

Original Article

Higher plasma level of STIM1, OPG are correlated with stent restenosis after PCI

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Abstract: Object: Percutaneous Coronary Intervention (PCI) is one of the most effective treatments for Coronary Heart Disease (CHD), but the high rate of In Stent Restenosis (ISR) has plagued clinicians after PCI. We aim to investigate the correlation of plasma Stromal Interaction Molecular 1 (STIM1) and Osteoprotegerin (OPG) level with stent restenosis after PCI. Methods: A total of 100 consecutive patients with Coronary Heart Disease (CHD) received PCI procedure were recruited. Coronary angiography was performed 8 months after their PCI. Then patients were divided into 2 groups: observation group was composed by patients who existing postoperative stenosis after intervention; Control group was composed by patients with no postoperative stenosis. The plasma levels of STIM, OPG in all patients were tested before and after intervention. Pearson correlation and multiple linear regression analysis were performed to analysis the correlation between STIM, OPG level and postoperative stenosis. Results: 35 cases were divided into observation group and other 65 were divided into control group. The plasma levels of STIM, OPG have no statistical difference before their PCI procedure, but we observed higher level of High-sensitivity C-reactive protein (Hs-CRP) existed in observation group. We observed higher level of plasma STIM, OPG in observation group when compared with control group after PCI procedure ($P < 0.05$). Regression analysis demonstrated that Hs-CRP, STIM1, OPG are independent risk factors for ISR. Conclusion: Elevated levels of plasma STIM1, OPG are independent risk factors for ISR in patients received PCI, which could provide useful information for the restenosis control after PCI.

Keywords: Percutaneous coronary intervention (PCI), in stent restenosis (ISR), stromal interaction molecular 1 (STIM1), osteoprotegerin (OPG), high-sensitivity C-reactive protein (Hs-CRP)

Introduction

Coronary Heart Disease (CHD) is a result of plaque buildup in coronary arteries, magnified as the narrowing of the small blood vessels that supply blood and oxygen to the heart, CHD is also called coronary artery disease [1]. CHD is a leading cause of death in many countries [2]. As for treatment of CHD, modern medicine and intervention procedure are mainly used to improve the death rate of CHD in recent years [3, 4]. Percutaneous Coronary Intervention (PCI) is one of the most effective treatments for CHD, despite the introduction of potent anti-platelet drugs and drug eluting stents can reduce the restenosis rate after stent implantation, the high rate of In Stent Restenosis (ISR) has plagued clinicians after PCI [5, 6]. ISR is mainly localized at vascular injury area and caused by

variety of vascular recoil factor, which include platelet deposition, thrombosis and other remnants of vascular repair response [7, 8].

The occurring of ISR after PCI could be caused by a variety of factors including drug therapy, stents itself, radiation therapy [9], patients' fundamental disease, the length of their coronary artery, the degree of artery stenosis and related non-surgical procedure [10-12]. A series of large-scale clinical trials indicated that there are still about 5% of ISR rate occurred in drug-eluting stent [13, 14]. And some researches mentioned some coronary heart disease risk factors, characteristics of angiographic lesions and technical parameters of stent also affect the occurrence of restenosis. Therefore, early intervention is particularly important for post-operative ISR.

Table 1. Demographic data of patients undergoing PCI procedure

	Control group (N = 65)	Observation group (N = 35)
Male/Female (N)	23/12	48/17
Age (yr)	58.9 ± 8.2	60.2 ± 9.5
Smoking history (%)	32 (49.2)	17 (48.6)
Hypertension (%)	35 (53.8)	19 (54.3)
Diabetes (%)	26 (40)	15 (42.3)
Hyperlipemia (%)	28 (43.1)	15 (42.6)
Hs-CRP (mg/L)	2.31 ± 0.54	3.24 ± 0.34*
TC (mmol/L)	4.59 ± 1.58	4.78 ± 1.65
HDL-C (mmol/L)	0.89 ± 0.56	0.95 ± 0.37
TG (mmol/L)	4.58 ± 1.27	4.95 ± 1.32
STIM1 (U/L)	4.77 ± 2.63	4.59 ± 2.99
OPG (ug/L)	0.096 ± 0.032	0.101 ± 0.029

*P < 0.05, compared with control group.

