Original Article
Serum bilirubin levels in acute stroke in Chinese population: a meta-analysis

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Abstract: Studies on serum bilirubin levels in acute stroke have yielded conflicting results. The objective of this meta-analysis was to investigate the correlation between serum bilirubin levels and acute stroke. We searched for relevant studies in PubMed, EMBASE, China BioMedicine, CKNI, Wanfang and VIP database until October 15, 2015. Studies reporting the serum bilirubin levels in acute cerebral infarction or hemorrhage were included. Pooled results were expressed as weighted mean difference (WMD) with 95% confidence intervals (CI). A total of 24 case-control studies were identified and analyzed. Overall meta-analysis indicated that serum bilirubin levels were significantly lower (WMD=-1.77 μmol/L; 95% CI=-3.08 to -0.47) in acute cerebral infarction patients than those in healthy controls. Subgroup analysis showed that the difference of serum bilirubin levels was insignificant within 24 hours after stroke. In cerebral hemorrhage patients, pooled data from 5 studies revealed that serum bilirubin levels were significantly higher (WMD=4.79 μmol/L; 95% CI=1.97 to 7.62) than those in healthy controls. This meta-analysis suggests that decreased serum bilirubin levels are correlated with acute cerebral infarction and elevated serum bilirubin levels may be correlated with acute cerebral hemorrhage.

Keywords: Bilirubin, stroke, cerebral infarction, cerebral hemorrhage, meta-analysis

Introduction

Stroke has been identified as the leading cause of death and disability worldwide [1, 2]. Depending on its etiology, stroke can be classified into both ischemic and hemorrhagic subtype [3]. Approximately 15 million people suffer from stroke each year and ischemic stroke is the dominant subtype of stroke [4]. Cerebral infarction, a type of ischemic stroke, is caused by atherothrombotic or embolic blockage of blood vessels of the brain. Intracerebral hemorrhage is a hemorrhagic stroke resulting from bleeding into the brain parenchyma. Multiple conventional risk factors have been involved in the pathogenesis of acute stroke. Therefore, early risk stratification for acute stroke based on the potential risk factors is critical in clinical practices.

Bilirubin, an end product of heme catabolism, has powerful antioxidant properties [5]. Serum bilirubin plays an important role in atherosclerotic processes [6]. Bilirubin levels were inversely correlated to the carotid intimal-medial thickening [7] and cardiovascular disease [8]. Bilirubin may reflect a systemic oxidative stress response following stroke. Thus, serum levels of bilirubin may be served as a potential biomarker for acute stroke. Decreased serum bilirubin levels were associated with increased risk of cerebral infarction in many studies [9-11]. By contrast, several studies [12-14] have showed higher serum bilirubin levels in the early phase of stroke. In addition, serum bilirubin levels also increased in the early phases of cerebral hemorrhage [15]. These conflicting findings may be correlated with the different types of stroke, phases of stroke, severity of disease, and site of the lesion.

To address these conflicting findings, we conducted this meta-analysis to investigate the serum bilirubin levels in acute phase of cerebral infarction and cerebral hemorrhage.
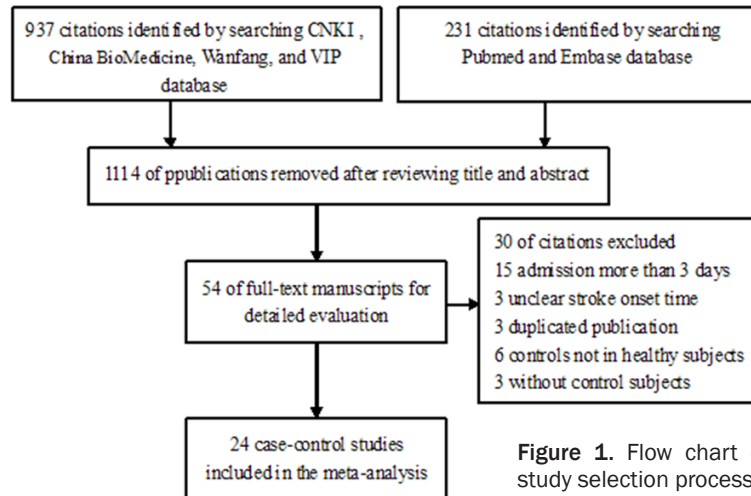
Figure 1. Flow chart of study selection process.

stroke type, number of cases and controls, gender, mean age, serum bilirubin levels (mean and standard deviation). The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for case-control studies [16]. Study achieving more than 6 stars was considered at low risk of bias.

