Asymptomatic Intracerebral Hemorrhage May Worsen Clinical Outcomes in Acute Ischemic Stroke Patients Undergoing Thrombectomy

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Background: Asymptomatic intracerebral hemorrhage (AICH) is a common phenomenon in patients with acute ischemic stroke (AIS) who were treated with endovascular thrombectomy (ET). This study aimed to evaluate the clinical effects of AICH and its risk factors in this patient population. *Methods:* This observational study was based on a prospective registry study. AIS patients with large-vessel occlusion in the anterior circulation and treated with ET were recruited. During thrombectomy procedures, intra-arterial infusion of thrombolytics or antiplatelet and permanent stenting were used as remedial therapies. The primary outcome was the overall distribution of modified Rankin scale (mRS) 90 days after ET. *Results:* This study included 102 patients (61.1 ± 12.7 years old), in whom 39 patients (38.2%) experienced AICH. At 90-day follow-up, the median mRS was 2 (interquartile range [IQR] 0-3) for patients without AICH and 4 (IQR 2-6) for those with AICH (adjusted $P = .005$). Fourteen patients with AICH and 7 patients without AICH died, which was significantly different (35.9% versus 11.1%, adjusted $P = .015$). Thirty-nine patients (61.9%) without AICH and 14 patients (35.9%) with AICH achieved functional independence at 3-month follow-up (adjusted $P = .117$). The length of intensive care unit staying was 5 days (IQR 2-10) in patients without AICH and 8 days (IQR 3-19) in those with AICH (adjusted $P = .840$). In multivariate analysis, lower Alberta Stroke Program Early CT Score (ASPECTS) (adjusted $P = .003$) and adjunctively intra-arterial thrombolysis (adjusted $P = .016$) were independently associated with AICH. *Conclusions:* In AIS patients treated with ET AICH appears to be associated with worse functional outcomes and high mortality. Lower ASPECTS and adjectively intra-arterial thrombolysis were independent risk factors of AICH.

Key Words: Acute ischemic stroke—intracerebral hemorrhage—endovascular thrombectomy—functional outcomes—quality of life

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Introduction

Several clinical trials have demonstrated the superiority of endovascular thrombectomy (ET) for acute ischemic stroke (AIS) caused by emergent large vessel occlusion in the anterior circulation.[1] However, intracerebral hemorrhage (ICH), including symptomatic or asymptomatic depending on the concomitant with neurological deterioration or not,[2,3] is not an uncommon complication in this patient population.[4,5] Symptomatic ICH (sICH) occurs in 5%-16% of patients with AIS after ET treatment, and it has been demonstrated to be associated with worse clinical outcomes.[1,6−8] Compared with sICH, asymptomatic ICH (AICH) is a more common complication in AIS patient undergoing ET, and previous studies found that approximately 30%-40% of AIS patients experienced AICH after thrombectomy.[4,6,8]

Intriguingly, AICH is also a common phenomenon in AIS patients receiving intravenous thrombolysis, and its incidence ranged 7%-40% depending on the study population; previous studies have demonstrated that AICH was associated with unfavorable outcomes.[9−11] To date, however, it is still unclear whether AICH has any influences on the clinical outcomes of AIS patients treated with ET. This study aimed to investigate the clinical effects of AICH on AIS patients treated with ET, and to evaluate the risk factors of AICH in these patients.

Methods

Study Population

This study was based on a prospective registry study in Xuanwu Hospital of Capital Medical University, which is a high-volume comprehensive stroke center. The details of the registry study (including patient's selection and treatment procedures) have been described in our previous studies.[6,12] The antiplatelet treatment protocols for patients treated with ET were based on our institution's experiences; except for Aspirin and Clopidogrel, tirofiban was used in some patients. Details of the antiplatelet treatment protocols have been described in our previous study.[6]