Stromal interaction molecule 1 (STIM1) is an endoplasmic reticulum (ER) Ca^{2+} sensor present in embryonic, neonatal, and adult cardiomyocytes, STIM1 play important role in hypertrophic signaling [15]. Research has demonstrated that STIM1 plays an essential role in normal cardiac function in the adult heart, which is important for the regulation of ER and mitochondrial function [16]. Moran *et al.* indicated that Osteoprotegerin (OPG) could up-regulate a series of downstream signal in cardiovascular disease [17]. We noticed the increasing of STIM1 and OPG in postoperative stenosis-patients, so we explore whether these 2 indicators could be used for postoperative restenosis monitoring. The aim of this study was to explore the association between plasma level of STIM1, OPG and ISR after PCI.

Patients and methods

Patients

The study was registered in Ethics Committee of Third Affiliated Hospital of Hebei Medical University in 2012, the related serial number is: HBU2-2012-03. The study was supervised by China Food and Drug Administration (CFDA) according to related law. The Ethics committee approved relating screening, treatment, data collection and follow-up of these patients. All subjects signed written informed consent form. All works were undertaken following the provisions of the Declaration of Helsinki.

Patients who have confirmed having acute coronary syndrome (ACS) combined with diabetes were recruited from Cardiology department of our hospital. Their included criteria were: 1. coronary angiography performed within 2 months, which could confirm their vascular lesion existed in at least one of the three main coronary vessels (left anterior descending artery, circumflex artery and right coronary artery); 2. The Gensini total scores [18] of ≥ 25 points after evaluation; 3. Patients whose blood glucose were controlled within the standard range (3.9-6.1 mmol/L); 4. Patients received percutaneous coronary stenting intervention according to Guideline of Percutaneous Coronary Intervention (Chinese, 2012); 5. Male or female patients their age ranged from 40 to 70 years; 6. Patients who have normal liver and kidney function. Patients were excluded if they have hepatobiliary diseases.

Collected clinical information

The demographic data of all subjects were collected before PCI procedure, including their gender, age, blood pressure, fundamental diseases, smoking history, C-reactive protein (CRP) level, total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), triglyceride (TG), blood glucose level and other biochemical parameters.

Currently, no literature of insulin effecting plasma STIM1 and OPG levels was found. After admission, all patients were asked discontinued their oral hypoglycemic agents, and subcutaneous injection of insulin was used to control their blood glucose. In addition, the following drugs were used for recruited patients to control their disease: aspirin 100 mg/day or clopidogrel 75 mg/day; atorvastatin 40 mg/days (1 weeks later 20 mg 1/day); dalteparin sodium 5000 units/daily; In addition, isosorbide mononitrate, metoprolol and benazepril were used according to the attack of angina pectoris, blood pressure and their heart rate.

Plasma STIM1 and OPG level testing

The plasma level of STIM1 and OPG in each patient was tested before and after PCI procedure. Briefly, a total of 2 ml venous blood was draw within 24 hours of admission and within 24 hours after PCI procedure, respectively. STIM1 and OPG were determined by enzyme-