Statistical analysis

Statistical analyses in this meta-analysis were conducted using STATA software (version 12.0; Stata Corp LP, College Station). Differences in serum bilirubin levels between stroke patients and the healthy controls were calculated using weighted mean difference (WMD) with 95% confidence intervals (CI). When the Cochran's Q statistic with P<0.05 or I^2 test >50%, a random effect model was applied in the pooled estimates. The existence of publication bias was detected by the Begg's rank correlation [17] and the Egger linear regression test [18].

Results

Literature search and baseline characteristics

A total of 1,168 potentially relevant citations were retrieved through the electronic literature search. After applied our predefined the inclusion criteria, a total of 24 case-control studies [19-42] were finally included in the meta-analysis. **Figure 1** presents the flow chart of the study selection process. Baseline characteristics as well as NOS of the included studies are shown in **Table 1**. A total of 1,741 cerebral infarction patients, 370 cerebral hemorrhage patients, and 1,437 healthy controls were included. All the studies were carried out in China and published from 2003 to 2014. Based on the NOS score, the overall methodological quality of the included studies was grouped as low risk of bias; NOS scores ranged from 5 to 8.

Meta-analysis of serum bilirubin levels in acute stroke

A total 23 studies [19-40, 42] reported the serum bilirubins levels in acute cerebral infarc-

Materials and methods

Search strategy

Two authors (HY Li and WH Liu) independently searched the PubMed, EMBASE, China Bio-Medicine, China National Knowledge Infrastructure, Wanfang database and VIP database until October 15, 2015. The search keywords included "stroke" OR "cerebral infarction" OR "ischemic stroke" OR "cerebral thrombosis" OR" brain infarction" OR "intracerebral hemorrhage" OR "cerebral hemorrhage" AND "bilirubin" OR "Heme Oxygenase-1". In addition, the reference lists of included studies were manually reviewed to identify additional new articles.

Study selection

Inclusion criteria: 1) case-control studies reporting the serum bilirubin levels in acute phase of cerebral infarction and cerebral hemorrhage; 2) reporting serum bilirubin levels as continuous data in the patients and healthy controls; 3) serum bilirubin levels obtained within the first 72 hours after stroke event; and 4) diagnosis of acute stroke was validated using computed tomography or magnetic resonance imaging scanning. Studies were excluded when patients with transient ischemic attack or an established history of hepatic disease.

Data extraction and quality assessment

The following data was extracted by two authors (HY Li and WH Liu) independently: surname of the first author, publication year, study design,