The present study included all AIS patients of the anterior circulation who were treated with ET by using a second-generation stent retriever device (i.e., Solitaire FR and Trevo) from January 2013 to February 2017. The eligibility criteria for the study were (1) AIS caused by the anterior circulation proximal large artery occlusion and treated with ET using a second-generation stent retriever; and (2) availability and accessibility of data for auxiliary examinations and functional outcomes. Patients with sICH were excluded. sICH was defined according to the ECASS-III definition, as any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration as defined by an increase of 4 points or more in the score on the National Institutes of Health Stroke Scale (NIHSS) score, or that led to death and that was identified as the predominant cause of the neurologic deterioration.[2]

Data Collection

We used the following variables from the database: age, sex, initial stroke severity assessed with the NIHSS score,[13] initial CT evaluated with the Alberta Stroke Program Early CT Score (ASPECTS),[14] time from onset to groin puncture and recanalization, cerebrovascular diseases risk factors,[15] etiology of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST),[16] location of occluded artery, operation details, successful recanalization defined as a Thrombolysis in Cerebral Infarction (TICI) score of 2b or 3, ICH on follow-up CT, and 3-month and long-term (if available) functional outcomes.

The study protocol was approved by the Ethic Committee of Xuanwu Hospital of Capital Medical University. All patients or their legally authorized representative provided written informed consent at admission to our hospital.

Antiplatelet Treatment

According to our local standard protocol, the antiplatelet treatment protocols include tirofiban, bridging with dual antiplatelet and dual antiplatelet directly. The use of tirofiban was at the discretion of the treating interventionists. If used, a low-dose bolus of Tirofiban Hydrochloride and Sodium Chloride Injection (Grand Pharmaceutical Co., Ltd. China; Standard: 5 mg of tirofiban diluted with 100 mL of normal saline) was administrated intra-arterially (at a standard rate of 1 mL/min; the dose ranged from .25 to .5 mg). Intravenous tirofiban was continued at a rate of 4-5 mL/h (i.e., .2 to .25 mg/h) for 12-24 hours, and bridged with dual antiplatelet therapy if the follow-up CT found no obvious ICH. Dual antiplatelet therapy and intravenous tirofiban overlapped for 4 hours, and then intravenous tirofiban was stopped.

For patients who were intubated or had difficulty eating and drinking, nasal administration was used for antiplatelet drugs. Dual antiplatelets therapy with 100 mg aspirin and 75 mg clopidogrel was used once daily. However, for patients naive to antiplatelet therapy prestroke, a loading dose of 300 mg aspirin plus 300 mg clopidogrel was used. For patients on aspirin alone prestroke, a loading dose of 300 mg clopidogrel plus 100 mg aspirin was used; and for patients used clopidogrel alone prestroke, a loading dose of 300 mg aspirin plus 75 mg clopidogrel was used.

Imaging Assessment

Dual-energy head CT was generally performed 12-24 hours post-treatment. Head CT or MRI repeated 3-7 days post-treatment, or whenever an ICH was indicated by clinical evidences. ICH and contrast agent extravasation were distinguished by using postprocedural dual-energy head CT, and the result was confirmed on CT or MRI scans at 3-7 days post-treatment by comparing with the previous CT scans. AICH was defined as any other ICH except sICH. All imaging, including angiograms, pre- and post-treatment CT, and post-treatment MRI (if available), were separately analyzed by a neurologist and a neuroradiologist. The ASPECTS was evaluated on pretreatment CT scans. ICH was evaluated on post-treatment images. Disagreement was resolved by a consensus between the neurologist and neuroradiologist, if no consensus could be reached, another reviewer made the final decision.

End points

The primary outcome was the overall distribution of modified Rankin scale (mRS) 90 days after ET. Secondary outcomes included (1) the proportion of patients who achieved functional independence (mRS ≤ 2) 90 days after ET; (2) mortality at 3-month follow-up; (3) the length of intensive care unit staying; and (4) the risk factors of AICH.

Statistical Methods

Baseline characteristics and outcomes were compared between patients with and without AICH. Multivariate logistic or linear regression analyses was performed with the 3-month outcomes as the dependent variable, and with AICH, age, NIHSS score, ASPECTS, time from onset to recanalization, and successful recanalization as the covariates, which has been reported to be the potential risk factors of functional outcomes in AIS patients treated with ET. When investigating the risk factors of AICH, multivariate logistic regression was performed with AICH as the dependent variable, and age, NIHSS score, ASPECTS, time from onset to recanalization, atrial fibrillation, stroke etiology, TICI, intra-arterial thrombolysis, and the use of Tirofiban as the covariates.

