



阻塞性睡眠呼吸暂停综合征对无心脑血管疾病 老年人夜间动态血压的影响

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【摘要】目的 观察阻塞性睡眠呼吸暂停综合征(obstructive sleep apnea syndrome, OSAS)对无心脑血管疾病老年人夜间动态血压的影响,探讨影响老年OSAS夜间血压波动的因素。**方法** 纳入169例无心脑血管疾病老年OSAS患者,按病情严重程度分为4组(正常组、轻度组、中度组和重度组)。比较各组基本资料的差异,并进一步分析睡眠监测参数与夜间动态血压的关系以及引起老年OSAS夜间血压波动的因素。**结果** 正常组、轻度组、中度组和重度组夜间血压波动(nocturnal blood pressure fluctuation, NBPF)指数分别为(1.89±1.58、3.35±5.40、3.90±6.40、16.60±27.70),显示随OSAS病情的加重,NBPF指数逐渐升高($P<0.05$);经偏相关分析显示:NBPF指数与呼吸暂停低通气指数(apnea-hypopnea index, AHI)、微觉醒指数(micro-awakening index, MAI)、氧饱和度低于90%时间与总睡眠时间的比值(percentage of oxygen saturation below 90% in total sleep time, TS90%)、氧减指数(oxygen desaturation index, ODI)以及最长呼吸暂停时间(longest apnea time, LAT)呈正相关($P<0.05$),与最低氧饱和度(lowest oxygen saturation, LSpO₂)和睡眠质量指数(sleep quality index, SQI)呈负相关($P<0.05$)。夜间血压(平均收缩压和平均舒张压)与AHI、ODI和TS90%均呈正相关($P<0.05$)。多因素回归分析显示:ODI每增加1个单位,NBPF指数升高0.26个单位($\beta=0.26$, 95%置信区间(confidence interval, CI): 0.03 ~ 0.50, $P=0.030$),TS90%每增加1个单位,NBPF指数升高26.78个单位($\beta=26.78$, 95%CI: 2.47 ~ 51.08, $P=0.031$)。**结论** 在无心脑血管疾病的老年OSAS患者中,随着疾病程度的加重,夜间血压波动越明显;ODI和TS90%是影响夜间血压波动的重要因素。

【关键词】 老年人 夜间血压波动指数 高血压 睡眠呼吸暂停综合征,阻塞性

Effect of Obstructive Sleep Apnea Syndrome on Nocturnal Ambulatory Blood Pressure Monitoring Results in Older Adults Without Cardiovascular or Cerebrovascular Diseases

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[Abstract] Objective To investigate the effect of obstructive sleep apnea syndrome (OSAS) on nocturnal ambulatory blood pressure monitoring results in older adults without cardiovascular or cerebrovascular diseases, and to identify factors causing fluctuations in nocturnal blood pressure in older adults with OSAS. **Methods** A total of 169 older adult OSAS patients with no history of cardiovascular or cerebrovascular diseases were enrolled. According to their severity of OSAS, the participants were divided into 4 groups, including a normal OSAS group, a mild OSAS group, a moderate OSAS group, and a severe OSAS group. The baseline characteristics of the 4 groups were compared to identify differences. The relationship between polysomnography parameters and nocturnal ambulatory blood pressure monitoring results and the factors causing nocturnal blood pressure fluctuations in older adults with OSAS were further analyzed. **Results** The nocturnal blood pressure fluctuation (NBPF) index of the normal OSAS group, the mild OSAS group, the moderate OSAS group, and the severe OSAS group were 1.89 ± 1.58 , 3.35 ± 5.40 , 3.90 ± 6.40 , and 16.60 ± 27.70 , respectively, indicating that the NBPF index gradually increased with the increasing severity of OSAS ($P < 0.05$). According to findings from the partial correlation analysis, the NBPF index was positively correlated with apnea-hypopnea index (AHI), micro-awakening index (MAI), percentage of cumulative time with oxygen saturation under 90% in the total sleep time (TS90%), oxygen desaturation index (ODI), and the longest apnea time (LAT) ($P < 0.05$), and negatively correlated with the lowest oxygen saturation (LSpO₂) and sleep quality index (SQI) ($P < 0.05$). The mean

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nocturnal systolic and diastolic blood pressures were positively correlated with AHI, ODI, and TS90% ($P < 0.05$). A multi-factor regression analysis showed that every time ODI increased by 1 unit, the NBPF index increased by 0.26 units ($\beta = 0.26$; 95% CI, 0.03-0.50; $P = 0.030$), and every time TS90% increased by 1 unit, the NBPF index increased by 26.78 units ($\beta = 26.78$; 95% CI, 2.47-51.08; $P = 0.031$). **Conclusion** In older adult OSAS patients without cardiovascular or cerebrovascular disease, fluctuations in blood pressure at night become more pronounced with increasing disease severity. ODI and TS90% are important factors that affect nocturnal blood pressure fluctuations.