Table 1. Baselin characteristics of the included studies

Study/Year	Design	Diagnosis	Detecting time	Cerebral infarction			Controls			Overall NOS
				Size and (%)	Age (Years)	TB (μmol/L)	Size and (%)	Age (Years)	TB (μmol/L)	
				Female	Mean ± SD	Mean ± SD	Female	Mean ± SD	Mean ± SD	
Zhu CM 2003 [19]	Case-control	CI	72 h	68 (38.2%)	65.6±8.7	12.4±4.71	52 (34.6%)	67.2±6.4	16.15±5.82	7
Yang B et al 2004 [20]	Case-control	CI	72 h	42 (28.6%)	67.9±8.2	11.03±4.01	28 (28.63%)	68.1±7.9	16.24±3.75	7
Jiang XQ et al 2005 [21]	Case-control	CI	72 h	87 (46.0%)	65.6±8.7	10.32±3.5	80 (50.0%)	67.2±6.4	14.87±6.5	8
Wu PF 2005 [22]	Case-control	CI	24 h	42 (33.3%)	55.42±12.46	16.36±6.13	30 (50%)	55.63±12.75	13.23±3.8	6
		CH		23 (43.4%)	54.12±13.11	18.00±6.43				
Wei RL et al 2005 [23]	Case-control	CI	24 h	30 (46.7%)	38-90	16.47±6.27	40 (NP)	NP	13.2±4.63	6
		CH		38 (47.4%)	37-83	15.89±5.71				
Rao HW 2007 [24]	Case-control	CI	24 h	50 (48%)	59.74±7.15	10.74±2.82	50 (42%)	60.48±6.88	14.83±5.95	7
Zhu MZ et al 2007 [25]	Case-control	CI	72 h	60 (46.7%)	64±4.8	11.81±6.52	50 (48.0%)	62±8.6	15.62±3.48	7
Xi G et al 2007 [26]	Case-control	CI	24 h	92 (39.1%)	61.2±6.7	14.04±0.54	50 (48.0%)	60.3±6.9	13.46±0.38	7
Jia GL 2007 [27]	Case-control	CI	72 h	89 (25.9%)	65.1±11.9	12.86±2.80	40 (30.0%)	61.3±10.91	15.72±3.48	7
Hao ZF et al 2007 [28]	Case-control	CI	72 h	61 (36.1%)	63.1±7.8	14.89±6.08	57 (38.6%)	64.3±6.7	16.94±4.89	7
Tian HJ et al 2008 [29]	Case-control	CI	12 h	40 (25%)	70±5.0	15±5.0	43 (34.9%)	69±7.0	16.5±4	6
Liu YM et al 2009 [30]	Case-control	CI	24 h	60 (46.7%)	65.3±8.1	10.54±3.98	50 (48.0%)	67.5±8.2	16.37±4.21	7
Zhang HH et al 2010 [31]	Case-control	CI	72 h	87 (46.0%)	65.6±8.7	9.3±3.5	80 (50%)	67.2±6.4	14.8±6.5	8
Qiu SL et al 2010 [32]	Case-control	CI	48 h	80 (35%)	53.8±12.5	9.05±3.51	50 (38%)	50.5±13.2	11.57±4.01	7
Pan RH et al 2011 [33]	Case-control	CI	24 h	138 (44.9%)	56.67±12.42	15.43±6.7	106 (47.2%)	53.21±10.27	12.96±4.5	8
Liu N et al 2011 [34]	Case-control	CI	24 h	100 (39.0%)	67.3±7.2	10.45±3.89	100 (40.0%)	65.5±9.2	17.38±3.21	8
Wang QF 2012 [35]	Case-control	CI	24 h	120 (46.7%)	65.3±8.1	10.54±3.98	100 (48%)	67.5±9.2	16.37±4.21	6
Zhang ZH et al 2013 [36]	Case-control	CI	48 h	150 (32.67%)	38-79	20.16±4.63	50 (NP)	NP	11.20±3.93	6
		CH		105 (43.81%)	42-78	18.76±4.45				
He K 2013 [37]	Case-control	CI	72 h	47 (44.7%)	67.2±3.4	12.20±2.13	50 (44.0%)	67.5±3.1	15.17±2.81	7
Wang YW 2013 [38]	Case-control	CI	12 h	70 (44.3%)	67.04±11.6	9.81±3.91	40 (52.9%)	64.31±9.0	14.37±3.14	8
Shou GL et al 2013 [39]	Case-control	CI	72 h	57 (33.3%)	64.21±10.43	10.48±2.42	22 (50%)	60.32±7.83	12.70±3.23	8
Feng CX et al 2013 [40]	Case-control	CI	72 h	105 (25.9%)	65.38±11.52	15.76±5.02	105 (29.5%)	65.06±10.28	12.34±2.59	8
		CH		105 (34.5%)	66.04±13.72	15.13±4.47	105 (29.5%)	65.06±10.28	12.34±2.59	
Zhang YX et al 2014 [41]	Case-control	CH	24 h	99 (53.5%)	62.87±13.57	18.39±9.79	80 (53.8%)	60.16±9.59	13.76±4.74	7
Jia Y et al 2014 [42]	Case-control	CI	24 h	66 (NP)	61.5±8.6	11.8±1.0	65 (49.2%)	58.0±7.9	8.6±0.9	8

