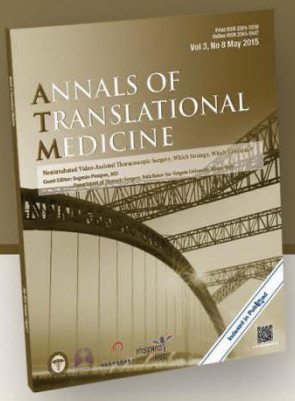
ANNALS OF TRANSLATIONAL MEDICINE



Peer Review File

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Reviewer A:

1. In the selection of patients, those that could not tolerate follow up CT were excluded. This is probably a selection bias for more severe strokes? What percentage of patients screened had not have follow up CT?

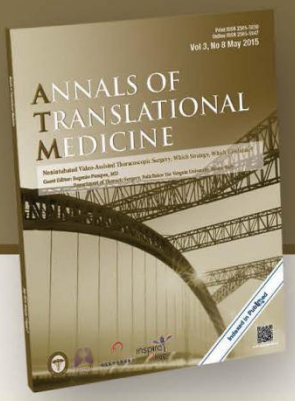
Reply: Thanks for your question. We agree that excluding patients who could not tolerate 24-48 hours CT probably caused a selection bias for more severe stroke. In this study, we had 4 patients excluded due to no follow-up CT scan. One patient had sustained severe MCA stenosis which failed to be recanalized through thrombectomy. His relatives gave up further treatment after the operation. Therefore, this patient had no follow-up CT images. The other 3 patients failed to accept CT scans at 24-48 hours as they stayed in ICU for severe pneumonia after stroke, although they achieved successful recanalization through thrombectomy.

In order to state the screening process clearly, we've modified the description of patient selection, and have added a study flowchart to perform the whole screening process.

Changes in the text:

Study subjects

We reviewed our consecutively collected acute LAO patients who received computed tomography perfusion (CTP) scan at admission and thrombectomy within 6 hours after stroke onset from May 2018 to May 2019. Patients were included if they had (1) middle cerebral artery M1 segment and/or intracranial internal carotid artery (ICA) occlusion on pretreatment 4D-CTA reconstructed from CTP; (2) pre-stroke modified Rankin Scale score (mRS) ≤ 2; (3) complete imaging and clinical data during hospitalization. Patients were excluded if they had (1) bilateral acute ischemic lesions; (2) poor image quality due to motion artifact (see Figure 1).



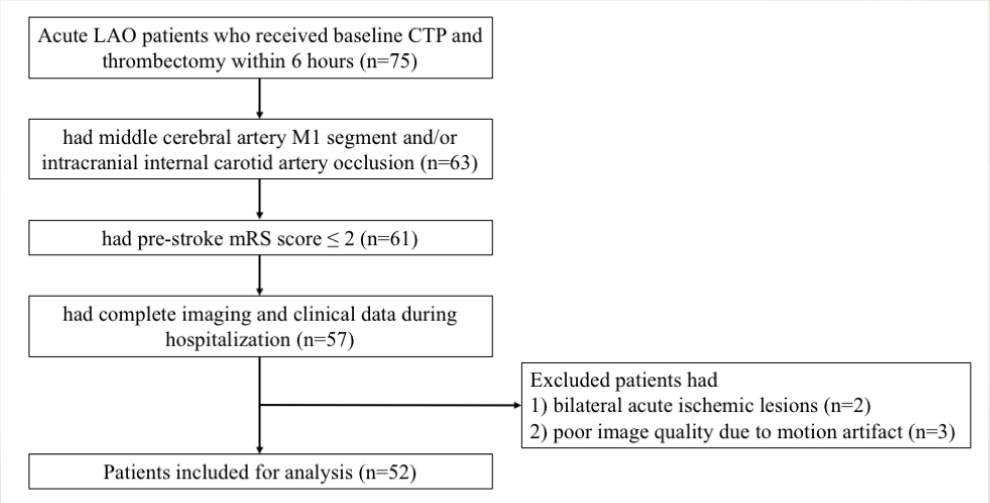


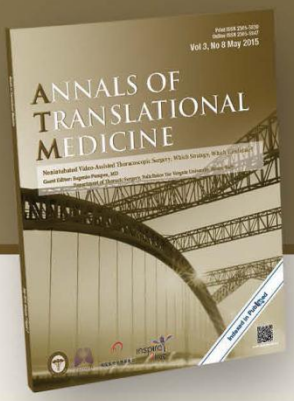
Figure 1. Study flowchart. LAO, large artery occlusion; CTP, computed tomography perfusion; mRS, modified Rankin Scale.

