REVIEW ARTICLE

Influence of blood glucose level on the prognosis of patients with diabetes mellitus complicated with ischemic stroke

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We carried out this meta-analysis for the aim of exploring the influence of diabetes mellitus (DM) on the prognosis of patients with ischemic stroke. Relevant studies were identified using computerized databases supplemented with manual search strategies. The included studies were strictly followed the inclusion and exclusion criteria. Case-control studies which related to the influence of DM on the prognosis of patients with ischemic stroke were selected. Statistical analyses were implemented with the STATA version 12.0 statistical software. Our current meta-analysis initially retrieved 253 studies (227 in Chinese and 26 in English), 13 studies (6 in English and 7 in Chinese) were eventually incorporated in this meta-analysis. These 13 case-control studies included 8463 patients altogether (3249 patients with DM complicated with ischemic stroke and 5214 patients with ischemic stroke). The results of this meta-analysis manifested that there was a significant difference of the blood glucose level at 48 h after stroke between patients with DM complicated with ischemic stroke and patients with ischemic stroke (standard mean difference [SMD] =1.27, 95% confidence interval [CI] =0.02–2.51, $P = 0.047$); however, the effectiveness, fatality, and the National Institutes of Health Stroke Scale (NIHSS) score in patients with DM complicated with ischemic stroke, and patients with ischemic stroke had no significant difference (effectiveness: risk ratio [RR] = 0.88, 95% CI = 0.75–1.03, $P = 0.121$; fatality: RR = 1.29, 95% CI = 0.97–1.71, $P = 0.081$; NIHSS score: SMD = −0.14, 95% CI = −1.56-1.28, $P = 0.849$). The current evidence suggests that there is statistical difference of the blood glucose level at 48 h after stroke between patients with DM complicated with ischemic stroke and patients with ischemic stroke, but there is no statistical difference of prognostic indicators between patients in two groups. Thus, our study provides certain clinical value.

Key words: Blood glucose level, diabetes mellitus, ischemic stroke, meta-analysis, prognosis

How to cite this article: Dong XL, Guan F, Xu SJ, Zhu LX, Zhang PP, Cheng AB, Liu TJ. Influence of blood glucose level on the prognosis of patients with diabetes mellitus complicated with ischemic stroke. J Res Med Sci 2018;23:10.

INTRODUCTION

Diabetes mellitus (DM) is known as a group of metabolic diseases, characterized by recurrent or persistent hyperglycemia.[1] It was estimated that 382 million people were diagnosed with DM worldwide in 2013 and type 2 accounted for 90% of the cases, which is equal to 8.3% of the adult population with equal rates in both women and men.[1,2] It is generally believed that the major risk factors for developing DM are embedded in the complex interactions between genetic, psychological, and social environment, including certain human leukocyte antigen genotypes, and obesity originated from excessive eating and reduced physical activity.[3,4] The classical symptoms of DM are frequent urination, increased thirst, increased hunger, and weight loss, and it is often accompanied by corresponding complications, such as diabetic ketoacidosis and nonketotic hyperosmolar coma, heart disease, ischemic stroke, kidney failure, foot ulcers, and damage to the eyes.[5,6] Ischemic stroke, also called cerebral infarction, results from a blockage in the blood vessels supplying blood to the brain.[7] It was well-documented that DM was important risk factor leading to ischemic stroke, and DM complicated with ischemic stroke can aggravate the mortality and morbidity of patients.[8,9]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/1735-1995.223951

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Received: 22-09-2015; **Revised:** 02-01-2016; **Accepted:** 04-11-2016