For continuous data, means ± standard deviation or medians (interquartile range, IQR) were used to summarize data, and two-sided *t* test for independent samples or the Mann-Whitney *U* tests was performed to detect differences between groups. Frequencies and percentages were used to summarize binary data, and between-group comparisons were performed using the chi-square or Fisher's exact tests when appropriate.

All data were analyzed using SPSS 23.0 (IBM Inc. 1 New Orchard Road Armonk, New York 10504-1722 United States) with a significance level of $P < .05$ (2 sides).

Results

From January 2013 to February 2017, a total of 102 AIS patients with emergent large vessel occlusion in the anterior circulation who were treated with ET were eligible for the analysis in this study.

Demographic and Clinical Characteristics

Among all 102 patients, 39 patients (38.2%) experienced AICH (AICH group) as compared with 63 patients (61.8%) did not (no AICH group). Baseline characteristics of all 102 patients were summarized in Table 1. The average age at stroke onset was 61.1 ± 12.7 years old; 70 patients (68.6%) were male; and 31 patients (30.4%) were treated with intravenous alteplase prior to ET procedures. The median baseline NIHSS score was 16 (IQR 12-21) points and median ASPECTS was 9 (IQR 8-10) points. The median time from onset to groin puncture was 288 (IQR 223-347) minutes, and median time from onset to recanalization was 379 (IQR 314-434) minutes. During the ET procedure, permanent stenting was performed in 27 patients (26.5%), 10 patients (9.8%) were treated with additional intra-arterial thrombolysis, and 52 patients (51.0%) were treated with adjunct tirofiban. Seventy-five patients (73.5%) achieved good reperfusion (TICI = 2b/3) after ET procedures. The cardiovascular disease risk factors, stroke etiology, and other operation details were also listed in Table 1.

Comparisons of the demographic and clinical characteristics of patients with and without AICH were also summarized in Table 1. The age, gender, stroke characteristics, cerebrovascular diseases risk factors, and treatment details showed no statistical difference between groups ($P > .05$ each), but there was numerically more patient with AICH received intra-arterial thrombolysis (17.9% versus 4.8%, $P = .067$).

Clinical Outcomes

The overall distribution of mRS score was shown in Figure 1. Ninety days after ET, the median mRS was 2 (IQR 0-3) for patients without AICH and 4 (IQR 2-6) for those with AICH, which was significantly different between groups (Table 2, $P < .001$). After adjusting other influential factors, the difference was still significant (adjusted $P = .005$). Compared with 39 of 63 patients (61.9%) without AICH achieved functional independence 3 months post-ET, 14 of 39 patients (35.9%) with AICH achieved functional independence which was significantly lower ($P = .011$). However, after adjusting other risk factors, the difference was not significant (odd ratio [OR], 2.48, 95% confidence interval [CI] .80-7.71 adjusted $P = .117$). Fourteen patients (35.9%) in the AICH group died (mRS scored 6) at 3 months after the index stroke, while only 7 patients (11.1%) died in those without AICH which was significantly different ($P = .003$). After adjusting for other potential risk factors of clinical outcomes, AICH was independently associated with the 3-month mortality (OR, 7.08; 95% CI, 1.47-34.1, adjusted $P = .015$). The length of intensive care unit staying was 5 days (IQR 2-10) for patients without AICH and 8 days (IQR 3-19) for those with AICH, but the difference was not statistically significant ($P = .058$).

Risk Factors of AICH

In order to evaluate the risk factors of AICH, potential factors were analyzed in the multivariate logistic regression analysis, and only ASPECTS (OR, .53; 95% CI, .35−.80; adjusted $P = .003$) and adjunctively intra-arterial thrombolysis (OR, 30.2; 95% CI, 1.90 to 47.9, $P = .016$) were independently associated with AICH on post-treatment CT (Table 3).