2. What criteria were used to select patients for MT? ASPECTS, CTA collaterals, CT perfusion?
Reply: Thanks for your question. We have corrected our patients' selection criteria for mechanical thrombectomy. In our study, we only enrolled acute LAO patients who admitted within 6 hours after stroke onset based on 2018 AHA/ASA guideline[1]. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (i) prestrike mRS score of 0-1; (ii) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (iii) age ≥18 years; (iv) NIHSS score of ≥6; (v) ASPECTS of ≥6; and (vi) treatment can be initiated (groin puncture) within 6 hours of symptom onset.

Reference

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, 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

We have modified our text into "Patients exhibiting no clinical improvement after thrombolysis and patients who arrived at 4.5-6 hours after stroke onset were thrombectomy candidates. According to 2018 AHA/ASA guideline, these candidates were selected for thrombectomy if they



meet all the following criteria: (1) prestrike mRS score of 0-1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset. Patients with any contraindication for thrombolysis who were eligible for thrombectomy also received thrombectomy directly." (see page 7, line 111-116)

3. Some patients received (off-label) tirofiban, further compromising study group homogeneity

Reply: Thanks for your question. We agree that the use of tirofiban might cause heterogeneity, Therefore, we added the following sentence in the limitation (see page 17, line 327-328). Additionally, although tirofiban use for thrombectomy patients is still in debate, in the latest Chinese expert consensus, tirofiban use is IIa class of recommendation, B level of evidence, supporting its auxiliary value of thrombectomy in clinical practice. Please see the screenshots below.

Changes in the text: the use of tirofiban would compromise study group homogeneity.

推荐意见：

·对于接受血管内治疗的急性缺血性卒中患者，预防性使用替罗非班目前仍存争议，可考虑术中动脉内使用小剂量替罗非班0.25～0.5 mg，以1 mL/min速度输注，随后静脉滴注0.2～0.25 mg/h维持12～24 h，并严格监测出血（Ⅱb级推荐，B级证据）。

·对于急性缺血性卒中血管成形或取栓后内皮损伤反复闭塞的患者，可以考虑使用替罗非班作为血管内治疗的辅助治疗。目前推荐的剂量方案为联合导管内动脉给药给予负荷剂量0.4 μg/（kg·min）持续30 min（总剂量不超过1 mg），随后静脉泵入0.1 μg/（kg·min）维持24～48 h，并结合CT复查结果调整用药（Ⅱa级推荐，B级证据）。

·替罗非班用药后桥接口服抗血小板治疗时，建议复查影像学检查排除出血，可以考虑重叠4～6 h（Ⅱb级推荐，B级证据）。

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·指南与共识·

替罗非班在动脉粥样硬化性脑血管疾病中的临床应用专家共识

■ 中国卒中学会，中国卒中学会神经介入分会，中华预防医学会卒中预防与控制专业委员会介入学组

(Chin J Stroke, Oct 2019, Vol 14, No.10)

4. The authors report SMCV status only ipsilateral to the occlusion. In Ref 4 it has been shown that In the PRECISE score and not the composite score on the affected hemisphere was an independent predictor of outcome on regression analysis and the likely reason for this is the variability in the venous structures. This variability necessitates bilateral assessment of SMCV status.

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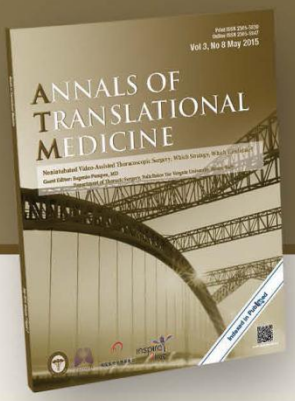


Reply: Thanks for your suggestions. Firstly, in our previous study[1], we have found that absent filling of SMCV in contralateral side only appeared in 3.9% of our patients, which was similar to the rate of absent SMCV presented in non-stroke subjects. In contrast, ipsilateral SMCV- was found as a stroke-related and prognostic imaging marker. Therefore, we in this study did not focus on the contralateral contrast filling of SMCV-.