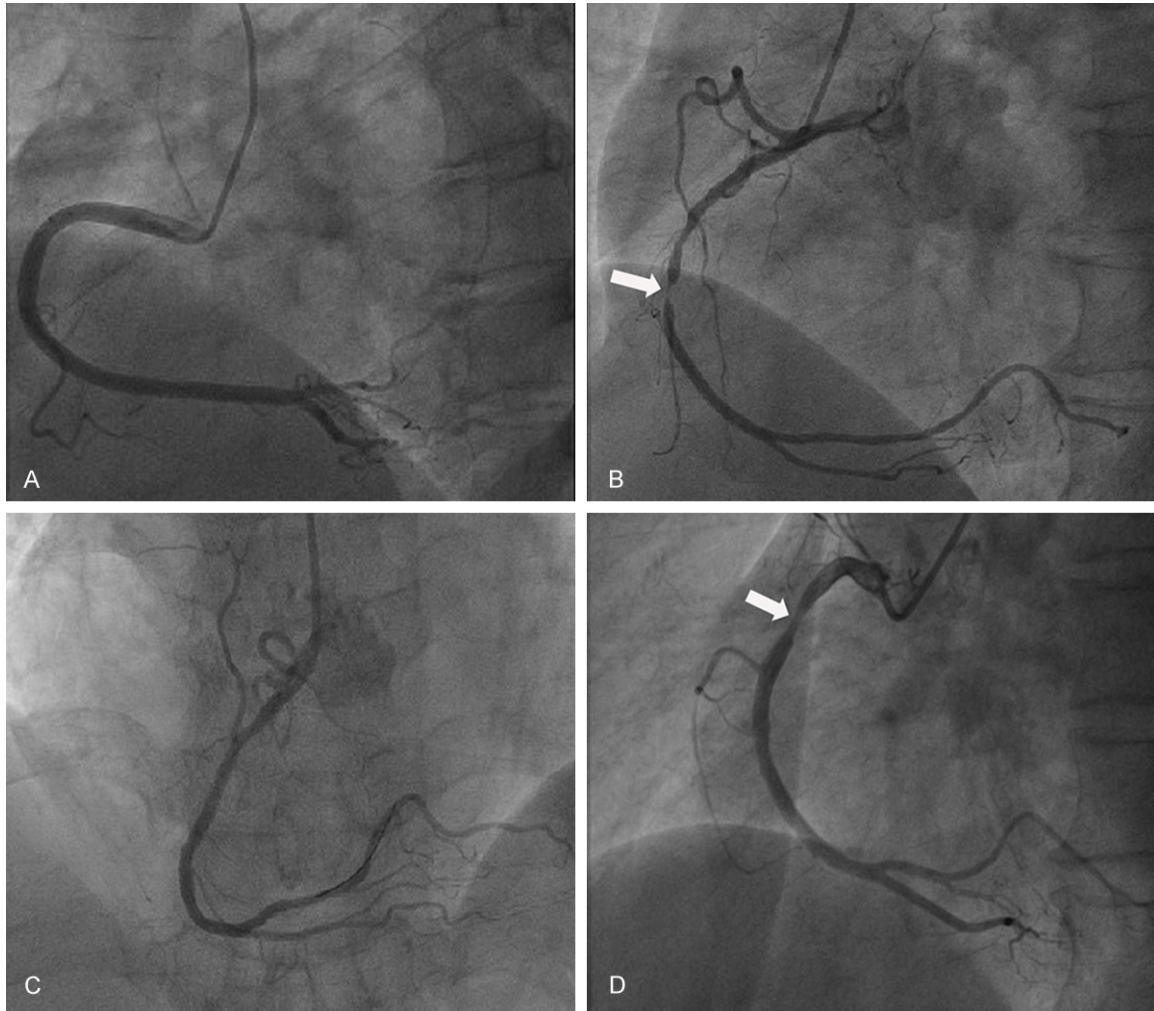


Figure 1. Angiography characters of right coronary artery before and after PCI procedure. A. Normal angiography of right coronary artery; B. Stenosis of right coronary artery (arrow pointed site); C. No restenosis occurred after implantation of stent; D. Restenosis occurred at the right coronary after the coronary stent was implanted.

linked immunoassay (ELISA) method according to instruction of manufacturer (Zhiyan Biotech, Shanghai, CHN).

Percutaneous coronary stenting

Percutaneous coronary stenting was performed according to the standard method described in Guideline of Percutaneous Coronary Intervention (Chinese, 2012). Sirolimus-eluting stents were used in all patients, after PCI procedure, patients received standard drug treatment of aspirin (100 mg) and clopidogrel (75 mg). Other standard treatment used drugs were mentioned above.

The operation criterion of success is determined by residual stenosis and distal blood

flow during operation; no formation of thrombosis for acute thrombosis within 24 hours of PCI procedure; in addition, no formation of sub-acute thrombosis occurred 1 month after PCI; the residual stenosis $\leq 30\%$; the forward flow TIMI grade III, and no acute complications.

Calculation of coronary restenosis rate

The coronary restenosis rate = [(the reference vessel diameter- reviewed minimal lesion diameter)/the reference vessel diameter]*100%.

The minimal lesion diameter: the most narrow diameter of coronary artery.

