Original Article

Acute effect of proprotein convertase subtilisin/kexin type 9 inhibitor on oxidized low-density lipoprotein and lipid profile in patients at cardiovascular risk

Yiming Li,[1] Minni Sun,[2] Ran Li,[1] Min Dou,[1] Haozhe Dong,[1] Liqi Xue,[1] and Guoju Sun[1,*]

[1]Department of Cardiovascular Medicine and [2]Department of Emergency Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, 450000, China

(Received 16 June, 2023; Accepted 6 August, 2023; Released online in J-STAGE as advance publication 1 September, 2023)

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of potent lipid-lowering drugs. Oxidized low-density lipoprotein (ox-LDL) is the key pathogenic factor leading to atherosclerosis. However, its effect on ox-LDL levels has not been clinically reported. The clinical data of 290 very high-risk atherosclerotic cardiovascular disease (ASCVD) patients diagnosed in the First Affiliated Hospital of Zhengzhou University from May 2022 to October 2022 were collected retrospectively. According to whether evolocumab (a PCSK9 inhibitor) was used after percutaneous coronary intervention (PCI), they were divided into evolocumab group (153 cases) and statin monotherapy group (137 cases). At hospital admission, ox-LDL, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteinA1 (apoA1), apolipoprotein B-100 (apoB), lipoprotein (a) [Lp(a)], and high-sensitivity reactive protein (hs-CRP) levels were collected and used as baseline data. After two weeks of treatment, ox-LDL in the evolocumab group and statin monotherapy group were significantly lower than those before treatment ($p<0.05$). The decrease of ox-LDL in the evolocumab group was more than in the stain monotherapy group ($p<0.05$). In conclusion, PCSK9 inhibitors reduce ox-LDL levels in very high-risk ASCVD patients in a short time.

***Key Words*:** **PCSK9 inhibitor, oxidized low-density lipoprotein, very high-risk atherosclerotic cardiovascular, lipid-lowering treatment**

Cardiovascular diseases (CVDs) are the leading cause of death globally.(1) In 2018, the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines for clinical practice management of cholesterol,(2) which further subdivided the risk of atherosclerotic cardiovascular disease (ASCVD) patients into very high-risk and non-very high-risk patients, and showed different treatment recommendations, emphasizing that the very high-risk population was treated with high-intensity maximum tolerated statin doses. At the same time, non-statins are also recommended in clinical applications. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is the most potent cholesterol-lowering drug and promote a relevant cardiovascular protective effect.(3) The FOURIER Asia Subgroup Study also showed significant benefits in Asian populations receiving evolocumab treatment.(4)

Atherosclerosis (AS) is the most common pathological basis of cardiovascular diseases, characterized by the accumulation of lipids and inflammatory factors in the vessel wall.(5) Numerous epidemiological studies, Mendelian randomization studies, and Randomized Clinical Trials (RCTs) have consistently demonstrated a log-linear relationship between the absolute changes in plasma LDL-C and the risk of ASCVD.(1) Cardiovascular events still occur even when risk factors such as LDL-C are well controlled. In addition, studies have shown that oxidized low-density lipoprotein (ox-LDL) plays a key role in developing AS.(6) Elevated ox-LDL concentration has a predictive effect on future coronary heart disease events. This association is independent of other coronary heart disease risk factors such as conventional lipoprotein profile and CRP.(7) Based on the importance of ox-LDL in the development of atherosclerosis, it has better clinical significance in assessing patient vulnerability than the vague concept of vulnerable plaque.(8) However, an insufficient number of studies have clinically evaluated the relationship between ox-LDL and Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