Blood glucose level, also known as blood sugar concentration, is the content of glucose or sugar presenting in a human or animal' blood.[10] Glucose provides the main source of energy for the body's cells and blood lipids remains the primary compact energy store in the form of fats and oils.[11] Transported from the liver or intestines to body cells by the way of bloodstream, glucose is also available for cell absorption through the hormone insulin in the pancreas.[12] Clinical research suggested that blood glucose levels that outside the normal range might be an indicator for medical conditions, and persistent high levels are described as hyperglycemia; low levels are described as hypoglycemia.[13,14] It has been inferred that hyperglycemia causes a variety of long-term health problems, such as heart disease, kidney, eyes, and nerve damage, whereas the symptoms for hypoglycemia included pale complexion, sweating, irritability, lethargy, paranoid, or aggressive mentality, impaired mental functioning, and loss of consciousness, etc.[15,16] There are also some causes that may lead to the fluctuation of blood glucose level, such as climatic factors, cold, insufficient dosage of drugs, long-term constipation, excessive intake of high fat food, and sudden change of work and live environment.[17,18] DM is the most prevalent disease associated with the failure of blood sugar regulation, which is featured by persistent hyperglycemia.[19] In view of above findings, there are scholars supported that blood glucose level had impact on the prognosis of patients with DM complicated with ischemic stroke.[20,21] However, some findings were not consistent with aforementioned opinions.[22,23] Consequently, the current meta-analysis based on the previous studies aimed to explore the influence of DM on the prognosis of patients with ischemic stroke.

MATERIALS AND METHODS

Data sources and keywords

With the application of computerized databases (PubMed, Web of Science, China BioMedicine, Cochrane Library, and China National Knowledge Infrastructure) updated in September 1, 2014, those published papers assessing the influence of DM on the prognosis of patients with ischemic stroke were obtained, utilizing selected common keywords related to blood glucose level, and DM as well as ischemic stroke. The keywords utilized in our initial literature search were ("ischemic stroke" or "cerebral ischemic stroke" or "ischemic cerebral apoplexy") and ("diabetes mellitus" or "diabetes" or "diabetic") and ("blood sugar level" or "blood sugar levels" or "blood glucose level" or "blood glucose levels"). Manual research was also conducted to identify the potential relevant papers.

Study selection

The inclusion criteria were (1) case-control studies about the influence of DM on the prognosis of patients with ischemic stroke; (2) patients diagnosed with DM complicated with ischemic stroke were in the case group, whereas patients with ischemic stroke were in the control group; (3) included studies had to provide complete data; and (4) included studies were either in Chinese or in English. Meanwhile, the studies which were latest or complete were included when published by the same authors. However, the studies with incomplete data, large differences of baseline characteristics of the patients between the case group and the control group and repeated publication were excluded.

Data extraction and quality assessment

We used a predefined reporting form to extract data from each enrolled study by two researchers independently, and collected the following information: the first author, publication time, country, ethnicity, language, disease, age, gender, detection method, study design, interventions, outcomes, etc., Disagreement on any problems was settled by discussion, or a third investigator was consulted. Two authors conducted quality assessment based on the critical appraisal skill program (CASP) criteria to assess the studies independently (http://www.casp-uk.net/). The CASP criteria are scored based on these aspects: whether the research problem is clear and definite (CASP01); whether the research problem is appropriate and whether the research design answers the research problem (CASP02); whether the selective mode is suitable for population in case study (CASP03); whether the selective mode is suitable for population in control study (CASP04); whether the measurement for exposure factors is accurate to reduce the bias (CASP05); whether the study controls other important confounding factors (CASP06); whether the research result is complete (CASP07); whether the research result is precise (CASP08); whether the research result is reliable (CASP09); whether the research result is applicable to the crowd (CASP10); and whether the research result is consistent with other evidence (CASP11).

Meta-analysis

All the analyses of this present meta-analysis were conducted with the STATA statistical software, version 12.0 (Stata Corp., College Station, TX, USA). A fixed-effects model or random-effects model was adopted for computing the risk ratio (RR), the summary standard mean difference (SMD) and 95% confidence interval (95%CI), and thereby evaluate the difference between the case group and the control group with the utilization of Z-test. Cochran's Q-statistic and I^2 tests were also used to quantify heterogeneity among studies.[24,25] Random-effects model was applied for the evidence of significant heterogeneity ($P < 0.05$ or $I^2 > 50\%$), whereas fixed-effects model was applied with the absence of statistical heterogeneity ($P > 0.05$ or $I^2 < 50\%$).[26] Meanwhile, if there was significant heterogeneity, subgroup analyses were performed to find potential explanatory variables. In addition, a sensitivity analysis was employed to evaluate

whether the removing of one single study would have impact on the overall estimate. The funnel plot and Egger's linear regression test were utilized to assess the publication bias of included studies.[27]