The reference vessel: The normal blood vessel of the proximal end of the lesion. If the stent is

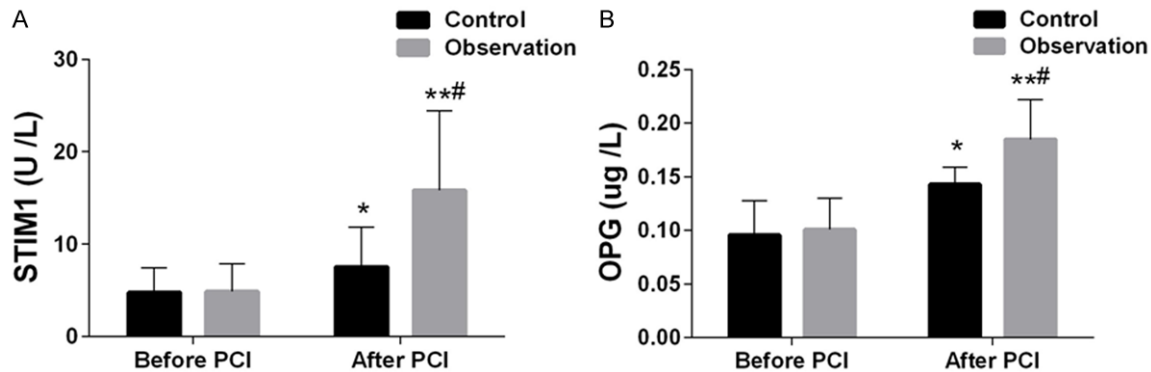


Figure 2. The comparison of plasma STIM1 and OPG level before and after PCI procedure. A. STIM1; B. OPG.

placed at the opening of the vessel and unable to select the proximal vessel, the normal blood vessels near the lesion could be referred.

Follow-up and correlation analysis

We performed following up at 6 months after patients' PCI procedure. Information including the attack of angina pectoris, activity tolerance, heart rate and blood pressure, whether mucosal bleeding in gingival and hematuria; laboratory examination including white blood cell count, platelet count, serum Creatine kinase, glutamic pyruvic transaminase etc.

Coronary angiography was performed 8 months after their PCI procedure for their ISR evaluation. According to their stenosis of coronary, patients were divided into 2 Groups: Observation group, the presence of stenosis of coronary angiography (in-stent stenosis > 50%) and Control group: there is no narrowing of coronary angiography (in-stent stenosis < 50%).

Statistical analysis

The sample size was calculated before the study. According to literatures, postoperative stenosis rate after PCI ranged from 20% to 40% [19-21]. Before study, a small size patients (N = 30) were adopted for sample size calculating, OPG level differentiations were used for sample size calculating. The sample size was estimated according to following formula:

$$n1 \text{ (tested group)} = [(\alpha + \beta)\sigma/\delta]^2 * (1 + C)/C; n2 \text{ (observation group)} = 2 * n1$$

Continuous variables were demonstrated as means \pm standard deviations (SD); the classifi-

cation data were expressed in terms of percentages. Differences in the means of continuous measurements were determined with t-test. Statistical analyses were made by using SPSS10.0 for Windows program. Multiple linear regressions were performed to analyze the relationship of plasma STIM1, OPG levels and restenosis. A *P*-value of less than 0.05 was considered as a statistically significant difference.

Results

After calculation, the calculated minimal sample size in our study should be 101 patients: 37 in observation group and 64 in control group. From March 2012, a consecutive 192 patients who received percutaneous coronary intervention were screened, 125 of them matched with the inclusion criteria, and 100 finished 8 months-coronary angiography finally. However, the actual results of patients' number were slightly lower than our expectation: there were 35 cases in observation group, including 23 males and 12 females (mean age of 58.9 ± 8.2 years); and 65 cases in control group, including 48 cases of male and 17 females (mean age of 60.2 ± 9.5 years).

Demographic data comparison before PCI procedure

There was no statistical difference between observation and control group at their age, gender distribution, hypertension, diabetes and hyperlipemia incidence rates and other laboratory parameters (Table 1), but we observed higher level of Hs-CRP existed in observation group. In addition, results demonstrated that their plasma STIM1 and OPG level have no statistical difference before PCI procedure.