According to your suggestion, we reviewed our data and found that, only 3 patients had no SMCV opacification in contralateral hemisphere (contralateral SMCV-), and none of them suffered PH after thrombectomy. As the sample size is too small (3/52, 5.8%), we did not continue to study on the impact of contralateral SMCV- on stroke outcome.

Reference

1. Zhang S, Lai Y, Ding X, Parsons M, Zhang JH, Lou M. Absent filling of ipsilateral superficial middle cerebral vein is associated with poor outcome after reperfusion therapy. Stroke. 2017;48:907-914

5. The authors do not prove that SMCV- is more predictive for the worse outcome than poor arterial collaterals. In ref 4 The PRECISE score significantly correlated with arterial collateral status and follow-up infarct volumes, and the anastomotic veins score difference with perfusion mismatch. Was there a correlation of arterial collaterals with SMVC?

Reply: Thanks for your question. Indeed, there was a correlation between SMCV- and collateral status (ϱ=0.555, P<0.001). Nevertheless, the interaction between SMCV- and poor collaterals was not an independent predictor for the occurrence of PH, and it did not interfere the impact of other factors on the occurrence of PH (please see the table below). Therefore, we don't consider it essential for our analysis. Additionally, the aim of our study was not to select which factor was more predictive for the worse outcome, but to explicit if the presence of ipsilateral SMCV- correlates with PH occurrence or reperfusion after thrombectomy. Therefore, we propose to not discuss the relationship between SMCV- and collateral status in this study.

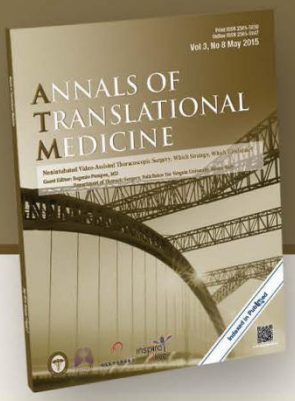


Table. Multivariate analysis for factors associating with PH after thrombectomy

	OR	95%CI	*P value*
SMCV-	2.159	0.284-16.379	0.457
Poor collaterals	9.263	0.750-114.471	0.083
SMCV- × poor collaterals	0.301	0.012-7.470	0.464
Intravenous thrombolysis	0.164	0.028-0.971	0.046

PH, parenchymal hematoma; SMCV, superficial middle cerebral vein.

6. Lower rate of IV tPA in the PH group probably means treatment in later time windows

Reply: Thanks for your question. We've added onset to puncture time (OPT) to test this relation, and found that there was no difference in OPT between PH and non-PH group (242.5±78.6min vs 222.5±87.2min,t=-0.767, *P*=0.447).

We also added OPT into multivariate analysis. It showed that OPT was not a factor influencing the the occurrence of PH, and intravenous thrombolysis was still the only independent factor associating with PH (see the following table). Therefore, lower rate of intravenous thrombolysis in the PH group could not indicate that PH patients were treated in late time windows.

Table. Multivariate analysis for factors associating with PH after thrombectomy

	OR	95%CI	*P value*
SMCV-	1.212	0.243-6.048	0.815
Poor collaterals	4.369	0.850-22.466	0.078
Intravenous thrombolysis	0.169	0.029-0.975	0.047
OPT	0.870	0.992-1.010	0.870

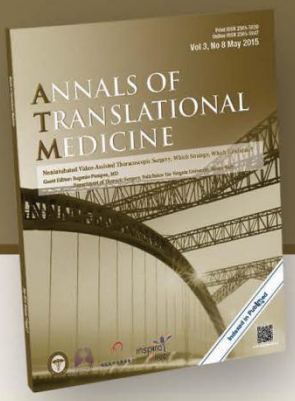
PH, parenchymal hematoma; SMCV, superficial middle cerebral vein; OPT, onset to puncture time.

Reviewer B:

The authors present data on SMCV in 52 patients undergoing thrombectomy.

I have several issues with the manuscript at this time.

Major:



1) There is an excessive rate of PH in this cohort, which is most probably due to the severe affection of the cohort (median NIHSS of 19). This renders the question of transferability quite important, yet this limitation is not discussed.

Reply: Thanks for your suggestion. We've added this into our limitation (see page 17, line 323-325).