RESULTS

Included studies

Our present meta-analysis initially extracted 253 studies through electronic database searching and manual search, followed by removing 72 duplicates, 39 letters, reviews or meta-analysis, 41 nonhuman studies, and 44 studies unrelated to research topics, the left 57 studies were reviewed and another 41 studies were removed with 11 studies were not case-control study, 13 irrelevant to blood glucose level, or 17 irrelevant to DM. After the left 16 studies being further reviewed, 13 studies were enrolled in the final analysis, after remove 3 studies for insufficient information.[28-40] Among these 13 studies, 8 studies were performed in Asian populations and 5 studies were in Caucasian populations, including a combined total of 8463 patients (3249 patients with DM complicated with ischemic stroke and 5214 patients with ischemic stroke), which were published between 2000 and 2013. The countries where the studies performed were the USA ($n = 2$), China ($n = 7$), and one study each in Croatia, Kuwait, Italy and Hungary. The baseline characteristics and CASP quality evaluation of the extracted studies were displayed in Table 1 and Figure 1.

Pooled outcome of meta-analysis

The blood glucose level at 48 h after stroke, effectiveness, fatality, and the National Institutes of Health Stroke Scale (NIHSS) Score between patients with DM complicated with ischemic stroke and patients with ischemic stroke were reported in 3, 5, 10, and 4 studies, respectively. In viewing of existing heterogeneity ($I^2 > 50\%$, $P < 0.05$), random-effects model was applied to pool the data of blood glucose level at 48 h after stroke, fatality, and NIHSS Score. However, fixed-effects model was utilized in effectiveness due to no heterogeneity ($I^2 < 50\%$, $P > 0.05$). As shown in Figure 2, the results implied that the blood glucose level

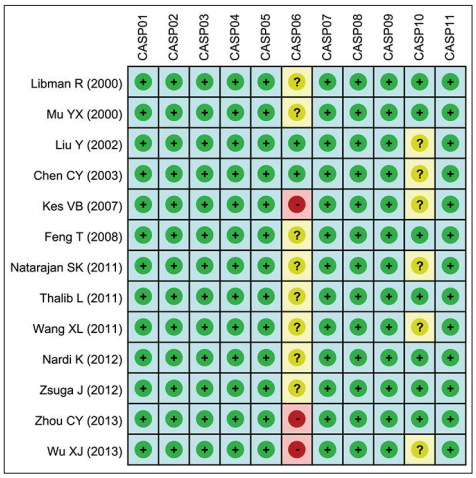

Figure 1: Quality assessment of included studies by critical appraisal skill program score. CASP = Critical appraisal skill program

Table 1: Main characteristics and methodological quality of all eligible studies

First author	Year	Country	Number		Gender (male/female)		Age (years)		Study design	Outcomes
			Case	Control	Case	Control	Case	Control		
Libman[28]	2000	USA	44	77	22/22	34/43	65	68	RCT	The GOS at follow-up; follow-up NIHSS; blood glucose
MO YX[29]	2000	China	26	135	100/61		63.5 (33-85)		Non-RCT	Fatality
Liu Y[30]	2002	China	13	62	54/21		68.5 (52-84)		Non-RCT	Fatality
Cheng CY[31]	2003	China	26	272	182/116		68.2±5.6 (44-87)		Non-RCT	Fatality
Kes[32]	2007	Croatia	220	410	NR		71 (70-77)		Non-RCT	In-hospital mortality within 28 days
Feng T[33]	2008	China	88	104	112/80		61.5 (50-77)		Non-RCT	Fatality; glycated serum protein levels Neurological impairment relations
Natarajan[36]	2011	USA	166	443	291/323		70 (14-98)		Non-RCT	Distribution of glucose values Predictors with a probability value of <0.2; NIHSS score
Thalib[37]	2011	Kuwait	1889	897	1272/617	724/173	59	56	RCT	STEMI; NSTEMI; LBBB MI; unstable angina; heart failure; cardiogenic shock; ventilation
Wang XL[35]	2011	China	43	77	58/62		61.2±1.2 (49-74)		Non-RCT	Fatality
Nardi[38]	2012	Italy	239	572	116/123	302/270	77 (70-83)	77 (68-83)	Non-RCT	72-h fatality; 7-day fatality; MRS score 5-6 at 7 days
Zsuga[39]	2012	Hungary	419	2077	1333/1163		68.2±12.3		RCT	On-admission serum glucose levels; 30-day case fatality
Zhou CY[40]	2013	China	54	68	NR		NR		Non-RCT	NIHSS scores; BI scores
Wu XJ[34]	2013	China	22	20	NR		NR		Non-RCT	NIHSS; BI; MRS

