

Cytoreductive radical prostatectomy or radiation therapy for metastases prostate cancer Evidence from meta-analysis

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Abstract

Background: Cytoreductive radical prostatectomy (RP), transurethral resection of the prostate, and radiation therapy were the main local treatments for oligometastatic prostate cancer (PCa). An optimal local treatment for metastases PCa was not consensus. The purpose of this study was to evaluate the effect on these local treatments for patients with metastases PCa.

Methods: All relevant studies were systematically searched through PubMed, Web of Science through November 1, 2021. Studies were screened by inclusion and exclusion criteria. Progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) were evaluated by this meta-analysis.

Results: Eleven studies were identified that met the inclusion criteria. 644 patients received cytoreductive surgery, 8556 patients received no surgery or radiation therapy (RT), and 461 patients received RP + androgen deprivation therapy compared with 746 patients who received RT. Pooled data indicated that cytoreductive surgery significantly prolonged the PFS (OR = 0.65, 95% CI 0.53–0.80, P < .0001), CSS and OS (OR = 0.49, 95% CI 0.43–0.56, P < .00001; and OR = 0.80, 95% CI 0.72–0.88, P < .00001; respectively). Comparing cytoreductive surgery with RT, CSS, and OS were similar (OR = 0.82, 95% CI 0.67–1.01, P = .06; and OR = 0.93, 95% CI 0.79–1.09, P = .39; respectively).

Conclusions: Cytoreductive radical prostatectomy significantly prolonged the PFS for metastatic PCa. Although OS was considered a-not-so significant difference between cytoreductive surgery and non-local therapy, non-local treatment was not recommended.

Abbreviations: ADT = androgen deprivation therapy, CSS = cancer-specific survival, mHSPC = metastatic hormone-sensitive prostate cancer, OR = odds ratio, OS = overall survival, PCa = prostate cancer, PFS = progression-free survival, RP = radical prostatectomy, SEER = Surveillance Epidemiology and End Results, TURP = transurethral resection of the prostate.

Keywords: cytoreductive surgery, meta-analysis, metastases, prostate cancer, radiation

1. Introduction

It was estimated 248,530 new cases and 34,130 deaths of prostate cancer (PCa) in the USA in 2021,^[1] Approximately 1.3 million new cases are diagnosed worldwide every year, and about 10 million men are presently living with prostate cancer. Approximately 700,000 of these are living with metastatic disease, and metastatic prostate cancer accounts for more than 400,000 deaths annually.^[2] Localized prostate cancer contained within the prostate gland was considered to be curable by radical prostatectomy, radiation therapy, etc.^[3] whereas epidural, pelvic lymph node, and bone metastatic prostate cancer were currently incurable and consequence of poor outcomes.^[4] Despite significant advances in systemic therapies, survival for men with metastatic prostate cancer has not significantly improved over the past 20 years.^[5]

ZP and AH contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Since it was prompted by Culp et al that local treatment in patients with metastatic PCa was associated with a survival benefit compared with no local treatment,^[6] local treatment was gradually applied in oligometastatic PCa which was typically defined as prostate cancer with three to five metastatic lesions.^[7] The role of local treatments including cytoreductive radical prostatectomy and radiation therapy were extensively researched in recent years; however, optimal local treatment for metastases especially oligometastatic prostate cancer was not consensus.^[4,8]

Cytoreductive radical prostatectomy, transurethral resection of the prostate (TURP), and radiation therapy were the main local treatments for oligometastatic PCa. In 2012, Chinese clinicians investigated the oncologic influence of TURP as a cytoreductive surgery in metastatic hormone-sensitive prostate cancer (mHSPC), and results showed TURP obtained a better

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and more prolonged response to hormone therapy in mHSPC, with a trend toward positive influence in disease-specific survival and overall survival.^[9] Two years later, Antwi and Culp separately evaluated the survival of men diagnosed with mPCa based on Surveillance Epidemiology and End Results (SEER) (2004–2010). Similar results were found that RP or brachytherapy appeared to confer a survival benefit.^[6,10] However, prospective data could not show a significant benefit of RP on survival,^[7,10] whereas, other data showed radiotherapy brings important benefits in overall treatment efficacy without major side effects.^[11] Thus, we performed this meta-analysis to compare the survival benefit of TURP, RP, and radiotherapy. Therefore, subgroup analysis was also performed according to the lesions number and study type.