Table 1. *Characteristics of patients with and without asymptomatic intracerebral hemorrhage*

Characteristics	All	Without AICH	With AICH	*P* value
	N = 102	N = 63	N = 39	
Age, mean (SD), y	61.1 (12.7)	60.6 (12.4)	61.7 (13.3)	.665
Male, n (%)	70 (68.6)	45 (71.4)	25 (64.1)	.438
NIHSS score, median (IQR)	16 (12-21)	15 (12-21)	16 (13-20)	.678
ASPECTS, median (IQR)	9 (8-10)	9 (8-10)	9 (7.75-9.25)	.061
Intravenous thrombolysis, n (%)	31 (30.4)	21 (33.3)	10 (25.6)	.412
OTP, median (IQR), min	288 (223-347)	268 (223-330)	315 (216-364)	.228
OTR, median (IQR), min	379 (314-434)	372 (312-433)	398 (323-439)	.378
Hypertension, n (%)	57 (55.9)	35 (55.6)	22 (56.4)	.933
Diabetic mellitus, n (%)	20 (19.6)	12 (19.0)	8 (20.5)	.856
Atrial fibrillation, n (%)	35 (34.3)	19 (30.2)	16 (41.0)	.261
Preantiplatelet, n (%)	31 (30.4)	22 (34.9)	9 (23.1)	.206
Smoking, n (%)	37 (36.3)	26 (41.3)	11 (28.2)	.182
Stroke etiology, n (%)				
Large-artery atherosclerosis	62 (60.8)	43 (68.3)	19 (48.7)	.050
Cardioembolic	30 (29.4)	16 (25.4)	14 (35.9)	.258
Others	10 (9.8)	4 (6.3)	6 (15.4)	.251
Occlusion site, n (%)				
ICA	50 (49.0)	33 (52.4)	17 (43.6)	.388
MCA	52 (51.0)	30 (47.6)	22 (56.4)	.388
Operation details				
Permanent stenting, n (%)	27 (26.5)	16 (25.4)	11 (28.2)	.755
Adjunctively intra-arterial thrombolysis, n (%)	10 (9.8)	3 (4.8)	7 (17.9)	.067
Adjunctive tirofiban, n (%)	52 (51.0)	30 (47.6)	22 (56.4)	.388
TICI, 2b or 3, n (%)	75 (73.5)	48 (76.2)	27 (69.2)	.439

Abbreviations: AICH, asymptomatic intracerebral hemorrhage; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, intracranial carotid artery; IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; OTR, onset to recanalization time; OTP, onset to groin puncture time; SD, standard deviation; TICI, modified Thrombolysis in Cerebral Infarction.

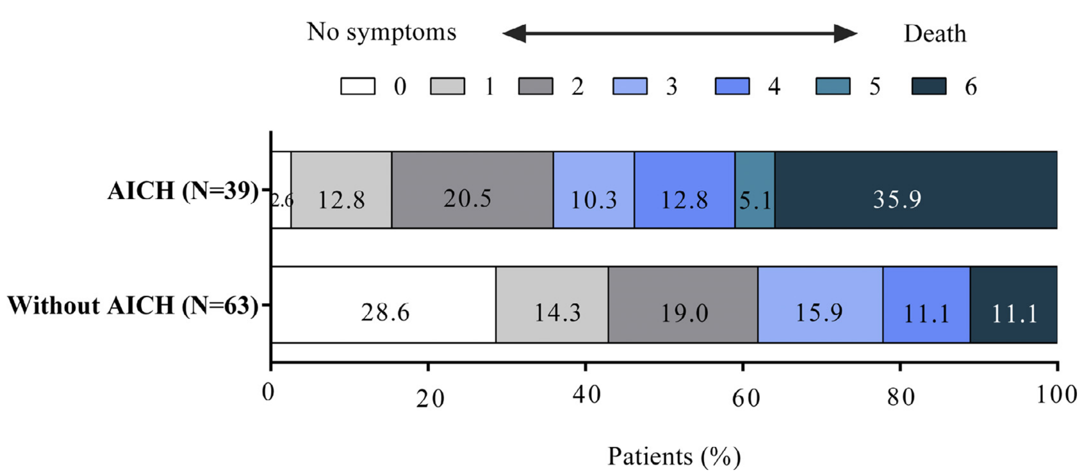

Figure 1. *Score on the modified Rankin Scale (mRS) at 3 months. AICH, asymptomatic intracerebral hemorrhage. Numbers in the figure are percentage of patients.*

Discussion

In this study, we found that AICH on post-treatment CT was associated with poor clinical outcomes and higher mortality in AIS patients with large artery occlusion in the anterior circulation who were treated with ET, and the length of intensive care unit staying was much longer in patients with AICH. In addition, lower ASPECTS and the use of intra-arterial thrombolysis were the independently risk factors of AICH.