NR = Not reported; RCT = Randomized controlled trial; Non-RCT = Nonrandomized controlled trial; GOS = Glasgow Outcome Score; NIHSS = National Institutes of Health Stroke Scale; STEMI = ST-elevation myocardial infarction; NSTEMI = Non-ST-elevation myocardial infarction; LBBB MI = Left bundle branch block myocardial infarction; BI = Barthel index

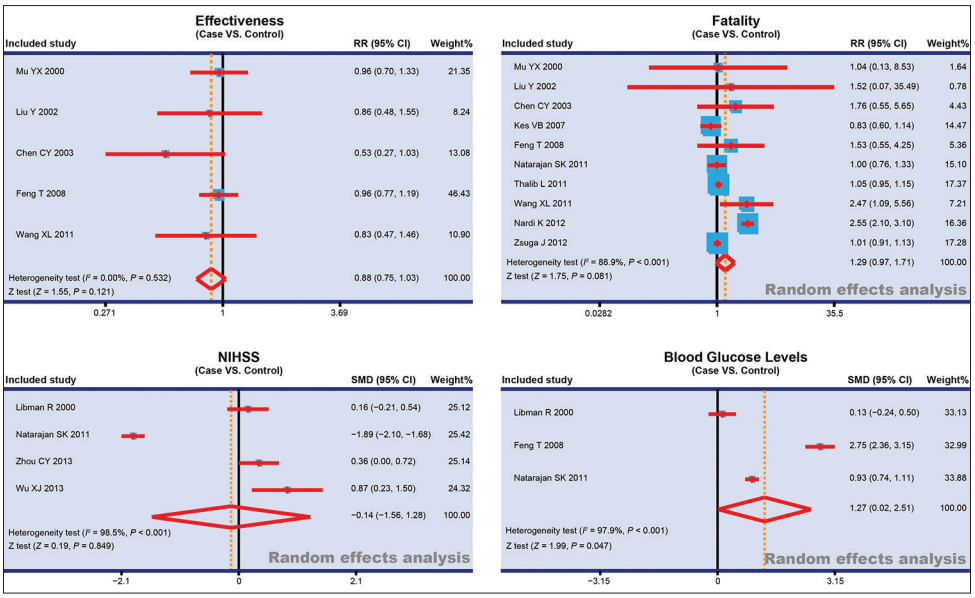

Figure 2: Forest plots for the blood glucose level, the effectiveness, fatality, and the NIHSS Score in patients with diabetes mellitus complicated with ischemic stroke and patients with ischemic stroke. NIHSS: National Institutes of Health Stroke Scale; RR = Risk ratio; CI = Confidence interval; SMD = Standard mean difference

at 48 h after stroke in patients with DM complicated with ischemic stroke was significantly higher when compared to that in patients with ischemic stroke (SMD = 1.27, 95% CI = 0.02–2.51, P = 0.047). However, the effectiveness, fatality, and NIHSS score in patients with DM complicated with ischemic stroke, and patients with ischemic stroke had no significant difference (effectiveness: RR = 0.88, 95% CI = 0.75–1.03, P = 0.121; fatality: RR = 1.29, 95% CI = 0.97–1.71, P = 0.081; NIHSS score: SMD = −0.14, 95% CI = −1.56–1.28, P = 0.849). A further ethnicity-stratified analysis was conducted. The fatality in patients with DM complicated with ischemic stroke and patients with ischemic stroke had no statistical significance (Asians: RR = 1.18, 95% CI = 0.92–1.51, P = 0.198; Caucasians: RR = 1.22, 95% CI = 0.73–2.02, P = 0.447). Meanwhile, NIHSS score of patients with DM complicated with ischemic stroke in Asians was obviously higher when compared to that of patients with ischemic stroke, and there was significant difference (SMD = 0.54, 95% CI = 0.07–1.02, P = 0.025); whereas there was no significant difference in Caucasians (SMD = −0.87, 95% CI = −2.89–1.15, P = 0.398). The results of subgroup analysis of blood glucose levels at 48 h after stroke based on ethnicity revealed that the blood glucose levels at 48 h after stroke of patients with DM complicated with ischemic stroke were significantly higher than those in patients with ischemic stroke (SMD = 2.75, 95% CI = 2.36–3.15, P < 0.001); whereas for the blood glucose levels at 48 h after stroke of patients in Caucasians, no significant difference was found between patients with DM complicated with ischemic stroke and patients with ischemic stroke (SMD = 0.54, 95% CI = −0.2–1.33, P = 0.172) [Figure 3].