Abbreviations: CI, cerebral infarction; CH, cerebral hemorrhage; TB, total bilirubin; NP, not provided; NOS, Newcastle-Ottawa Scale.
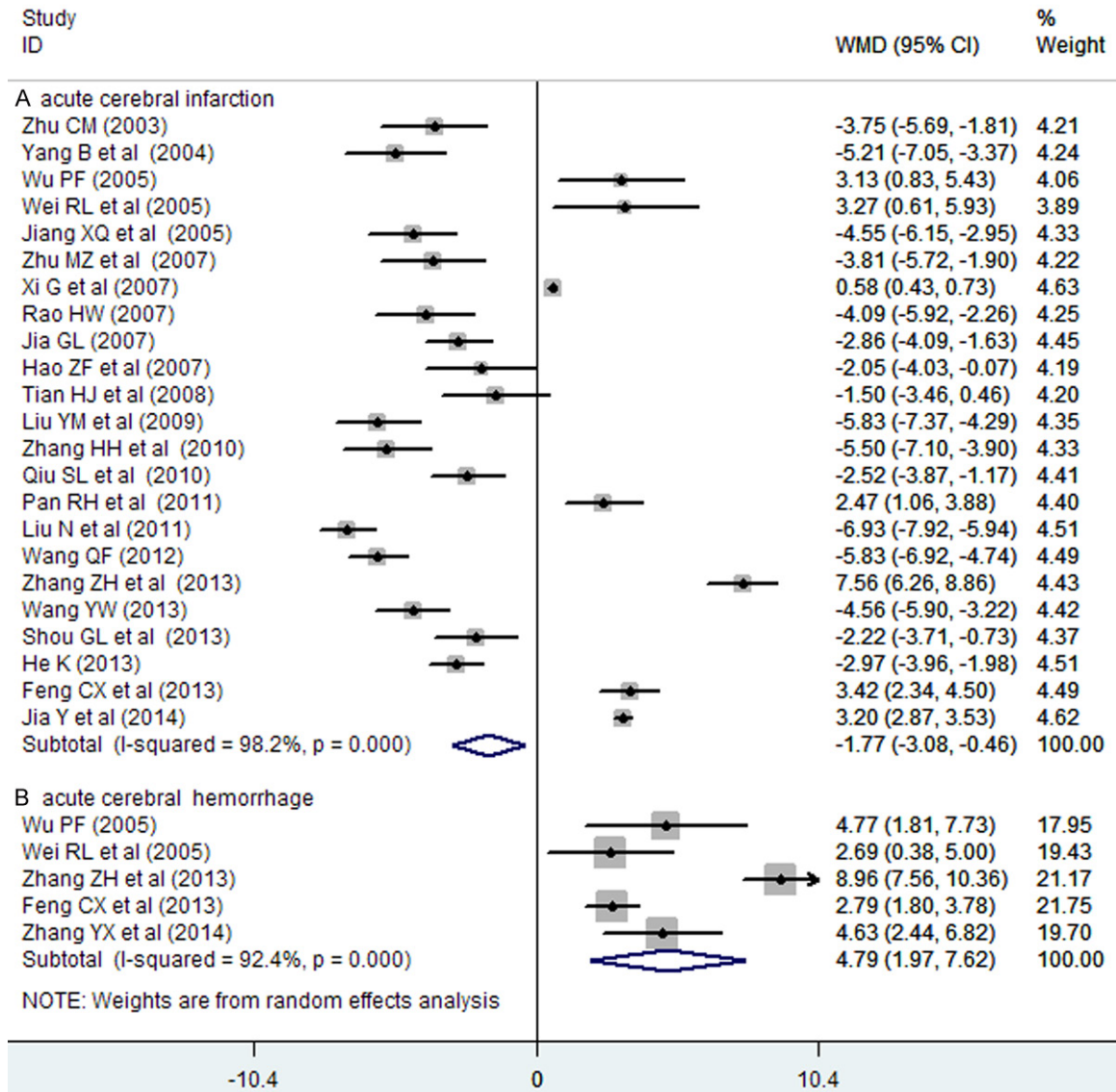
Figure 2. Forest plots showing WMD with 95% CI of difference in serum bilirubin levels between cerebral infarction or cerebral hemorrhage patients and healthy controls.

tion patients and healthy controls. As shown in **Figure 2A**, a random effect model was applied for the presence of significant heterogeneity across the included studies (I^2=98.1%, P<0.001). Serum bilirubin levels in acute cerebral infarction patients were significantly lower than those in healthy controls (WMD=-1.77 μmol/L; 95% CI=-3.08 to -0.47). Both of the Begg's rank correlation test (P=0.653) and the Egger's linear regression test (P=0.053) did not show evidences of publication bias.