Table 2. Correlation analysis results of correlated factor of occurring ISR after PCI

Analyzed factors	Group	Value	t	P
Gender ration (male: female)	Control	48:17	0.204	P > 0.05
	Observation	23:12		
Age (yrs)	Control	60.2 ± 9.5	0.304	P > 0.05
	Observation	58.9 ± 8.2		
Systolic blood pressure (mmHg)	Control	142.6 ± 14.5	0.352	P > 0.05
	Observation	148.8 ± 15.3		
Diastolic blood pressure (mmHg)	Control	96.1 ± 6.9	0.426	0.0027
	Observation	88.8 ± 7.5		
Hs-CRP (mg/L)	Control	2.31 ± 0.54	0.547	0.003
	Observation	3.24 ± 0.34		
HDL-C (mmol/L)	Control	0.89 ± 0.56	0.536	P > 0.05
	Observation	0.95 ± 0.37		
TG (mmol/L)	Control	4.58 ± 1.27	0.267	P > 0.05
	Observation	4.95 ± 1.32		
FBG (mmol/L)	Control	6.9 ± 1.2	0.275	P > 0.05
	Observation	6.5 ± 1.3		
STIM1 (U/L)	Control	7.5 ± 4.3	0.654	0.0019
	Observation	15.8 ± 8.6		
OPG (ug/L)	Control	0.143 ± 0.016	0.549	0.0038
	Observation	0.185 ± 0.037		

Angiographic characteristics

Figure 1A was a normal angiography of right coronary artery, as we can see, the right coronary artery was normal and no stenosis was found; Before percutaneous coronary stenting, angiography demonstrated a stenosis of right coronary artery (**Figure 1B**, arrow pointed site) in right coronary; No restenosis occurred after implantation of the right coronary stent (**Figure 1C**), while restenosis occurred in observation group after the coronary stent was implanted (**Figure 1D**, restenosis occurred at the right coronary stent).

Comparison of plasma STIM1 and OPG level after PCI procedure

The plasma level of STIM1 and OPG were all elevated after PCI procedure, the differences were significant in both groups ($P < 0.05$, **Figure 2A, 2B**). For patients in observation group, we observed significantly higher plasma level of STIM1, OPG when compared with patients in control group ($P < 0.05$) after PCI. The cut off value was 15 U/L for STIM1, there accounted for 66% in observation group when STIM1 level ≥ 15 U/L (OR: 8.3, 95% CI: 1.8-19, $P < 0.001$ when compared with control group). The cut off

value of OPG was 0.18 $\mu\text{g/L}$, and account for 62% in observation group when $\text{OGP} \geq 0.18 \mu\text{g/L}$ (OR: 7.9, 95% CI: 0.006-0.022, $P < 0.001$ when compared with control group).

Correlation analysis

The correlation analysis of ISR -based clinical data showed that the diastolic blood pressure levels, CRP, STIM1 and OPG levels were significantly associated with postoperative ISR, the concrete results are shown in **Table 2**; Stepwise regression analysis of ISR with diastolic blood pressure, plasma CRP, STIM1, OPG level, smoking status and blood glucose levels showed that CRP, STIM1, OPG levels were independent risk factors of postoperative

patients with ISR, the elevated CRP, STIM1, OPG levels were high risk of restenosis after stent implantation.

Discussions

With the advancement of interventional techniques, an increasing number of patients received PCI to treat coronary artery disease. PCI could achieve revascularization well, which significantly reduce the patient's symptoms, improve patient's quality of life, and reduce acute myocardial infarction (AMI) morbidity and mortality. Despite the introduction of potent anti-platelet drugs and drug eluting stents can reduce the restenosis rate after stent implantation, PCI still could cause vascular restenosis, and it still cannot be ignored.

ISR means the net loss rate of lumen is over 50% 6-9 months after stent implantation, which is more occurred in 2 months after stent implantation with the occurrence rate of 15%-35%. ISR are commonly occurred in patients with diabetes, long lesions, multi-vessel diseases and bifurcation lesions [22-24].