Sensitivity analysis and publication bias

Sensitivity analysis was applied in our meta-analysis, and the removal of any single study had minimal impact on the findings of this meta-analysis, indicating the stability of our analysis. The sensitivity analysis results suggested that all included studies had no obvious effect on merging effect value RR and SMD. The graphical funnel plots presented symmetrical, suggesting there was no publication bias. The Egger's linear regression analysis further confirmed the absence of publication bias (all P > 0.05).

DISCUSSION

This meta-analysis managed to probe into the influence of DM on the prognosis of patients with ischemic stroke. The main outcomes demonstrated that the blood glucose level at 48 h after stroke in patients with DM complicated with ischemic stroke was significantly higher when compared to that in ischemic stroke patients, while the effectiveness, fatality, and NIHSS Score in patients with DM complicated with ischemic stroke and patients with ischemic stroke showed no significant difference. DM is an important independent factor that resulting in ischemic stroke and the incidence of patients with DM is higher in the comparison of patients with nondiabetic patients.[41] DM is reported to cause the fat metabolism disorder, accelerate atherosclerosis, and increase the blood viscosity, which lead to the poor platelet function and anticoagulant effect *in vivo* as well as the changes of blood components, thereby causing ischemic stroke.[42] Hyperglycemia after stroke can be caused by previous DM, or may also be caused by stress reaction after stroke. The reason for stress causing a rise in