Serum bilirubin levels in acute cerebral hemorrhage patients from 5 studies [22, 23, 36, 40, 41] were significantly higher compared with the

healthy controls (WMD 4.79 μmol/L; 95% CI 1.97 to 7.62; I^2=92.4%, P<0.001) in a random effect model (**Figure 2B**). Publication bias was not observe by the Begg's rank correlation test (P=0.806) and Egger's linear regression test (P=0.808).

Sensitivity analysis and subgroup analyses

Sensitivity analysis was conducted by leaving out one study in each time to test the stability of the pooling results. The results of sensitivity analyses revealed that the individual study had no significant impact on the overall pooled effect sizes (data not shown). Subgroup analy-
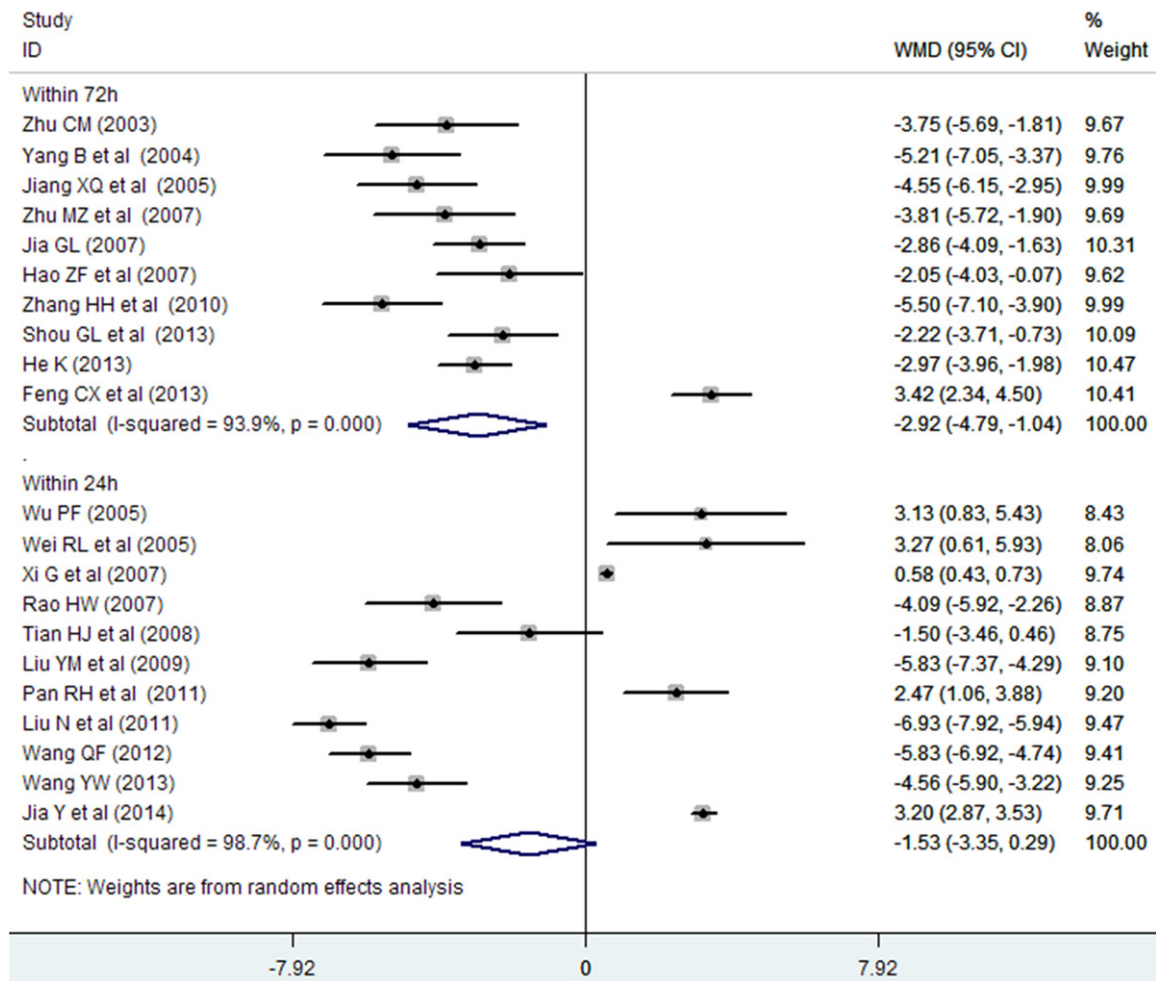
Figure 3. Subgroup analysis of difference in serum bilirubin levels within 24 hours and 72 hours between cerebral infarction patients and healthy controls.