[Key words] Older adults Nocturnal blood pressure fluctuation index Hypertension Sleep apnea syndromes, Obstructive

阻塞性睡眠呼吸暂停综合征(obstructive sleep apnea syndrome, OSAS)是耳鼻喉科的常见病。一项关于OSAS对世界经济影响的报告显示:在全球近10亿的OSAS患者中,大约1.76亿来自中国^[1]。随老年人口的增多以及受人们不规律的生活习惯等因素的影响,我国OSAS患病人数持续升高^[2]。老年人常伴有一种或多种慢病,导致OSAS在老年人中发病率更高(约20%~40%)^[3-4],这无疑加重了老年人群的疾病负担。

OSAS可因缺氧或睡眠紊乱导致一系列包括循环、代谢、内分泌等若干系统的并发症,其中以高血压为主的心血管疾病广受人们关注^[5]。OSAS不仅影响血压数值的高低,还可干扰血压正常昼夜节律^[6],且夜间血压升高比白天血压升高对机体的危害更大^[7-8]。前期研究发现OSAS患者夜间血压跟病情有关^[9]。但关于老年OSAS夜间动态血压的研究较少,既往研究对象也大多合并有高血压、冠心病、心功能不全等疾病^[10-11]。据临床观察发现,在同时有多种疾病的老年患者中,诊断和评估OSAS对血压的独立影响变得极为复杂,导致难以制定精准有效的干预措施。

OSAS在老年人群中发病率较高,但早期血压变化可能因其他并发疾病而被掩盖或混淆。本研究通过聚焦于无心脑血管疾病这一相对单纯的群体,可以更精准地捕捉OSAS引发血压变化的关键信号,揭示其在疾病早期阶段的潜在影响机制,这不仅对早期预防和干预OSAS相关性高血压具有重要的临床意义,还可为后续在更广泛老年人群中的综合防治提供基础数据和理论依据。因此,本研究基于睡眠血压同步监测的方法,探讨OSAS对无心脑血管疾病老年人夜间动态血压的影响以及引起夜间血压波动的相关因素。

1 资料与方法

1.1 研究对象

选择2017年8月-2024年6月以“打呼噜”为主诉在四川大学华西第四医院耳鼻咽喉头颈外科/睡眠医学中心就诊的169例老年患者,根据OSAS分级标准^[12]分组:正常组,呼吸暂停低通气指数(apnea-hypopnea index, AHI)<5次/h;

轻度组,5次/h $\leq$ AHI<15次/h;中度组,15次/h $\leq$ AHI<30次/h;重度组,AHI $\geq$ 30次/h。本研究经四川大学华西第四医院医学伦理委员会批准(批件号:HXSJ-EC-2024109)。

纳入标准:①60岁及以上;②知情同意研究。

排除标准:①伴有(原发性/继发性)高血压、(1型/2型)糖尿病、冠心病、脑卒中、房颤等病理性心律失常者;②患有OSAS以外的可能影响血压的疾病,如焦虑、抑郁、失眠、恶性肿瘤性疾病等^[13];③已行OSAS相关治疗的患者(手术或呼吸机治疗对于血压有降低作用)^[14];④资料缺失或不完整者。