PCSK9 is mainly secreted in the liver and expressed in the arterial wall, which can affect atherosclerosis.(9) As an adjunct to statin therapy, PCSK9 inhibitors can reduce LDL-C by 50–60% by preventing LDL receptor destruction, which is higher than statin monotherapy.(10) Studies have shown that patients have disease progression even on maximally intensive statin therapy.(11) Previous research also found that PCSK9 inhibitors combined with high-dose statins may reduce cardiovascular events and all-cause mortality in patients with clinical ASCVD.(10) Studies during the period of statins have revealed the "lag effect" and "legacy effect" of lipid-lowering therapy.(12–14) The "lag effect" refers to the fact that patients cardiovascular risk does not decrease immediately after initiation of lipid-lowering treatment.(15) The "legacy effect" is not the carryover effect of the drug effect but the carryover effect of the difference in LDL-c between the groups.(16) For very high-risk ASCVD patients, reaching the blood lipid target as soon as possible benefits the long-term prognosis.(17) However, few observations currently evaluate the early efficacy of PCSK9 inhibitors in Chinese with very high-risk ASCVD. So, we further analyzed the short-term effect of one-time administration of evolocumab (a PCSK9 inhibitors) on the blood lipid parameters and inflammation parameters in very high-risk ASCVD Chinese patients.

*To whom correspondence should be addressed.
E-mail: guojusun666@outlook.com

doi: 10.3164/jcbn.23-45

Material and Methods

Clinical data. This is a retrospective cohort study, including 290 patients who were diagnosed with very high-risk ACSVD in the First Affiliated Hospital of Zhengzhou University from May 2022 to October 2022. There were 139 females and 151 males, aged 57.51 ± 8.30 years. All the selected patients had been treated with moderate to high-intensity statins for more than four weeks before admission. According to whether evolocumab was used after PCI, they were divided into evolocumab (420 mg) group (153 subjects) and statins monotherapy group (137 subjects).

Inclusion criteria were: (1) patients with diagnosis of a very high-risk ASCVD according to 2018 AHA/ACC cholesterol management guidelines;[2] (2) patients that had been treated with moderate to high-intensity statins for more than four weeks before admission; (3) patients that received revascularization therapy during hospitalization; (4) patients with complete clinical data.

Exclusion criteria were: (1) uncontrolled blood glucose in diabetic patients; (2) uncontrolled blood pressure in hypertensive patients; (3) acute and chronic infectious diseases; (4) autoimmune diseases and cancer patients; (5) combined liver and kidney dysfunction; (6) patients who had received lipid-lowering therapy using analysis techniques such as evolocumab or lipoprotein apheresis before admission; (7) patients with missing admission and follow-up data.

The baseline data of the two groups were compared, including gender, age, history of hypertension, history of diabetes, and history of PCI. The following parameters were collected and used as baseline date: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C, apolipoprotein(a) [apo(a)], apolipoprotein B-100 (apoB), ox-LDL, lipoprotein(a) [Lp(a)], high-sensitivity Reactive Protein (hs-CRP) levels at hospital admission. The above-mentioned indexes were collected from the outpatient chart in the outpatient clinic approximately two weeks after discharge. We compared the lipid profiles and inflammatory markers between baseline and two weeks later. All methods were carried out in accordance with relevant guidelines and regulations. This project was approved as "Early therapeutic effect of evolocumab on oxidized low-density lipoprotein levels in patients with ultra-high-risk atherosclerotic cardiovascular disease" with number 022-KY-1237-001.

Ethics approval and consent to participate. This research was approved by the ethics committee of The First Affiliated Hospital of Zhengzhou Universit, Zhengzhou, Henan Province, 450000, China – 2022-KY-1237-001.

Statistical analysis. SPSS 26 was used for analysis. Continuous variables were expressed as mean ± SD or median (IQR) where not normally distributed. Categorical variables were expressed as percentages. Wilcoxon rank sum tests were used for non-normally distributed continuous variables, and *Chi*-squared tests were used for categorical variables. Independent sample *t* test was used to compare the two samples with normal distribution between the two groups. Before-after treatment comparisons were performed using paired *t* tests. Statistical significance was established at $p<0.05$.

Results

General clinical data. A total of 290 Chinese patients with an average age of 57.51 ± 8.30 years were enrolled in this study. There were 151 males (52.1%); 79 (51.6%) in the evolocumab group, and 72 (52.6%) in the statin monotherapy group. All enrolled patients have received high-intensity statin therapy for more than four weeks. There was no significant difference in gender, age, combined medical diseases, Previous PCI history, blood lipid profile, lipid-lowering regimen, and follow-up time between the control and observation groups ($p>0.05$), as shown in Table 1.