2. Materials and Methods

2.1. Search strategy

This meta-analysis was performed by searching PubMed and Web of Science through November 1, 2021. Additional records were identified through other sources (by screening the reference in the identified studies). Searches included the terms "metastatic prostate cancer" and "survival." The citations in the retrieved articles were reviewed to identify other potentially relevant studies.

2.2. Inclusion and exclusion criteria

Two researchers independently extracted the data, and an agreement was reached after discussion when divergences appeared. Studies that met the following criteria were included in this meta-analysis: all patients were pathologically diagnosed with prostate cancer; computed tomography, magnetic resonance imaging, or other examinations indicated cancer metastases; comparison between RP and radiotherapy, or no local treatment; and sufficient survival data were available to analysis. Major exclusion criteria were: single-arm research or no comparison; incomplete data for the analysis; books, meta-analysis, reviews, conference abstracts, case report, letters to editors/commentaries/editorials, and articles published in a language that cannot be translated; and duplicate data (these were removed and only the updated data were selected).

2.3. Data extraction

Author, publication year, the patient number for cytoreductive surgery or control group, type of study, cancer-specific survival, overall survival, follow-up time, and lesion number were collected from the included publication. The status of oligometastatic PCa was defined by the following standard: presence of five or few metastatic bone lesions, without visceral metastases by imaging diagnosis.

2.4. Statistical analysis

The statistical analysis was performed by using Review Manager Software (version 5.4) and STATA 12 (Stata Corp., College Station, TX). For dichotomous variables, the Mantel Haenszel method will be used for analyses. Relative risk with 95% confidence intervals will be reported for effect size. For continuous variables, the inverse variance method will be used for analyses and treatment effect will be reported as mean difference with 95% confidence intervals. Odds ratio (OR) with 95% confidence interval (CI) were analyzed, and the weighted mean difference with 95% CI was calculated. The heterogeneity in the studies was evaluated using I^2 statistics (value ranged from 0 to 100%). I^2 value > 50% was considered indicative of substantial heterogeneity that is due to real differences in

protocols, trial populations, interventions, and/or outcomes. Cochran Q test P value < .05 indicates that the heterogeneity is beyond chance or random error. The random-effect model will be used if I^2 value > 50%. Funnel plots were drawn to estimate publication bias. P < .05 was defined as statistically significant.

3. Results

3.1. The characteristic of included studies

A total of 1117 records were identified through datasets; after excluding records according to the inclusion and exclusion criteria, 11 researches were included in this meta-analysis (Fig. 1).^[5–7,9,12–18] Of these researches, one compared TURP + ADT with ADT alone,^[9] the other ten compared RP + ADT with non-local therapy,^[5–7,12–18] and three compared radical prostatectomy with RT.^[5,6,12] In total, 644 patients received cytoreductive surgery, 8556 patients received no surgery or radiation therapy, and 461 patients received RP + ADT were compared with 746 patients received RT. It was noted that only four studies were prospective trials, and five studies evaluated oligometastatic prostate cancer (Table 1).

3.2. Outcomes of cytoreductive surgery versus non-local therapy

We defined RP and TURP as cytoreductive surgery, non-local therapy included non-surgery or radiation, ADT alone, and systemic therapy. Seven studies including 250 patients who received cytoreductive surgery and 404 patients who received non-local therapy evaluated the progression-free survival (PFS),^[7,9,13,14,16-18] and pooled data indicated that cytoreductive surgery significantly prolonged the PFS (OR = 0.65, 95% CI 0.53–0.80, P < .0001, Fig. 2A). Similar results were found for cancer-specific survival (CSS) and overall survival (OS) (OR = 0.49, 95% CI 0.43–0.56, P < .00001, Fig. 2B; and OR = 0.80, 95% CI 0.72–0.88, P < .00001, Fig. 2C; respectively).