Changes in the text: Additionally, our subjects might be more severe than other centers in neurological deficit (median NIHSS of 19), therefore, the results based on our data should be interpreted with caution.

Reference

1. Kimberly WT, Dutra BG, Boers AMM, Alves H, Berkhemer OA, van den Berg L, et al. Association of Reperfusion with Brain Edema in Patients with Acute Ischemic Stroke: A Secondary Analysis of the MR CLEAN Trial. JAMA Neurol. 2018;75(4):453-61.

2) The overall number of subjects is low, but in the field of what is usual in thrombectomy studies. Nevertheless, the sample size limitation should not only be discussed for the n=8 subgroup, but for all analyses (and especially the multivariate calculations).

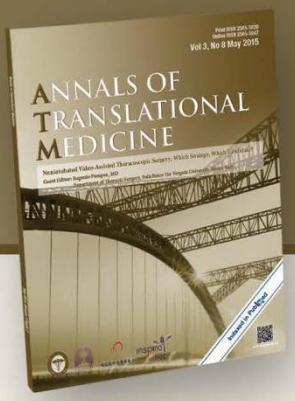
Reply: Thanks for your suggestions. We have modified our description for small sample size in limitation part as advised (see page 17, line 322-323)

Changes in the text: This study had several limitations. First, it was a small-sample and retrospective study, which created a potential risk of selection bias.

3) which Kappa statistic was used for variability-testing?

Reply: Thanks for your question. Cohen's kappa coefficient was used for variability-testing. We have modified our text as advised (see page 17, line 192).

Changes in the text: **Cohen's kappa coefficient** was used to assess the level of inter- and intra-observer agreement for detecting the presence of SMCV-, poor collaterals, midline shift, and PH. Excellent inter- and intra-observer agreement was seen in distinguishing the SMCV- (κ=0.918 and 0.879), poor collaterals (κ=0.912 and 0.824), midline shift (κ=0.906 and 0.803) and PH (κ=0.924 and 0.954).



4) I would recommend omitting the testing for PH in the reperfusion subgroups. The numbers are too small to draw meaningful conclusions. This would strongly streamline the article and make it much easier to follow.

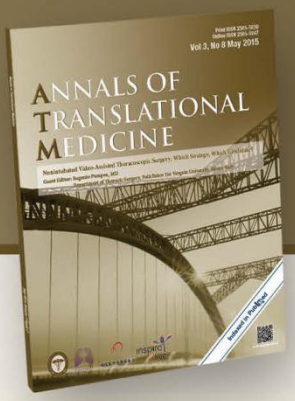
Reply: Thanks for your suggestion. We've deleted the testing for PH in the reperfusion subgroups as you advised.

5）Essentially, one would then be interested in 3 tables: table 1 from the current manuscript and the same table split not by PH but by repercussion and by SMCV positivity. This could even be packed into one large table.

Reply: Thanks for your suggestions. We've added the other two tables as supplementary.

Supplementary table I. Baseline and post-thrombectomy clinical and imaging characteristics that stratified by SMCV+ vs SMCV-.

Characteristics	SMCV+ n=31	SMCV- n=21	Test value	*P* value
Female, n (%)	9 (29.0)	6 (28.6)	□²=0.001	0.971
Age (year), median (IQR)	69 (61-81)	73 (59.5-79)	Z=-0.131	0.896
Transferred from local hospitals, n (%)	16 (51.6)	12 (57.1)	□²=0.154	0.695
OIT (min), mean±SD	200.9±107.4	212.5±91.2	t=-0.401	0.69
OPT (min), mean±SD	228.5±101.7	238.0±84.4	t=-0.353	0.725
Baseline NIHSS score, median (IQR)	17 (13-22)	21 (18-23.5)	Z=-1.982	0.047
Hypertension, n (%)	21 (67.7)	13 (61.9)	□²=0.188	0.664
Diabetes mellitus, n (%)	4 (12.9)	4 (19.0)	□²=0.363	0.547
Atrial fibrillation, n (%)	11 (35.5)	7 (33.3)	□²=0.026	0.873
Previous stroke, n (%)	4 (12.9)	7 (33.3)	□²=3.133	0.095
Coronary artery disease, n (%)	4 (12.9)	6 (28.6)	□²=1.979	0.16
Temperature (°C), mean±SD	36.8±0.4	36.7±0.5	t=0.776	0.441
Baseline systolic blood pressure (mmHg), mean±SD	149.4±25.0	154.4±28.0	t=-0.684	0.497