After two weeks of treatment, TC, TG, LDL-C, apo B, and ox-LDL in the evolocumab group and statin monotherapy group were significantly lower than those before treatment ($p<0.05$) (Table 2 and Fig. 1). The decrease of these parameters in the evolocumab group was more evident than in the atorvastatin group ($p<0.05$). In the evolocumab group, the LDL-C level

Table 1. Clinical characteristics

Variable	Evolocumab group (*n* = 153)	Statin monotherapy group (*n* = 137)	*p*
Age (years)	57.69 ± 7.69	57.31 ± 8.95	0.876
Male, *n* (%)	79 (51.6)	72 (52.6)	0.875
History of myocardial infarction, *n* (%)	30 (19.6)	25 (18.2)	0.73
Hazard, *n* (%)			
Hypertension	96 (62.7)	78 (56.9)	0.313
Diabetes	80 (52.3)	71 (51.8)	0.937
Previous PCI	79 (51.6)	67 (48.9)	0.589
Smoking	60 (39.2)	68 (49.6)	0.377
Peripheral vascular disease	7 (4.6)	5 (3.6)	0.639
Cerebral disease	10 (6.5)	8 (5.8)	0.773
Total cholesterol (mmol/L)	4.67 ± 0.77	4.71 ± 1.05	0.739
Triglycerides (mmol/L)	1.87 ± 0.38	1.79 ± 0.34	0.073
HDL-C (mmol/L)	1.06 ± 0.24	1.09 ± 0.22	0.431
LDL-C (mmol/L)	3.02 ± 0.49	3.08 ± 0.51	0.359
ox-LDL (U/L)	87.52 ± 15.49	89.61 ± 15.40	0.25
Lp(a) (mg/dl)	0.42 (0.31, 0.62)	0.39 (0.26, 0.58)	0.066
hs-CRP (mg/dl)	5.57 ± 1.99	5.54 ± 2.38	0.888
ApoA1 (mmol/L)	1.24 ± 0.21	1.24 ± 0.21	0.926
ApoB (mmol/L)	1.15 ± 0.23	1.14 ± 0.20	0.66

Apo, apolipoprotein; HDL-C, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein; PCI, percutaneous coronary intervention.

doi: 10.3164/jcbn.23-45

Table 2. Comparison of serum index levels between the two groups before and after treatment

Parameter	Statin monotherapy group (n = 137)			Evolocumab group (n = 153)		
	Week 0	Week 2	Change rate (%)	Week 0	Week 2	Change rate (%)
TC (mmol/L)	4.71 ± 1.05	3.72 ± 1.01	−22.09	4.67 ± 0.77	2.13 ± 0.44[a]	−54.59[b]
TG (mmol/L)	1.79 ± 0.34	1.68 ± 0.32	−6.15	1.87 ± 0.38	1.53 ± 0.29[a]	−17.60[b]
HDL-C (mmol/L)	1.09 ± 0.22	1.05 ± 0.22	−2.81	1.06 ± 0.24	1.05 ± 0.25	−0.03
LDL-C (mmol/L)	3.08 ± 0.51	2.34 ± 0.37	−23.65	3.02 ± 0.49	1.08 ± 0.32[a]	−64.49[b]
ox-LDL (U/L)	89.61 ± 15.40	67.90 ± 14.45	−24.62	87.52 ± 15.49	28.55 ± 9.34[a]	−68.09[b]
apoA1 (mmol/L)	1.24 ± 0.21	1.24 ± 0.20	0.08	1.24 ± 0.21	1.25 ± 0.21	1.3
apoB (mmol/L)	1.14 ± 0.20	0.93 ± 0.20	−19	1.15 ± 0.23	0.57 ± 0.15[a]	−51.04[b]
Lp(a) (g/L)	0.39 (0.26, 0.58)	0.39 (0.25, 0.56)	−0.18	0.42 (0.31, 0.62)	0.30[a] (0.19, 0.38)	−36.22[b]
hs-CRP (mg/dl)	5.54 ± 2.38	9.23 ± 4.08	66.61	5.57 ± 1.99	7.06 ± 2.34[a]	+45.84[b]

Apo, apolipoprotein; HDL-C, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein; ox-LDL, oxidized-LDL; TC, total cholesterol; TG, triglycerides. [a]compared with before treatment, p<0.05; [b]compared with statin monotherapy group, p<0.05.