3.3. Subgroup analysis

Subgroup analysis was performed according to the type of trial and lesion number. Pooled data indicated OS was no significant difference between cytoreductive surgery and non-local therapy in prospective studies (OR = 1.40, 95% CI 0.91–2.15, P = .12, Fig. 3A). Pooled data for retrospective studies indicated OS benefit for cytoreductive surgery (OR = 0.77, 95% CI 0.70–0.86, P < .0001, Fig. 3B). Three studies assessed the OS of oligometastatic PCa,^[7,12,13] and pooled data showed cytoreductive surgery did not significantly affect the OS (OR = 1.33, 95% CI 0.87– 2.02, P = .19, Fig. 4).

3.4. Outcomes of cytoreductive surgery versus RT

Comparing cytoreductive surgery with RT, CSS, and OS were similar between the two group (OR = 0.82, 95% CI 0.67-1.01, P = .06, Fig. 5A; and OR = 0.93, 95% CI 0.79-1.09, P = .39, Fig. 5B; respectively).

3.5. Sensitivity analysis and publication bias analysis

In sensitivity analysis, we access the stability of the result by deleting one single study each time to reflect the impact of the individual overall. For OS, after deleting the literature one by one, we found that the results were affected by one study.^[6] Finally, we assessed publication bias using funnel plots. We did not identify any evidence of publication bias for Egger's test (P = .764) and Begg's test (P = .810; Fig. 6).



Figure 1. Flow diagram of the details of the study.

Table 1

The characteristics of included studies.

Study	Country		Cytoreduc	tive surgery	Cont	rol group			
Study		Year	Surgery type	No. of patients	Treatment	No. of patients	Type of study	Follow-up (mo)	Lesions number
Qin	China	2012	TURP	39	ADT	107	Retrospective	15	NA
Culp	USA	2014	RP	245	NSR	7811	Retrospective	16	NA
Culp	USA	2014	RP	245	RT	129	Retrospective	16	NA
Steuber	European	2017	RP	43	NSR	40	Prospective	32.7 and 82.2	≤3
Sheng	China	2017	RP	23	ADT	26	Retrospective	41 and 37	1-10+
Patel*	USA	2018	RP	75	NSR	283	Retrospective	14.9	NA
Patel*	USA	2018	RP	75	RT	268	Retrospective	14.9	NA
Jang	China	2018	RP	38	NSR	41	Retrospective	40	≤5
Sow	Senegal	2019	RP or TURP	45	ADT	57	Prospective	16	1-2+
Simforoosh	Iran	2019	RP	26	NSR	23	Prospective	19.5	≤5 and >5
Lan	China	2019	RP	35	ADT	76	Retrospective	35	≤5
Si	China	2021	RP	27	ADT	57	Retrospective	68.4	≤5
Lumen	Belgium	2021	RP	48	NSR	35	Prospective	32	≤3
Lumen	Belgium	2021	RP	48	RT	26	Prospective	32	≤3

ADT = androgen deprivation therapy, NSR = no surgery or radiation, RP = radical prostatectomy, RT = radiation therapy, TURP = transurethral resection of the prostate.

*Metastatic castration-resistant prostate cancer.

4. Discussion

Our meta-analysis indicated that PFS, CSS, and OS were benefiting from cytoreductive surgery (Fig. 2); however, OS was no significant difference between cytoreductive surgery and non-local therapy in prospective studies and oligometastatic PCa patients (Figs. 3A and 4). Although several meta-analyses comparing the cytoreductive radical prostatectomy versus systemic therapy and radiation therapy in metastatic prostate cancer,^[3,19,20] several improvements could be made. First, duplicated data existed in the previous meta-analysis Results from the Local Treatment of Metastatic Prostate Cancer were reported in two studies,^[12,21] and data from SEER program were reported in three studies.^[6,10,19] D