sis showed that difference in serum bilirubin levels between cerebral infarction patients and healthy controls was not significant within 24 hours after the stroke event (**Figure 3**).

Discussion

The main finding of this meta-analysis was that serum bilirubin levels changes of acute cerebral infarction patients differed from that of acute cerebral hemorrhage. Compared with the healthy controls, serum bilirubin levels of acute cerebral infarction patients were apparently lower; while serum levels of bilirubin in acute cerebral hemorrhage patients were significantly increased. Thus, measurement of serum bilirubin levels may be identified as a potential predictor in the early phase of acute stroke event.

There are different findings on the changes of serum bilirubin during the early phase of stroke. Considering that the phase of stroke onset may affect the association of serum bilirubin levels and cerebral infarction, further subgroup analysis showed that significantly low serum bilirubin levels were observed in the first 72 hours after cerebral infarction onset but not in the first 24 hours of cerebral infarction event. This result implied that the inverse correlation between serum bilirubin and cerebral infarction was more apparent from the first 48 to 72 hours after cerebral infarction. Consistent with our results, Li et al [9] revealed that decreased serum bilirubin was associated with silent cerebral infarction. Furthermore, despite ischemic stroke patients showed a lower than normal serum bilirubin concentration, those with relatively higher bilirubin levels were correlated

with increased stroke severity [43-46]. In contrast, in acute cerebral hemorrhage, consistent evidences indicated that bilirubin levels were significantly increased than the healthy controls. Together these findings, implying that serum bilirubin levels may be a potential predictor in the early phase of stroke.

The underlying mechanisms of bilirubin production following episodes of stroke remain to be clarified. In the current study, changes of serum bilirubin levels were in the absence of liver dysfunction, suggesting this alteration mainly attributable to the local oxidative stress caused by vascular and brain damage. Bilirubin reduces oxidative stress by binding free oxygen radicals under transformation to biliverdin [47]. Low serum bilirubin levels in healthy controls tended to increase ischemic stroke risk. Kimm et al's [11] and Liang *et al*'s study [48], low serum bilirubin levels were an independent predictor of ischemic stroke. Similarly, Perlstein *et al* [49] found that each 0.1 mg/dL increase in serum bilirubin led to a 9% decreased odds of stroke. However, low levels of serum bilirubin were not an independent predictor of hemorrhagic stroke [11]. Higher levels of serum bilirubin in cerebral hemorrhage patients may reflect the intensity of oxidative stress. Bilirubin limiting brain injury after stroke has been further supported by bilirubin decreased inflammation and edema after intracerebral hemorrhage [50]. It should be pointed out that markedly elevated bilirubin levels may exert neurotoxic effects [8].

Nevertheless, several limitations in this meta-analysis should be noted. First, all the selected studies were case-control design and selection bias cannot be excluded. Second, all the participants were Chinese; this could have reduced the generalizability of the findings to other populations. Third, significant heterogeneity was observed in the overall analysis may be attributable to the differences in age or gender of patients, degree of stroke severity, and time point of bilirubin measurement. Finally, all the patients were recruited for acute ischemic stroke from a hospital setting, suggesting that our findings may not be applicable to those with silent cerebral infarction.

The current meta-analysis suggests that decreased serum bilirubin levels are correlated with acute cerebral infarction and elevated serum bilirubin levels may be correlated with acute cerebral hemorrhage. Serum levels of bilirubin may be a useful biomarker for the prediction of acute stroke. However, more well-design studies with large sample sizes are needed to confirm our findings.

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Disclosure of conflict of interest

None.

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