1.2 研究方法

1.2.1 收集基本信息

由经过培训的专业人员指导患者填写四川大学华西第四医院《阻塞性睡眠呼吸暂停综合征病人档案》,①问卷信息:姓名、年龄、性别、打鼾年限,既往史;②测量身高、体质量等。

1.2.2 多导睡眠监测

本研究睡眠监测采用的仪器型号为德国SOMNO screen™ plus PSG+,所有患者监测时间都不低于7 h,监测当天嘱患者不能喝酒、喝茶、喝咖啡或口服影响睡眠的药物,中午不午睡。收集反映OSAS严重程度的指标(AHI),反映夜间低氧的指标[氧饱和度低于90%时间与总睡眠时间的比值(percentage of oxygen saturation below 90% in total sleep time, TS90%)、氧减指数(oxygen desaturation index, ODI)和最低氧饱和度(lowest oxygen saturation, LSpO₂)],反映睡眠中觉醒的指标[微觉醒指数(micro-awakening index, MAI)],以及反映呼吸事件时间长短的指标[最长呼吸暂停时间(longest apnea time, LAT)和最长短低通气时间(longest hypoventilation time, LHT)]。根据各期睡眠占总睡眠时间的百分比,计算睡眠质量指数(sleep quality index, SQI)。SQI=(N3期占比+REM期占比)/(N1期占比+N2期占比)。

1.2.3 夜间动态血压的测定

在进行多导睡眠监测的同时,结合脉搏传导时间(pulse

transit time, PTT)测压法为所有患者进行整夜动态血压的测定。主要收集夜间平均血压(平均收缩压和平均舒张压)、平均夜间每小时发生收缩压升高大于 12 mmHg(1 mmHg=0.133 kPa)事件的次数,即夜间血压波动(nocturnal blood pressure fluctuation, NBPF)指数^[9]。基础血压的测定:患者坐位安静休息 5 min 以后,用欧姆龙 HBP1320 电子血压计测量上臂血压 2 次(前后间隔 0.5~1 min,患者上臂伸直、自然地放在与心脏齐平的位置),取 2 次血压的平均值并记录,若 2 次血压值相差大于 10 mmHg 或更多,需测量 3 次,最后取这 3 次血压的平均值予以记录,并将记录的血压数值输入多导睡眠监测系统校正。

1.3 统计学方法

统计分析运用 SPSS 20.0 软件。计量资料符合正态分布的以 $\bar{x} \pm s$ 表示,多组间比较采用协方差分析,组间两两比较采用 LSD 法;计数资料采用卡方检验;采用偏相关分

析 OSAS 患者夜间动态血压与多导睡眠监测参数间的相关性;采用单因素和多因素回归分析引起 OSAS 患者夜间血压波动的相关因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组患者基本资料和睡眠监测指标比较

见表 1。在 169 例老年患者中,正常组 14 例,平均年龄(62.71±3.20)岁;OSAS 组 155 例,平均年龄(62.65±3.89)岁,其中轻度组 42 例,中度组 46 例,重度组 67 例。4 组间比较 AHI 呈升高趋势($P < 0.001$),LSpO₂ 和 SQI 呈下降趋势($P < 0.01$),BMI、MAI、LAT、ODI 以及 TS90% 的组间差异均有统计学意义($P < 0.001$);性别、年龄、打鼾年限、LHT 及白天收缩压和白天舒张压在 4 组间差异无统计学意义。

2.2 各组间夜间血压相关指标的比较

见表 2。调整年龄、性别、BMI 及打鼾年限,采用协方差分析显示:在 4 组间比较,夜间平均舒张压及 NBPF 指数

表 1 四组间基本资料和睡眠监测指标比较

Table 1 Comparison of basic data and sleep monitoring indicators between the four groups