	Experim	ental	Contr	ol				Peto Odds ratio		Peto Oc	lds ratio	
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V]. Fixed, 95% C	1	Exp[(O-E) / V	Fixed, 95% Cl	
Jang 2018	19	38	15	41	-7.48	16.51	17.4%	0.64 [0.39, 1.03]				
Lan 2019	17	35	23	76	-6.28262287	16.1525	17.1%	0.68 [0.42, 1.10]		-	t	
Qin 2012	13	39	56	107	-9.91178217	13.50802214	14.3%	0.48 [0.28, 0.82]				
Sheng 2017	20	23	24	26	-10.80388501	10.95876718	11.6%	0.37 [0.21, 0.67]				
Si 2021	7	27	22	57	-3.34891821	6.3252551	6.7%	0.59 [0.27, 1.28]			-	
Sow 2019	25	45	36	57	-8.6921723	15.03892734	15.9%	0.56 [0.34, 0.93]				
Steuber 2017	37	43	17	40	5.9	16.15	17.1%	1.44 [0.88, 2.35]			•	
Total (95% CI)		250		404			100.0%	0.65 [0.53, 0.80]		+		
Total events	138		193									
Heterogeneity: Chi2 =	15.28, df =	6(P = 0	.02); /2 =	61%						1		
Test for overall effect:	Z = 4.18 (F	< 0.000	01)						0.01 Favo	0.1 ours (experimental)	Favours [control]	100

D	Experim	ental	Contr	ol				Peto Odds ratio	Peto	Odds ratio	
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V]. Fixed, 95% C	CI Exp[(O-E)	/ V]. Fixed, 95% CI	
Culp 2014	186	245	3804	7811	-119.2059063	119.8950302	56.0%	0.37 [0.31, 0.44]			
Jang 2018	31	38	24	41	-11	15.12	7.1%	0.48 [0.29, 0.80]	i	-	
Lan 2019	31	35	65	76	-0.80500508	3.4125	1.6%	0.79 [0.27, 2.28]	· -		
Lumen 2021	41	48	25	35	-4.25821605	4.1679742	1.9%	0.36 [0.14, 0.94]		-	
Patel 2018	13	75	23	283	-14.37	65.83	30.7%	0.80 [0.63, 1.02]]	-	
Qin 2012	34	39	83	107	-2.84786369	5.67728467	2.7%	0.61 [0.27, 1.38]	. —	-	
Total (95% CI)		480		8353			100.0%	0.49 [0.43, 0.56]	•		
Total events	336		4024								
Heterogeneity: Chi2 =	27.03, df =	5 (P < 0	0.0001); /4	= 81%	6					1 10	400
Test for overall effect:	Z = 10.42	(P < 0.00	0001)						Favours [experiment	al] Favours [control]	100

	Experimental		Control					Peto Odds ratio		Peto Od	ds ratio	
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V]. Fixed, 95% C	I	Exp[(O-E) / V]	Fixed, 95% CI	
Culp 2014	160	245	3299	7811	-77.84	303.98	75.7%	0.77 [0.69, 0.87]				
Lumen 2021	41	48	22	35	-5.7134054	4.48826352	1.1%	0.28 [0.11, 0.71]				
Patel 2018	13	75	23	283	-14.37	65.83	16.4%	0.80 [0.63, 1.02]				
Qin 2012	34	39	78	107	-4.1232537	6.65612685	1.7%	0.54 [0.25, 1.15]			-	
Si 2021	21	27	43	57	-0.9506296	4.3622449	1.1%	0.80 [0.31, 2.06]				
Simforoosh 2019	20	26	15	23	-0.05851801	3.48688047	0.9%	0.98 [0.34, 2.81]				
Steuber 2017	10	43	33	40	12.83	13	3.2%	2.68 [1.56, 4.62]				
Total (95% CI)		503		8356			100.0%	0.80 [0.72, 0.88]		+		
Total events	299		3513									
Heterogeneity: Chi ² =	25.51, df =	6(P = 0)).0003); /2	= 76%					0.04		10	400
Test for overall effect:	Z = 4.50 (F	< 0.00	001)						0.01 Favours	0.1 [experimental]	Favours [control	100

Figure 2. Forest plot OR for PFS (A), CSS (B), and OS (C) of cytoreductive surgery compared to non-local therapy. CI = confidence interval, CSS = cancer-specific survival, OR = odds ratio, OS = overall survival, PFS = progression-free survival.