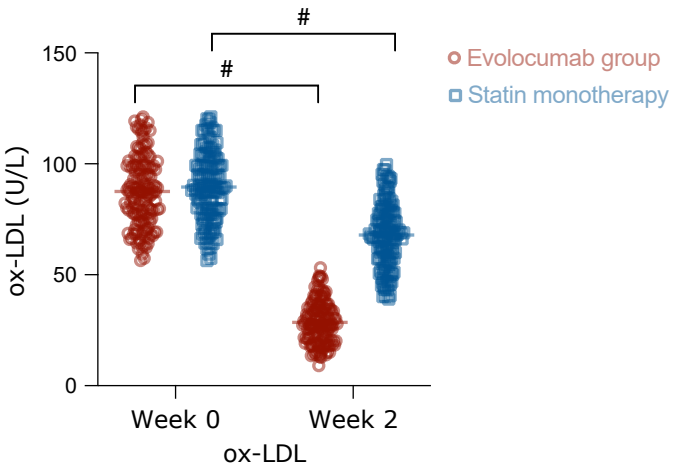

Fig. 1. Comparison of ox-LDL before and after treatment between the two groups. [#]compared with before treatment, p<0.05.

decreased 64.49%. The ox-LDL level decreased 68.09%. The levels of TC and TG decreased 54.59% and 17.60%, respectively. The Apo B level decreased 51.04%. However, the levels of HCL-C and Apo A1 were not significantly different, regardless of evolocumab administration. The hs-CRP level in each group was higher than the baseline level; the difference was statistically significant.

The compliance rate of LDL-C ≤1.4 mmol/L in the evolocumab group (88.89%) was significantly higher than that in the statin monotherapy group (0.73%) (p<0.05). The compliance rate of LDL-C ≤1.8 mmol/L in the evolocumab group (98.69%) was significantly higher than that in the statin monotherapy group (6.57%) (p<0.05). The very high-risk ASCVD patients in the evolocumab group achieved 85.62% of the blood lipid targets after two weeks, while none of the patients in the statin monotherapy group achieved the target blood lipids after two weeks (p<0.05) (Table 3).

Discussion

PCSK9 inhibitor has been widely used in clinic as a new type of lipid-lowering drug. Ox-LDL plays an important role in the pathophysiology of atherosclerosis, and there is also evidence that its plasma levels are associated with the risk of ASCVD events.[18] However, the acute effect of PCSK9 inhibitors on ox-LDL levels in very high-risk patients has not been reported in Chinese. In this study, we found that in the same treatment background, PCSK9 inhibitors was able to reduce ox-LDL compared with the control group effectively. Moreover, we show that TC, TG, LDL-C, and ApoB were reduced significantly in both groups. However the patients in the evolocumab group showed more significative reductions than the statin monotherapy group.

LDL-C has long been used as a circulating biomarker to reflect cardiovascular risk, and clinically lowering LDL-C levels are used as a therapeutic target.[19] But, there is still a need to find some specific biomarkers with pathological correlation to improve the clinical risk prediction of cardiovascular events, especially for very high-risk ASCVD patients. The pathological basis of the acute coronary syndrome (ACS) is damaged plaque, and its outcome is plaque rupture secondary to intraluminal thrombus.[20] For very high-risk ASCVD patients, vessel walls with heavy ox-LDL burden may have a higher risk of plaque rupture in the future,[21] making ox-LDL an important marker of "vulnerable plaque". It is for diagnosing vulnerable plaque, and the targeted therapy provides new ideas. This study showed that

Table 3. Comparison of recent compliance rate between the two groups

Parameter	Evolocumab group (n = 153)		Statin monotherapy group (n = 137)	
	n	%	n	%
LDL-C <1.4 mmol/L	136	88.89*	1	0.73
LDL-C <1.8 mmol/L	151	98.69*	9	6.57
LDL-C reduction ≥50%	143	93.46*	1	0.73
LDL-C <1.4 mmol/L and decrease ≥50%	131	85.62*	0	0

LDL-C, low-density lipoprotein. [a]compared with statin monotherapy group, *p<0.05.