Consistent with previous studies,[6,8] we found approximately 40% of patients experienced AICH after ET in this

Table 2. *Clinical outcomes at 3-month follow-up*

	Without AICH	With AICH	*P* value	β/adjusted OR (95CI)*	*P* value*
	N = 63	N = 39			
mRS, median (IQR)	2 (0-3)	4 (2-6)	<.001	1.34 (.42-2.26)	.005
mRS ≤ 2, n (%)	39 (61.9)	14 (35.9)	.011	2.48 (.80-7.71)	.117
mRS, 6, n (%)	7 (11.1)	14 (35.9)	.003	7.08 (1.47-34.1)	.015
ICU days, median (IQR), d	5 (2-10)	8 (3-19)	.058	.42 (-3.73-4.57)	.840

Abbreviations: AICH, asymptomatic intracerebral hemorrhage; ICU, intensive care units; IQR, interquartile range; mRS, modified Rankin Scale.

*AICH was adjusted by variables including age, National Institute of Health Stroke Scale score, Alberta Stroke Program Early CT Score, onset to recanalization time and successful recanalization (Thrombolysis in Cerebral Infarction score of 2b or 3).

Table 3. *Risk factors of asymptomatic intracerebral hemorrhage*

	Adjusted*		*P* value
	OR	95% CI	
Age	.98	.93-1.04	.565
NIHSS score	1.07	.95-1.20	.266
ASPECTS	.53	.35-.80	.003
OTR	1.00	.99-1.01	.402
AF	2.15	.36-12.8	.400
TOAST	1.69	.95-3.01	.074
TICI,2b/3	.76	.18-3.27	.717
Adjunctively intra-arterial thrombolysis	30.2	1.90-47.9	.016
Tirofiban	4.73	.95-23.5	.057

Abbreviations: AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NIHSS, National Institute of Health Stroke Scale; OTR, onset to recanalization time; TOAST, classification according to the Trial of Org 10172 in Acute Stroke Treatment; TICI, Thrombolysis in Cerebral Infarction.

*Age, National Institute of Health Stroke Scale score, Alberta Stroke Program Early Computed Tomography Score, time from onset to recanalization, atrial fibrillation, stroke etiology, Thrombolysis in Cerebral Infarction, intra-arterial thrombolysis, and the use of Tirofiban were used as covariates in multivariate logistic regression.

study. In previous studies recruiting AIS patients treated with intravenous thrombolysis, AICH has been demonstrated to be associated with worse clinical outcomes.[9,17] Intriguingly, in this study, we found that AICH was also associated with poor functional outcomes and high mortality in AIS patients treated with ET. Therefore, the “asymptomatic” hemorrhage may not always be asymptomatic and benign in AIS patients treated with reperfusion therapy. Heidelberg Bleeding Classification,[3] another classification of bleeding events after reperfusion therapy, includes ICH and intracranial-extracerebral hemorrhage especially subarachnoid hemorrhage (SAH). In the database, no patients experienced subdural or intraventricular hemorrhage. Two patients who experienced SAH were excluded because one concomitant with SICH and the other was posterior circulation stroke. The occurrence of SAH was lower than reported study in about 5% of the cases.[18] This discrepancy may be attributed to the following reasons. First and foremost, in Yilmaz's study, conventional CT scan immediately after the procedure was used to detect intracranial hemorrhage. Contrary to Yilmaz's study, in our study, dual-energy CT was conducted 12-24 hours. Previous study has determined that dual-energy CT could reliably differentiate high density areas related to iodine contrast extravasation or hemorrhage.[19] In addition, in our study, second-generation stent retriever device was used, and the previous study had found that second-generation stent retrievers had fewer complications than first-generation device.[20]