	Experim	ental	Contr	ol				Peto Odds ratio	Peto Od	ds ratio	
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V]. Fixed, 95% C	Exp[(O-E) / V], Fixed, 95% CI	
umen 2021	41	48	22	35	-5.7134054	4.48826352	21.4%	0.28 [0.11, 0.71]		-	
Simforoosh 2019	20	26	15	23	-0.05851801	3.48688047	16.6%	0.98 [0.34, 2.81]			
Steuber 2017	10	43	33	40	12.83	13	62.0%	2.68 [1.56, 4.62]			
fotal (95% CI)		117		98			100.0%	1.40 [0.91, 2.15]		•	
Total events	71		70								
Heterogeneity: Chi ² =	17.56, df =	2(P = 0	.0002); /2	= 89%							10/
est for overall effect:	Z = 1.54 (P	= 0.12)							Eavours [experimental]	Favours [control]	100
	Experim	Experimental Control					Peto Odds ratio	Peto Oc	Ids ratio		
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V]. Fixed. 95% CI	ExpI(O-E) / V	I. Fixed. 95% CI	
Culp 2014	160	245	3299	7811	-77.84	303.98	79.8%	0.77 [0.69, 0.87]			
Patel 2018	13	75	23	283	-14.37	65.83	17.3%	0.80 [0.63, 1.02]	-	1	
	34	39	78	107	-4.1232537	6.65612685	1.7%	0.54 [0.25, 1.15]		+	
2in 2012								0.00 10.01 0.001			
Si 2021	21	27	43	57	-0.9506296	4.3622449	1.1%	0.80 [0.31, 2.06]			
Si 2021 Total (95% CI)	21	27 386	43	57 8258	-0.9506296	4.3622449	1.1%	0.80 [0.31, 2.06]	•		
in 2012 Si 2021 Fotal (95% CI) Fotal events	21 228	27 386	43 3443	57 8258	-0.9506296	4.3622449	1.1% 100.0%	0.80 [0.31, 2.06]	•		
Gin 2012 Si 2021 Fotal (95% CI) Fotal events Heterogeneity: Chi ² = 1	21 228).98, df = 3	27 386 (P = 0.1	43 3443 81); /² = 0	57 8258 %	-0.9506296	4.3622449	1.1% 100.0%	0.80 [0.31, 2.06]	•		

Figure 3. Forest plot OR for OS of cytoreductive surgery compared to non-local therapy in prospective (A) and retrospective (B) studies. Cl = confidence interval, OR = odds ratio, OS = overall survival.

Only latest and complete data were included in our meta-analysis. Second, many studies were retrospective trials previously, the value would be weakening than prospective studies, and subgroup analysis would be more convincing. Third, several studies were published in recent years, but were not included in the previous meta-analyses.^[12–16] Thus, we performed this meta-analysis to comprehensively evaluate the local treatment methods and figure out optimal local treatment for metastases prostate cancer. Our results and previous study indicated oligometastatic represents a clinical state of metastatic disease that is limited in the number of metastatic sites and extent of disease.^[22] Another reason may be that ADT had been the only evidenced treatment option prolonging outcomes for metastatic PCa; however, various new systemic treatment options may improve prognosis.^[20] A recent population-matched study indicated palliative TURP could reduce OS and CSS compared to non-surgical group for metastatic PCa



Figure 4. Forest plot OR for OS of cytoreductive surgery compared to non-local therapy in oligometastatic PCa. Cl = confidence interval, OR = odds ratio, OS = overall survival, PCa = prostate cancer.