PCSK9 inhibitors have an effect on ox-LDL, and it has a faster onset of lipid-lowering than statins in Chinese patients with very high-risk ASCVD. Moderate to high-intensity statin treatment can effectively reduce circulating ox-LDL in the early stage, but statin combined PCSK9 inhibitors treatment significantly reduces circulating ox-LDL concentrations compared to statin monotherapy treatment. Plaque regression assessed by PCSK9 inhibitor as measured by intravascular ultrasound in the GLAGOV study showed more significant atherosclerotic plaque reversal in patients treated with statin plus evolocumab compared with statin alone.[22] Evolocumab produced absolute reductions of 36.15 to 78.1 U/L at the highest dose administered after two weeks. This is a new finding of this study. Statins have been proven effective in reducing LDL-C levels to prevent cardiovascular events, but some cardiovascular events continue to occur due to insufficient reduction of atherosclerotic lipoproteins.[23] As an independent risk factor for AS, ox-LDL can directly reflect the oxidative stress state in patients.[6,24,25] In addition, ox-LDL is associated with vulnerable plaque, which refers to those plaques that are unstable and prone to thrombosis.[26]

Plaque rupture caused by vulnerable plaque is the cause of coronary thrombosis and heart disease, which is the leading cause of cardiovascular events.[8] Powerful lipid-lowering treatment can reduce plaque volume, reduce inflammation, stabilize vulnerable plaques, and even reverse plaque progression.[22] Based on our findings that the reduction in ox-LDL levels was higher in the evolocumab group, PCSK9 inhibitors may be more protective against atherogenesis. As shown by Naruko *et al.*,[27] after PCI and percutaneous transluminal angioplasty, ox-LDL increased significantly and returned to baseline after 6 h. This may be due to PCI-caused atherosclerotic plaque rupture, ox-LDL released into the blood. However, we demonstrated previously for the first time that for very high-risk patients, using PCSK9 inhibitors after PCI can effectively reduce the level of ox-LDL. This finding suggests the potent antioxidant and lipid-lowering capabilities of PCSK9 inhibitors. In previous studies, antioxidant therapy against atherosclerosis was successful in animal experiments.[28]

The selection of suitable antioxidant compounds to delay the progression of atherosclerosis has been a hot issue in the cardiovascular field. A previous clinical study found that evolocumab can reduce ox-LDL concentration in plasma in patients with coronary heart disease and does not affect antioxidant enzymes such as glutathione peroxidase.[29] Our study confirms that PCSK9 inhibitors have antioxidant effects, which may explain the cardioprotective effects of PCSK9 inhibitors far beyond their lipid-lowering effects. The statistically significant association between ox-LDL reduction and LDL-C and Apo B reduction may provide insight into the underlying mechanism by which PCSK9 inhibition leads to ox-LDL reduction. These findings could help us to explore further the mechanism by which PCSK9 inhibitors improve the long-term prognosis of patients, which also allows us to explore further the pleiotropic effects of inhibiting PCSK9.

Previous research has demonstrated LDL-C, and other atherosclerotic lipoproteins are major causes of coronary heart disease.[30] The 2018 AHA/ACC cholesterol management guidelines require that LDL-C should be controlled below 1.8 mmol/L in very high-risk patients.[2] The 2019 European Society of Cardiology/European Society of Arteriosclerosis (ESC/EAS) Guidelines for the Management of Dyslipidemia also recommend stricter LDL-C control goals.[1] For very high-risk ASCVD patients, a significant reduction in LDL-C levels help to reduce the risk of recurrent cardiovascular events.[30] Previous studies confirmed that a reduction in LDL-C of approximately 1 mmol/L reduces vascular mortality and morbidity by approximately 1/4 without increasing the risk of nonvascular mortality or morbidity over approximately five years of treatment.[16,31] In this study, we confirm that the overall lipid-lowering effect of the combination was significantly better than that of the statin monotherapy group ($p<0.05$). The level of LDL-C in the evolocumab group decreased after treatment, which was basically consistent with the results of large-scale clinical trials of evolocumab abroad, such as FOURIER.[15]