At present, the mechanisms of ISR is not yet fully understood, it is generally considered that

ISR is related with inflammation, endothelial dysfunction, Reticular Activating System (RAS) system over activation and other factors [8, 25, 26], including migration of vascular smooth muscle cells, a large number of excessive proliferation and extracellular matrix synthesis. Among these factors, the excessive proliferation is considered as the most important mechanism, which leads to intimal thickening and chronic stenosis. PCI is an invasive non-surgical procedure can cause mechanical stimulation of blood vessels, this sustained stimulation can activate endothelial cells, monocytes, platelets, smooth muscle cells, neutrophils, lymphocytes and other cells [27], thus causing acute and chronic inflammatory reaction, synthesis and secretion of inflammatory responses, including MMP reactive protein [28], reactive protein C (CRP), interleukin 1, 6, 8 (IL-1, 6, 8), TNF-reactive protein (8), adhesion molecule (AM), etc. [29]. These cytokines induce inflammatory reaction, promote the adhesion and aggregation of leukocytes and platelets to endothelial cells, and the vascular smooth muscle cell is changed from the contraction status to the synthesis status, migrate and proliferate from the middle membrane to the intima membrane, as well as the synthesis of extracellular matrix, leading to the occurrence of restenosis. Restenosis after PCI is the pathophysiology results of local vascular injury and repair, the repair process involved vascular elastic recoil, thrombosis, inflammation factor activation, vascular smooth muscle cell proliferation and apoptosis process [30].

Inflammatory cytokines play an important role in the development of atherosclerotic coronary heart disease, and acute coronary syndrome is believed to cause the inflammatory process of atherosclerosis plate rupture, leading to activation of the coagulation system of inflammatory cytokines, and coronary thrombosis cause myocardial injury [31]. PCI postoperative inflammatory factors could lead to activation of Hs-CRP; this has been shown to be an independent risk factor for ISR after PCI. Wang *et al.* reported the Hs-CRP level was high in patients at 12 h, 24 h, and 48 h after PCI compared with healthy control [32]; Woo *et al.* indicated that for patients undergoing coronary stenting, patients with high platelet reactivity (maximal platelet aggregation by 5 mmol/L of adenosine diphosphate \geq 50%) has significant elevated Hs-CRP level, as a results, elevated Hs-CRP level was significantly associated with poorer

outcomes [33]. It is noteworthy that the Hs-CRP level was higher in restenosis patients than non-restenosis patients before PCI procedure in our study, and this difference are statistically significant, unfortunately, we did not make a further comparison for Hs-CRP level after the PCI procedure. It remains to be analyzed whether this difference affect our final results.

Receptors stromal interaction molecule (stromal interaction molecule, STIM) I could regulate the influx of calcium, and affect biological behaviors such as cell proliferation, migration and differentiation [34]. Endothelial progenitor cells (EPC) could damage to the local homing accelerating re-endothelialization of vascular damage, and inhibit neointimal formation process [35]. Coronary heart disease is related with physiological process of vascular injury, while EPC play an important role in endothelial proliferation of ISR [36]. Kuang *et al.* [37] indicated that STIM1 and EPC are relevant, STIM1 could inhibit the proliferation and migration of endothelial progenitor cells, and play important role in the process of vascular injury repair. ISR after PCI is a local vascular injury repair process, the level of STIM1 might reflect the damage repairing in some extent, the higher level reflects the more severe damage of postoperative ISR, our study indicate that the STIM1 is important risk predictors of ISR, it could independently predicted the occurrence of ISR.

OPG (Osteoprotegerin), as a superfamily of tumor necrosis factor receptor, is a soluble receptor induction [38], and act as anti-apoptotic factor in endothelial cells. Expression of OPG could prevent vascular calcification. A prospective study of 490 elderly women confirmed that there is a positive correlation between OPG levels and cardiovascular disease mortality [39]. Other studies have confirmed the severity of coronary artery disease is related with increased OPG levels. Increased OPG levels in endothelial cells may be a compensatory reflection of vascular injury, which is consistent with ISR pathological process after PCI. Our study has demonstrated that higher OPG levels occurred in patients with restenosis after PCI.

There are some limits in current study: first, the sample size is not satisfied with the minimum calculated value, which makes the reliability of the conclusion affected; Secondly, we did not analysis and compare the postoperative

Hs-CRP levels in both group, which makes our data has certain inconsistency; Third, compelling reports have points out that the Hs-CRP increased after PCI, and whether this increase is related with the increase of STIM1 and OPG levels need further analysis.

Conclusion

In conclusion, our study showed that the STIM1, OPG levels have predictive effect for ISR after PCI in diabetes patients, the higher level STIM1, OPG are, the greater risk of restenosis is. However, given the relative small sample size of our study, larger sample size is still needed in order to further verify this conclusion; this could provide more accurate evidence for the clinical application of our finding.

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Disclosure of conflict of interest

None.

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