patients, respectively), followed by TSH (32%), ACTH (28%), and antidiuretic hormone (ADH) (7%). In the current study, we did not evaluate the pituitarygonadal axis or the pituitary GH-IGF-1 axis, and the most common abnormalities in pituitary hormones were decreased TSH (17.7%) followed by increased PRL (17.2%) and decreased

ACTH (6.3%). The differences in research results may be related to the different age ranges of the patients.

BMI at diagnosis

A retrospective analysis of CO-CP patients indicated that increased weight was evident before the diagnosis.[25] Weight gain may be an indicator of underlying hypothalamic-pituitary dysfunction.[36] In our study, the average BMI was 18.09±4.37 (9.92–33.30) kg/m^2, and 117 of the 192 patients (60.9%) were underweight or had a normal BMI for their age, whereas 75 (39.1%) were obese or overweight. We did not find any correlation between BMI and age, gender, tumor size, or tumor calcification. A poor correlation was observed between BMI and hydrocephalus, with patients with hydrocephalus having higher BMI values than those without hydrocephalus. It suggests that CO-CP patients with hydrocephalus have a higher risk of hypothalamic-pituitary dysfunction.

Neuroimaging characteristics at diagnosis

The neuroimaging characteristics at diagnosis evaluated in this study were tumor size, consistency, localization, hydrocephalus, and calcification. MRI is the standard imaging technique for the diagnosis of CP, and CT is necessary and recommended for the detection of calcification. When the tumor was large or giant cystic and unfavorable tumor localization (hypothalamic involvement), these factors will hinder surgical strategy.

Tumor size

The tumor size has a significant effect on the management of CP in children. Tumor size affects the initial symptoms and metabolic outcomes along with other factors.[33] In a British study published in 1996,[37,] tumor diameter ≥ 3.5 cm was identified as a predictor of tumor recurrence. A 2020 study[38] found that a large or giant tumor (defined as tumor diameter > 4–5 cm) was correlated with a higher rate of recurrence. Tumor size may be dissimilar at presentation, which may affect our understanding of CP. Tumor diameters less than 20 mm are relatively rare, and tumors larger than 10 cm in diameter have been found in patients younger than 15 years old.[21] In the present study, 18 patients (9.3%) had tumor diameters less than 20 mm, and no tumors smaller than 10 mm or larger than 10 cm were observed.

Tumor consistency

The tumor consistency was characterized as one of three types: cystic (cyst volume-occupying more than 50% of the tumor volume), solid, or mixed. ACP is most often cystic with/without a solid component.[39] In a Korean study published in 2012,[22,] solid tumors accounted for 37.1% of cases (13/35). In contrast, in our study, solid tumors accounted for only 4.1% of cases (8/192). This may be related to advances in imaging made since 2012.

Tumor localization

The localization of craniopharyngioma tumors was classified as intro-/suprasellar, suprasellar, or intrasellar. Purely intrasellar craniopharyngiomas are relatively rare.[27] In a study conducted in the Netherlands,[23] only 5% of 63 CO-CP patients had intrasellar tumors. In our study, intrasellar tumors accounted for 13 cases (6.7%).

Calcification

Among CO-CP patients, 70%–90% show calcification.[22] In our study, calcification was found in 171 (89.0%) patients. The imaging evidence of calcification is also important for the differential diagnosis of other intrasellar and suprasellar tumors.[9] In our study, we found an age-based difference in the presence of tumor calcification, with the incidence of calcification decreasing with increasing age.

Hydrocephalus

Hydrocephalus is one of the most common comorbidities associated with brain tumors. Hydrocephalus occurs in 20%–40% of CO-CP patients.[40] In our present study, hydrocephalus was found in 55 (28.6%) patients and was associated with tumor size and localization. In a previous report,[41] cases of obstructive hydrocephalus were associated with large tumors (maximum dimension ≥4.5cm), and severe hydrocephalus was a predictor of tumor recurrence. Hydrocephalus might be considered a risk factor for hypophysial and hypothalamic dysfunction[42] because the rate of hypothalamic dysfunction occurrence is significantly higher when the edema extends to the internal capsule or the optic tract.

This study has some limitations. First, this was a retrospective study. Second, all the patients in this study were preadolescents with immature pituitarygonadal function; as a result, the gonadal axis was not evaluated. Third, the patients did not undergo insulin tolerance tests, and the serum IGF-I concentrations were not measured; thus, the GH-IGF-1 axis was not evaluated. Fourth, the total number of patients was not sufficiently large to provide high statistical power. These limitations may lead to bias in this study. Multi-center studies with larger sample sizes are needed to validate the current results.

In conclusion, CP is a complex tumor because of its clinical heterogeneity. In our CO-CP patients, 192 children in this study was 7.32±3.94 (0–16) years, 91.0% were diagnosed when under 14 years old, and 92.7% of patients present with at least one deficient hypothalamic-pituitary axis, and 90.7% of tumors have a diameter greater than 2cm, and 95.9% of tumor consistency was mixed or cystic, and 89.0% of tumors found calcification. The patients with hydrocephalus had higher BMI values than those without hydrocephalus, and the incidence of calcification of tumors significantly decreased with age. Meanwhile, CO-CP patients with early CP tumors experience varying clinical outcomes and have a quality of life. A comprehensive, accurate, and detailed understanding of the clinical characteristics of CO-CP patients will aid in early detection, early diagnosis, and early intervention in children, thereby helping to improve their quality of life and prognosis.

ETHICAL APPROVAL

This study was approved by the local ethics committee according to the Declaration of Helsinki (IRB of Beijing Tiantan Hospital, Capital Medical University, KY2022-024-01, 2022.3.16). All procedures involving human participants followed the ethical standards of the institutional and/or national research committee and complied with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS CONTRIBUTION

Study conception and design: Lihua Tian, Liyong Zhong; data collection: Lihua Tian; analysis and interpretation of results: Lihua Tian, Liyong Zhong; draft manuscript preparation: Lihua Tian, Liyong Zhong. All authors reviewed the results and approved the final version of the manuscript.

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