Index	Normal OSAS group (n = 14)	Mild OSAS group (n = 42)	Moderate OSAS group (n = 46)	Severe OSAS group (n = 67)	P
Sex/case (%)					0.893
Male	9 (64.29)	22 (52.38)	25 (54.35)	37 (55.22)	
Female	5 (35.71)	20 (47.62)	21 (45.65)	30 (44.78)	
Age/yr., $\bar{x} \pm s$	62.71 ± 3.20	61.88 ± 2.53	63.09 ± 4.29	62.82 ± 4.27	0.492
Years of snoring/yr., $\bar{x} \pm s$	8.71 ± 5.80	11.64 ± 10.11	12.50 ± 10.36	15.46 ± 10.52	0.065
BMI/(kg/m ²), $\bar{x} \pm s$	24.13 ± 2.75	23.79 ± 2.81	24.12 ± 2.96	26.23 ± 3.02	< 0.001
AHI/h ⁻¹ , $\bar{x} \pm s$	2.36 ± 1.41	10.15 ± 5.60	20.70 ± 6.40	50.20 ± 20.60	< 0.001
LSpO ₂ %, $\bar{x} \pm s$	88.57 ± 6.50	86.50 ± 3.00	83.00 ± 6.00	77.00 ± 12.00	< 0.001
MAI/h ⁻¹ , $\bar{x} \pm s$	23.61 ± 10.02	28.29 ± 12.62	25.92 ± 10.92	42.45 ± 17.90	< 0.001
LAT/s, $\bar{x} \pm s$	29.93 ± 30.71	43.64 ± 18.20	51.83 ± 20.00	67.07 ± 20.34	< 0.001
LHT/s, $\bar{x} \pm s$	40.07 ± 20.84	49.76 ± 22.93	54.61 ± 25.43	49.73 ± 20.05	0.201
ODI/h ⁻¹ , $\bar{x} \pm s$	3.63 ± 6.30	9.82 ± 3.57	21.72 ± 7.32	52.63 ± 16.67	< 0.001
TS90% ($\bar{x} \pm s$)	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.03	0.18 ± 0.15	< 0.001
SQI ($\bar{x} \pm s$)	0.71 ± 0.48	0.68 ± 0.34	0.62 ± 0.40	0.45 ± 0.26	0.002
DSBP/mmHg, $\bar{x} \pm s$	118.21 ± 6.99	120.40 ± 10.23	121.28 ± 12.71	123.96 ± 9.77	0.161
DDBP/mmHg, $\bar{x} \pm s$	73.79 ± 8.73	76.12 ± 8.55	77.20 ± 7.91	78.91 ± 7.08	0.089

OSAS: obstructive sleep apnea syndrome; BMI: body mass index; AHI: apnea-hypopnea index; LSpO₂: lowest oxygen saturation; MAI: micro-awakening index; LAT: longest apnea time; LHT: longest hypoventilation time; ODI: oxygen desaturation index; TS90%: percentage of cumulative time with oxygen saturation under 90% in the total sleep time; SQI: sleep quality index; DSBP: daytime systolic blood pressure; DDBP: daytime diastolic blood pressure. 1 mmHg = 0.133 kPa.

表 2 四组间夜间血压相关指标的比较

Table 2 Comparison of nocturnal blood pressure-related indexes among the four groups

Index	Normal OSAS group (n = 14)	Mild OSAS group (n = 42)	Moderate OSAS group (n = 46)	Severe OSAS group (n = 67)	F	P
NBPF/h ⁻¹ , $\bar{x} \pm s$	1.89 ± 1.58	3.35 ± 5.40	3.90 ± 6.40	16.60 ± 27.70 ^{a, b, c}	15.44	< 0.001
MNSBP/mmHg, $\bar{x} \pm s$	112.71 ± 13.11	109.88 ± 13.87	111.59 ± 14.18	117.60 ± 14.58 ^{b, c}	1.08	0.359
MNDBP/mmHg, $\bar{x} \pm s$	68.21 ± 11.54	74.21 ± 9.91	73.85 ± 9.95	77.87 ± 9.51 ^{a, c}	2.84	0.040

NBPF: nocturnal blood pressure fluctuation; MNSBP: mean nocturnal systolic blood pressure; MNDBP: mean nocturnal diastolic blood pressure. ^a $P < 0.05$, vs. normal group; ^b $P < 0.05$, vs. mild group; ^c $P < 0.05$, vs. moderate group. 1 mmHg = 0.133 kPa.

差异均有统计学意义($P<0.05$), 且与轻、中度OSAS组以及正常组相比, 重度OSAS组的NBPF指数均升高($P<0.05$)。

2.3 夜间动态血压与睡眠监测指标的相关性

见表3。调整年龄、性别、BMI及打鼾年限, 经偏相关分析表明, AHI与夜间3个血压指标(NBPF指数、夜间平均收缩压及夜间平均舒张压)呈正相关($r=0.58$ 、 0.17 、 0.18 , P 均 <0.05); LSpO₂与NBPF指数呈负相关($r=-0.43$, $P<0.05$); SQI与NBPF指数呈负相关($r=-0.24$, $P<0.05$), MAI、LAT与NBPF指数呈正相关($r=0.36$ 、 0.29 , P 均 <0.05); ODI($r=0.60$ 、 0.17 、 0.24 , P 均 <0.05)、TS90%($r=0.52$ 、 0.19 、 0.22 , P 均 <0.05)与夜间3个血压指标均呈正相关(P 均 <0.05)。