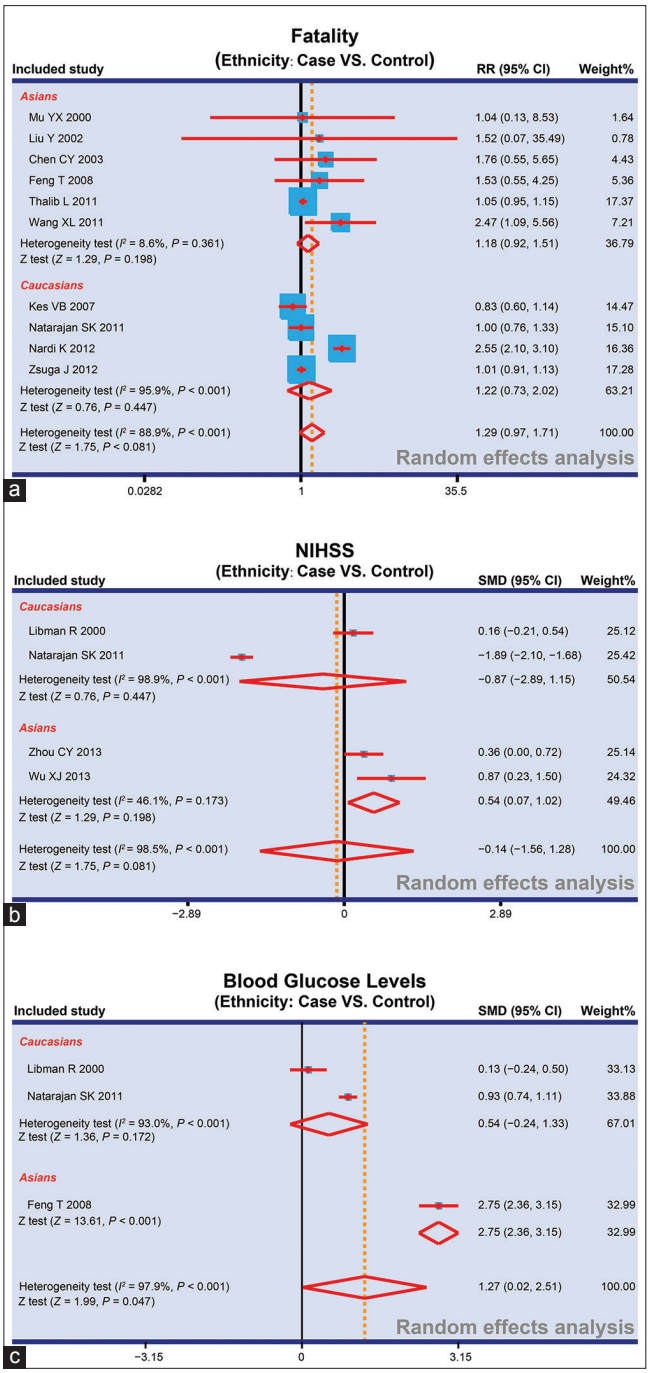

Figure 3: Subgroup analyses for the fatality, the NIHSS Score, and blood glucose levels in patients with diabetes mellitus complicated with ischemic stroke and patients with ischemic stroke. a: Subgroup analysis for the fatality in patients with DM complicated with ischemic stroke and patients with ischemic stroke; b: Subgroup analysis for NIHSS Score in patients with DM complicated with ischemic stroke and patients with ischemic stroke; c: Subgroup analysis for blood glucose levels in patients with DM complicated with ischemic stroke and patients with ischemic stroke; NIHSS = National Institutes of Health Stroke Scale; RR = Risk ratio; CI = Confidence interval; SMD = Standard mean difference

blood glucose is that stress reaction results in the deficiency of islet function, activation of the sympathetic adrenal and pituitary-adrenal system, changes of cell receptor activity, and decreased insulin sensitivity.[43] The study has shown that the poor prognosis of DM complicated with ischemic stroke was associated with hyperglycemia, indicating that the higher the glycosylated hemoglobin (HgbA1C) and glycosylated serum protein, the poorer the efficacy and prognosis, which induced by the increase of intracellular lactate anaerobic metabolism.[44,45] A previous systematic review demonstrated that the elevation of blood glucose level at the time of inhospital admission is accompanied by increased risk for 30-day case fatality in patients previously identified as nondiabetic and the diabetic state alters the effect blood glucose level has on stroke outcome.[39] It was reported that the acute stage of exacerbation of either ischemic or hemorrhagic cerebrovascular disease was closely correlated with the increase of blood glucose, and the severity degree was positively associated with the increase of blood glucose, indicating that DM and ischemic stroke had close relationship on the occurrence and prognosis of disease.[46,47]

We also implemented subgroup analysis in consideration of other factors such as ethnicity to explore the influence of DM on the prognosis of patients with ischemic stroke. An ethnicity-stratified analysis results have indicated that there was no statistical significance for the fatality in patients with DM complicated with ischemic stroke and patients with ischemic stroke. In addition, NIHSS Score of patients with DM complicated with ischemic stroke in Asian populations was obviously higher when compared to that of patients with ischemic stroke, and there was significant difference whereas no significant difference was found in Caucasians. All these findings implied that the ethnicity factor may not be the heterogeneity source to impact the results.

Some specific limitations were also acknowledged for careful consideration. First, there existed data missing of age and gender in some enrolled studies, which may affect the overall results. Another major concern may be the selective publication bias, for the screened references of papers only published in English and Chinese, while the studies in other languages were not included. Third, diabetes is one of the risk factors of ischemic stroke, and the reasons of hyperglycemia in ischemic stroke were stress hyperglycemia and diabetic hyperglycemia. Fasting blood glucose and elevated random blood glucose may be caused by stress hyperglycemia, and HgbA1C, as a common indicator for the diagnosis of diabetes, reflects the whole blood glucose level for the inspected person, which helps to establish the diagnosis of DM complicated with ischemic stroke. However, we cannot carry out further analysis on this aspect because of limited information in these included studies, which might result in slight deviation for our study. Last, the research methods were not unified, which may lead to some minor differences for the results in this meta-analysis.

CONCLUSIONS

The current evidence suggests that there is statistical difference of the blood glucose level at 48 h after stroke between patients with DM complicated with ischemic stroke and patients with ischemic stroke, but there is no statistical difference of prognostic indicators between patients in two groups. Thus, our study provides certain clinical value.

Acknowledgments

We would like to acknowledge the reviewers for their helpful comments on this paper.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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