4	Experim	ental	Contro	ol				Peto Odds ratio	Peto Od	ds ratio	
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V]. Fixed, 95% C	Exp[(O-E) / V]. Fixed, 95% CI	
Culp 2014	160	245	84	129	-7.28717381	24.62856387	27.3%	0.74 [0.50, 1.10]	-	+	
Lumen 2021	41	48	23	26	0.15870148	2.06210154	2.3%	1.08 [0.28, 4.23]			
Patel 2018	13	75	33	268	-10.73	63.68	70.5%	0.84 [0.66, 1.08]			
Total (95% CI)		368		423			100.0%	0.82 [0.67, 1.01]	•	•	
Total events	214		140								
Heterogeneity: Chi ² = 0	0.45, df = 2	(P = 0.8)	30); <i>1</i> ² = 0 ⁴	%					0.01 0.1	1 10	100
Test for overall effect:	Z = 1.88 (P	P = 0.06)							Eavours (experimental)	Eavours (control)	100
3	Experimental Control		ol				Peto Odds ratio	Peto Od	ds ratio		
Study or Subaroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp((O-E) / VI, Fixed, 95% CI	Exp[(O-E) / V	1. Fixed, 95% CI	
Culp 2014	160	245	84	129	0.11	82.87	55.8%	1.00 [0.81, 1.24]	1		
Lumen 2021	41	48	23	26	0.15870148	2.06210154	1.4%	1.08 [0.28, 4.23]			
Patel 2018	13	75	33	268	-10.73	63.68	42.8%	0.84 [0.66, 1.08]		1	
Total (95% CI)		368		423			100.0%	0.93 [0.79, 1.09]			
Total events	214		140								
	1 00 41 - 2	P = 0	$58): I^2 = 0$	%					+ +	+ + +	
Heterogeneity: Chi ² =	1.00, 01 = 2		00/1						0.01 0.1	4 40	

Figure 5. Forest plot OR for OS of cytoreductive surgery compared to RT. CI = confidence interval, OR = odds ratio, OS = overall survival, RP = radical prostatectomy.



Figure 6. Begg's test for OS of cytoreductive surgery compared to non-local therapy. OS = overall survival.

patients with bladder outlet obstruction.^[23] It was a retrospective study that included patients in the SEER database. The evidence level was relatively low, and our research found a clue that TURP could play an important role in metastatic PCa.^[9,16]

Radiotherapy brings benefits in overall treatment efficacy without major side effects.^[11] Few studies compared the outcomes of RP and RT. Our data showed RT was as good as RP (Fig. 5). Prospective study indicated 2-years OS was 93%, 100% and 2-years CSS was 93%, 100% for RP, RT, respectively.^[11] Thus, current data showed RP and RT exerted comparable effects for the survival on metastatic PCa patients. According to the adverse effects or complications, a meta-analysis found acceptable rates of acute and late grade 3 to 5 toxic effects less than 13% for RT.^[24] The genitourinary and gastrointestinal toxicity were the main adverse effects for RT.^[25] The postoperative incontinence and sexual dysfunction were the complications for

RP.^[26] Thus, to choose RT or RP, optimal local treatment may be distinct for different demands of patients.

Some aspects of these data would require careful interpretation as it was not without limitations. First, after deleting Culp's literature (data from SEER) but not any other study, OS benefit was not obvious (OR = 0.88, 95% CI 0.72–1.07, P = .21) in the meta-analysis, we proposed the pooled data from prospective studies (Fig. 3A) would be higher level evidence. Second, few studies compared TURP with RP, as it was a simpler operation and had fewer complications for TURP, yet its role needed more research. Third, adverse effects or complications were not compared between groups, and these should be considered when choosing treatments. Fourth, the follow-up time varies in included studies, which also reduces the reliability of the conclusions. Fifth, the positive margin rate was not reported in the RP group, and patients may be poorer outcomes with a positive margin. However, this is the first comprehensive meta-analysis comparing RT, RP, TURP, and non-local treatment for metastatic PCa. We found cytoreductive radical prostatectomy significantly prolonged the PFS, and TURP may also be helpful for particular patients, while non-local treatment was not recommended.

5. Conclusions

Cytoreductive radical prostatectomy significantly prolonged the PFS for metastatic PCa. Although OS was no significant difference between cytoreductive surgery and non-local therapy, non-local treatment was not recommended for metastatic PCa.

Author contributions

All authors have read and approved the manuscript. Project development: Z.P.; data collection or management: A.H.; data analysis and interpretation: Z.P.; manuscript writing: Z.P., A.H.; manuscript editing: Z.P.; and study supervision: Z.P. Conceptualization: Zhixiong Peng.

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Formal analysis: Zhixiong Peng, Andong Huang.

Methodology: Zhixiong Peng.

Validation: Andong Huang.

Writing – original draft: Zhixiong Peng.

Writing – review & editing: Zhixiong Peng, Andong Huang.

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