2.4 影响老年OSAS夜间血压波动的相关因素

见表4。结合相关性分析的结果, 以AHI、AHI分级、LSpO₂、SQI、MAI、LAT、ODI、TS90%为自变量, 以NBPF指数为因变量, 调整年龄、性别、BMI及打鼾年限后采用多因素回归分析, 结果显示: ODI每增加1个单位, NBPF指数升高0.26个单位[$\beta=0.26$, 95%置信区间

表 3 夜间动态血压与睡眠监测指标的相关性 (偏相关系数)
Table 3 Correlation between nocturnal ambulatory blood pressure monitoring results and sleep monitoring indicators (partial correlation coefficient)

Index	NBPF/h ⁻¹	MNSBP/mmHg	MNDBP/mmHg
AHI/h ⁻¹	0.58 [*]	0.17 [*]	0.18 [*]
LSpO ₂ /%	-0.43 [*]	-0.13	-0.13
SQI	-0.24 [*]	0.00	-0.02
MAI/h ⁻¹	0.36 [*]	0.01	0.05
LAT/s	0.29 [*]	0.12	-0.02
LHT/s	-0.15	0.02	-0.01
ODI/h ⁻¹	0.60 [*]	0.17 [*]	0.24 [*]
TS90%	0.52 [*]	0.19 [*]	0.22 [*]

All abbreviations are explained in the note to Table 1. ^{*} $P<0.05$.

(confidence interval, CI): $0.03 \sim 0.50$, $P=0.030$], TS90%每增加1个单位, NBPF指数升高26.78个单位($\beta=26.78$, 95%CI: $2.47 \sim 51.08$, $P=0.031$)。提示在无心脑血管疾病的老年OSAS患者中, ODI及TS90%与夜间血压波动存在一定的相关性。

表 4 影响老年OSAS夜间血压波动 (NBPF) 的相关因素回归分析

Table 4 Regression analysis of the relevant factors affecting nocturnal blood pressure fluctuation in older adults with OSAS

OSAS index	Univariate regression			Multifactor regression [*]		
	β	95% CI	P	β	95% CI	P
AHI/h ⁻¹	0.38	0.30-0.46	<0.001	-0.03	-0.29-0.23	0.818
AHI degree						
Normal OSAS group	(Reference)					
Mild OSAS group	2.93	-4.83-10.69	0.457	1.49	-5.63-8.61	0.680
Moderate OSAS group	5.36	-2.31-13.04	0.169	0.49	-7.24-8.22	0.900
Severe OSAS group	18.57	11.18-25.96	<0.001	-1.89	-12.07-8.29	0.715
LSpO ₂	-0.83	(-1.08)-(-0.59)	<0.001	-0.02	-0.41-0.38	0.938
SQI	-10.41	(-16.50)-(-4.32)	0.001	-3.50	-8.97-1.97	0.209
MAI	0.36	0.24-0.49	<0.001	0.09	-0.04-0.22	0.165
LAT	0.19	0.10-0.28	<0.001	0.00	-0.10-0.10	0.940
ODI	0.39	0.31-0.47	<0.001	0.26	0.03-0.50	0.030
TS90%	65.53	50.73-80.33	<0.001	26.78	2.47-51.08	0.031

CI: confidence interval; the other abbreviations are explained in the note to Table 1. ^{*} The data are adjusted for age, sex, BMI, and years of snoring.

3 讨论

OSAS在老年人群中不仅发病率高, 还与多种慢病相关, 更加剧了其潜在的危害^[15-16]。OSAS诱发或导致血压升高的机制复杂^[17-19]。如何早期发现老年OSAS相关性高血压, 防止不良心血管事件的发生, 是目前亟需解决的问题之一。

本研究排除其他心血管疾病因素对血压的干扰, 能够更直观地观察和分析OSAS本身对血压的影响。以往研究表明, 即使日间血压正常的老年人, 若患有OSAS, 后期发生夜间高血压的风险比无OSAS者要高^[20]。本研究纳入的所有研究对象在白天血压差异无统计学意义, 但夜间平均舒张压以及血压波动情况在4组间差异有统计学意义(P 均 <0.05), 重度组的NBPF指数明显高于中度组、