Unlike other analyses that have observed the lipid-lowering effect of evolocumab, this study observed the early blood lipid compliance rate in very high-risk ASCVD patients. We found that after two weeks of subcutaneous injection of evolocumab, the compliance rate of LDL-C levels in very high-risk ASCVD patients was 85.62%, while no patients in the group using statin monotherapy reached the compliance rate. The "legacy effect" results of the FOURIER-OLE study suggest that earlier application is more beneficial.[3] Depending on different drugs, it takes days to weeks to lower LDL-C, weeks to months to observe changes in the arterial wall, and months to years to reduce the risk of cardiovascular events.[31] Therefore, the earlier LDL-C drops to the standard level, the earlier the patient benefits. Especially for very high-risk patients prone to cardiovascular events, their blood lipids should reach the target as soon as possible to prevent cardiovascular events. Over the past few decades, much evidence has shown that lower levels of LDL-C are associated with lower cardiovascular risk.[32] So far, there is no obvious lower threshold of LDL-C, and no serious safety problems have been seen, especially in the early stage of ACS.[33] There is evidence that in patients with atherosclerotic cardiovascular disease, chronically low LDL-C levels, even <20 mg/dl (<0.5 mmol/L), lowered the risk of cardiovascular endpoints without significant security issues.[34]

Although hs-CRP levels have also been shown to be clearly associated with future coronary events in Chinese,[35–37] there is little evidence regarding the early efficacy of PCSK9 inhibitor therapy in Chinese patients. Unfortunately, our findings would seem to show that the hs-CRP of the two groups of patients was higher than the baseline level. We consider that the early elevation may be due to surgical stress and the inflammatory response caused by the compression of the plaque by interventional therapy during surgery. Since hs-CRP is greatly affected by factors such as patient infection and self-condition, further research is needed to explore the effect of PCSK9 inhibitors on hs-CRP. A remarkable fact is that inflammation and lipid metabolism play important roles in the progression of atherosclerosis. Enhanced systemic inflammation did not diminish the ability of evolocumab to induce regression in statin-treated patients. This underscores the potential benefits of intensive lipid-lowering, even in an exacerbated inflammatory state. Therefore, a further study focusing on the relationship between PCSK9 inhibitors and postoperative hs-CRP in very high-risk ASCVD patients is suggested.

Lp(a) is an independent risk factor for cardiovascular disease.[38] Lp(a) tends to oxidize after entering the blood vessel wall, producing pro-inflammatory oxLDL.[39] However, the drugs that can effectively reduce Lp(a) are still in the research process. Statins have been reported not to affect Lp(a), and some studies have shown that statins can increase Lp(a) by 10% to 20%, which may contribute to the "residual risk" noted in outcomes trials and at the bedside.[40] Our study found that statins do not affect Lp(a), but PCSK9 inhibitors can reduce Lp(a) levels. This is consistent with previous research at home and abroad.

We can see that the PCSK9 inhibitor has little effect on TG while reducing cholesterol. The FOURIER study found that PCSK9 inhibitors can reduce TG by 15.5% (compared with the placebo group, $p<0.05$), and TG decreased by 16.2% compared with baseline.[15] We found that after two weeks of application of PCSK9 inhibitors, TG decreased by 17.60% compared with baseline. Results from previous clinical trials have demonstrated

doi: 10.3164/jcbn.23-45

that inhibition of PCSK9 increases HDL-C concentrations, but the effects are small and not always statistically significant.[41] In this study, no significant effect on HDL-C was observed after treatment with evolocumab. We consider that due to the short observation period.

The limitation of this study is that the sample size is small, and no clinical outcomes were observed due to the short observation period. Because this experiment is a retrospective study, the diet and living habits of the patients during the observation period have not been confirmed. This study found that compared with statin monotherapy, adding PCSK9 inhibitors can effectively reduce ox-LDL levels in the early stage. This study improved the lipid-lowering data of evolocumab in Chinese ACS patients, which is helpful in predicting the risk of coronary heart disease and guiding lipid-lowering therapy.

Author Contributions

Data curation, formal analysis, investigation, methodology, and writing - original draft, GS; supervision and writing - review and editing, methodology, YL and LX; methodology, MS and RL; conceptualization, supervision, funding acquisition, validation, project administration, and writing - review and editing, MD and HD. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

The National Natural Science, Foundation of China (Grant nos. 82100252).

Conflict of Interest

No potential conflicts of interest were disclosed.

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doi: 10.3164/jcbn.23-45