The underlying mechanisms of AICH results in poor clinical outcomes are still unclear, the early disruption of the blood-brain barrier may be attributable to this phenomenon.[21] In AIS patients treated with ET, in addition to brain tissue infarction, procedure-related vessel damage and the toxicity of intra-arterial contrast material also cause disruption of the blood-brain barrier,[22] and the injured blood-brain barrier may result in the leakage of blood and contrast agent into cerebral parenchyma. The elimination of contrast staining and ICH may cause injuries to the brain tissue, which may lead to worse clinical outcome in AIS patients.[23,24] In addition, the AICH may indicate more severe of stroke, which may not be detected by the neurological assessment scales (e.g., NIHSS score, ASPECTS, or other scales).

Consistent with previous studies,[8,25] we found that both lower ASPECTS and intra-arterial thrombolysis were independently associated with AICH in this study. This may be explained by the lower ASPECTS on pretreatment CT scans are associated with large infarct volume and severe disruption of the blood-brain barrier,[26] and the thrombolysis agent itself may increase the risk of ICH in AIS patients.[27] However, different with previous studies, cardioembolic stroke (indicated by atrial fibrillation) and delayed recanalization were not found to be the risk factors of ICH in our study, this discrepancy may be attributable to the relatively small sample size and the exclusion of sICH in our study.

In the present study, the stroke etiology of most patients was large artery atherosclerosis, a large percentage of AIS patients were treated with tirofiban, which was a glycoprotein IIb/IIIa antagonist with a short half-life and could be used to prevent local platelet aggression. Although, the study found high dose of tirofiban was associated with risk of fatal ICH in AIS patients treated with ET,[28] low dose of tirofiban was used in this study, and our previous report has demonstrated that this treatment protocol did not increase the incidence of ICH and sICH.[6] In this study, multivariate regression analysis was performed and its results further confirmed that tirofiban was not associated with AICH.

There are several limitations in this study. First, this was a single-center study and only a relatively small number of patients were recruited, which might lead to false-positive results. Therefore, the findings of this study should be interpreted cautiously. Second, CT was used to assess radiologic characteristics and may not be as sensitive as gradient echo T2*-weighted MRI.[29] Accordingly, some patients with microbleeding may have been classified into the no-AICH group. In addition, this was an observational study, and potential confounders (including both known and unknown factors) could have influenced the study results.

Conclusions

AICH appears to result in lower odds of functional independence and higher odds of deaths in AIS patients treated with ET, and lower ASPECTS and intra-arterial thrombolysis were independent risk factors of AICH. Much larger studies are needed to confirm these results and investigate the underlying mechanisms.

Author Contributions Statement

F.J. W.Z. and X.J. were involved in the conception and design of the study. F.J. contributed to analysis and interpretation of the data, and drafting the manuscript. W.Z. contributed to acquisition of data and critical revision. Z.Z. and W. H. contributed to critical revision. C.W., C.L., R.C., J.C., H.S., and J.D. contributed to acquisition of data. X.J. approved the final version to be published.

Conflicts of Interest

The authors declare no financial or other conflicts of interest.

Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2019.02.006.