轻度组和正常组;经偏相关分析,本研究发现AHI与夜间血压水平(夜间平均收缩压及夜间平均舒张压)及NBPF指数均呈正相关($r=0.17、0.18、0.58, P$ 均 <0.05)。这与国外威斯康星州睡眠队列关于OSAS与高血压的前瞻性研究结果相符,OSAS患者的血压水平与AHI间有线性相关性^[21]。提示在临床诊疗中对老年OSAS患者不仅要早期采取干预,防止疾病程度加重,还需要关注患者夜间的血压,尤其是对重度患者,以期早期识别OSAS相关性高血压。

以往研究表明,OSAS患者睡眠中反复发生的低氧是导致心血管损害、血压升高的重要机制。本研究发现,反映患者夜间缺氧的3个指标(LSpO₂、ODI及TS90%) in 正常组和OSAS各组间比较差异均有统计学意义($P<0.05$),LSpO₂与NBPF指数呈负相关($P<0.05$),ODI及TS90%与NBPF指数呈正相关(P 均 <0.05),这与以往研究相符。此外,也有研究表明,在呼吸事件发生时微觉醒对血压的影响比LSpO₂以及呼吸暂停时间更明显^[22]。OSAS患者呼吸事件的时长在一定程度上也反映了患者夜间缺氧的严重程度,本研究也发现MAI、LAT与NBPF指数呈正相关(P 均 <0.05)。睡眠片段化、慢波睡眠减少也与血压的升高密切相关^[23]。在OSAS患者中,随着AHI的增加,N3期和REM期呈下降趋势^[24]。本研究通过对(N3期占比+REM期占比)与(N1期占比+N2期占比)的比值(SQI)的分析,发现SQI与NBPF指数呈负相关($P<0.05$),提示睡眠结构破坏与夜间血压波动有关,这与REN等^[25]的研究结果相符。因此对老年OSAS患者通过采取积极的干预措施、改善睡眠结构,可在一定程度上降低夜间血压的波动,防止或延缓进展为高血压。本研究进一步针对年龄、性别、BMI及打鼾年限等相关混杂因素进行调整后,采用多因素回归分析显示:ODI每增加1个单位,NBPF指数可升高0.26个单位($P=0.030$),TS90%每增加1个单位,NBPF指数可升高26.78个单位($P=0.031$),说明血氧饱和度低于90%的时间增加,可导致OSAS患者夜间血压的明显波动。这与国外的一项针对社区老年OSAS的研究结果相符,他们发现TS90%大于1.5%与心血管疾病患者的失眠有关,随访3年发现OSAS介导的缺氧可导致更高的心血管病死率^[26]。

综上,本研究发现,在无心脑血管疾病的老年OSAS患者中,随着疾病程度的加重,NBPF指数越高;ODI及TS90%是影响夜间血压波动的重要因素。对老年OSAS患者不仅要早期干预、改善睡眠结构,还要监测夜间血压及血氧饱和度,防止或延缓进展为高血压。由于本研究纳入的对象为我院睡眠中心的患者,60岁以上的老年人

中没有心脑血管基础疾病的患者相对较少,再排除合并症的患者后,绝大部分患者在60至65岁左右,70岁以上的患者人数较少;除外,在我院睡眠中心就诊的患者中,女性患者合并有脑血管疾病的比例相比男性患者要少,因此在这个阶段收集的病例中男女比例较接近,正常组人数相对较少,因此可能存在一定的人组偏倚,今后还需扩大样本量、纳入更广泛的人群进一步研究。

* * *

作者贡献声明 李小英负责论文构思和研究方法,张晨旭负责数据审编和正式分析,曾萍负责调查研究,余良才负责研究方法,张晓晴负责审读与编辑写作。所有作者已经同意将文章提交给本刊,且对将要发表的本进行最终定稿,并同意对工作的所有方面负责。

Author Contribution LI Xiaoying is responsible for conceptualization and methodology. ZHANG Chenxu is responsible for data curation and formal analysis. ZENG Ping is responsible for investigation. YU Liangcai is responsible for methodology. ZHANG Xiaoqing is responsible for writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

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(2025-01-08收稿, 2025-03-09修回)

编辑 余琳



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