References

1. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-1731.
2. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.
3. von Kummer R, Broderick JP, Campbell BC, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. Stroke 2015;46:2981-2986.
4. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (thrace): a randomized controlled trial. Lancet Neurol 2016;15:1138-1147.
5. Yaghi S, Eisenberger A, Willey JZ. Symptomatic intracerebral hemorrhage in acute ischemic stroke after thrombolysis with intravenous recombinant tissue plasminogen activator: a review of natural history and treatment. JAMA Neurol 2014;71:1181-1185.
6. Zhao W, Che R, Shang S, et al. Low-dose tirofiban improves functional outcome in acute ischemic stroke patients treated with endovascular thrombectomy. Stroke 2017;48:3289-3294.
7. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke 2018;49:e46-e110.
8. Hao Y, Yang D, Wang H, et al. Predictors for symptomatic intracranial hemorrhage after endovascular treatment of acute ischemic stroke. Stroke 2017;48:1203-1209.
9. Park JH, Ko Y, Kim WJ, et al. Is asymptomatic hemorrhagic transformation really innocuous. Neurology 2012; 78:421-426.
10. Lei C, Wu B, Liu M, et al. Asymptomatic hemorrhagic transformation after acute ischemic stroke: is it clinically innocuous? J Stroke Cerebrovasc Dis 2014;23:2767-2772.
11. Kimura K, Iguchi Y, Shibazaki K, et al. Hemorrhagic transformation of ischemic brain tissue after t-pa thrombolysis as detected by MRI may be asymptomatic, but impair neurological recovery. J Neurol Sci 2008;272:136-142.
12. Zhao W, Shang S, Li C, et al. Long-term outcomes of acute ischemic stroke patients treated with endovascular thrombectomy: a real-world experience. J Neurol Sci 2018;390:77-83.
13. Mikulik R, Ribo M, Hill MD, et al. Accuracy of serial national institutes of health stroke scale scores to identify artery status in acute ischemic stroke. Circulation 2007; 115:2660-2665.
14. Barber PA, Demchuk AM, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Aspects study group. Alberta stroke programme early CT score. Lancet 2000;355:1670-1674.

15. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurol Clin 2008;26:871-895. vii.
16. Adams Jr. HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. Stroke 1993;24:35-41.
17. Dzialowski I, Pexman JH, Barber PA, et al. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke effectiveness study registry. Stroke 2007;38:75-79.
18. Yilmaz U, Walter S, Korner H, et al. Peri-interventional subarachnoid hemorrhage during mechanical thrombectomy with stent retrievers in acute stroke: a retrospective case-control study. Clin Neuroradiol 2015;25:173-176.
19. Hong An W.Z., Jianguo Wang, Joshua C. Wright, et al. Contrast staining may be associated with intracerebral hemorrhage but not functional outcome in acute ischemic stroke patients treated with endovascular thrombectomy. *Aging Dis*. [ahead of print].
20. Akins PT, Amar AP, Pakbaz RS, et al. Complications of endovascular treatment for acute stroke in the swift trial with solitaire and merci devices. AJNR 2014;35:524-528.
21. Jang JW, Lee JK, Hur H, et al. Rutin improves functional outcome via reducing the elevated matrix metalloproteinase-9 level in a photothrombotic focal ischemic model of rats. J Neurol Sci 2014;339:75-80.
22. Mokin M, Kan P, Kass-Hout T, et al. Intracerebral hemorrhage secondary to intravenous and endovascular intra-arterial revascularization therapies in acute ischemic stroke: an update on risk factors, predictors, and management. Neurosurg Focus 2012;32:E2.
23. Renu A, Amaro S, Laredo C, et al. Relevance of blood-brain barrier disruption after endovascular treatment of ischemic stroke: dual-energy computed tomographic study. Stroke 2015;46:673-679.
24. Wang X, Lo EH. Triggers and mediators of hemorrhagic transformation in cerebral ischemia. Mol Neurobiol 2003;28:229-244.
25. Kaesmacher J, Kaesmacher M, Maegerlein C, et al. Hemorrhagic transformations after thrombectomy: risk factors and clinical relevance. Cerebrovasc Dis 2017;43:294-304.
26. Haussen DC, Dehkharghani S, Rangaraju S, et al. Automated ct perfusion ischemic core volume and noncontrast ct aspects (alberta stroke program early ct score): correlation and clinical outcome prediction in large vessel stroke. Stroke 2016;47:2318-2322.
27. Rahme R, Yeatts SD, Abruzzo TA, et al. Early reperfusion and clinical outcomes in patients with m2 occlusion: pooled analysis of the proact ii, ims, and ims ii studies. J Neurosurg 2014;121:1354-1358.
28. Kellert L, Hametner C, Rohde S, et al. Endovascular stroke therapy: tirofiban is associated with risk of fatal intracerebral hemorrhage and poor outcome. Stroke 2013; 44:1453-1455.
29. Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA 2004;292:1823-1830.