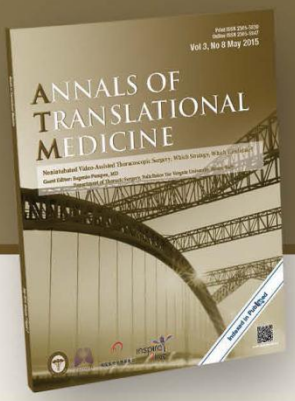


Baseline diastolic blood pressure (mmHg), mean±SD	81.1±13.1	82.6±13.0	t=-0.413	0.682
Baseline serum glucose (mmol/L) , mean±SD	8.0±3.0	8.1±3.1	t=-0.067	0.947
Baseline ASPECT score, median (IQR)	8 (7-9)	7 (6-8.8)	Z=-1.311	0.19
Cardiogenic stroke, n (%)	15 (48.4)	12 (57.1)	□²=0.384	0.535
Poor collaterals, n (%)	4 (12.9)	14 (66.7)	□²=15.988	<0.001
Intravenous thrombolysis, n (%)	12 (38.7)	6 (28.6)	□²=0.569	0.451
Times of thrombectomy passes	2 (2-4)	2 (2-3)	□=-0.148	0.882
Tirofiban, n (%)	4 (12.9)	0 (0)	□²=2.935	0.138
Recanalization, n (%)	28 (90.3)	17 (81.0)	□□□□□□□□	0.331
Reperfusion, n (%)	29 (93.5)	15 (71.4)	□²=4.705	0.039
24-72h NIHSS, median (IQR)	14 (7-21)	21 (18-23.5)	□□□□□□□□	<0.001
Decompressive craniectomy, n (%)	1 (3.2)	9 (42.9)	□²=12.659	<0.001
Midline shift, n (%)	1 (3.2)	13 (61.9)	□²=21.910	<0.001
Poor outcome, n (%)	10 (32.3)	17 (81.0)	□²=11.892	<0.001

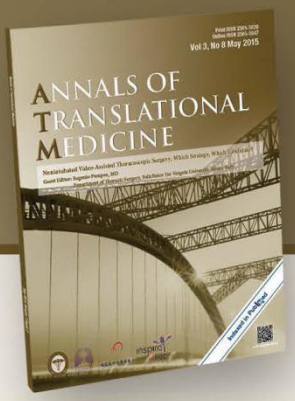
PH, parenchymal hematoma; SD, standard deviation; IQR, interquartile range; OIT: onset to imaging time; NIHSS, national institute of health stroke scale; SMCV-, absent filling of ipsilateral superficial middle cerebral vein.

Supplementary Table III. Baseline and post-thrombectomy clinical and imaging characteristics that stratified by no reperfusion vs reperfusion.

Characteristics	No reperfusion n=8	reperfusion n=44	Test value	*P* value
Female, n (%)	2 (25.0)	13 (29.5)	□²=0.068	0.794
Age (year), median (IQR)	73 (67.8-81.8)	71 (57.3-79)	Z=0.329	0.335



Transferred from local hospitals, n (%)	6 (75.0)	22 (50.0)	□²=1.702	0.192
OIT (min), mean±SD	234.9±105.2	195.5±86.7	t=1.138	0.261
OPT (min), mean±SD	254.4±94.0	223.5±82.8	t=0.946	0.349
Baseline NIHSS score, median (IQR)	20.5 (18.5-21.8)	19.5 (14.5-23)	Z=0.629	0.645
Hypertension, n (%)	6 (75.0)	28 (63.6)	□²=0.386	0.534
Diabetes mellitus, n (%)	2 (25.0)	6 (13.6)	□²=0.671	0.413
Atrial fibrillation, n (%)	2 (25.0)	16 (36.4)	□²=0.386	0.534
Previous stroke, n (%)	3 (37.5)	8 (18.2)	□²=1.515	0.218
Coronary artery disease, n (%)	1 (12.5)	9 (20.5)	□²=0.276	0.599
Temperature (°C), mean±SD	36.8±0.5	36.8±0.5	t=0.058	0.954
Baseline systolic blood pressure (mmHg), mean±SD	160.8±27.9	149.7±25.7	t=1.103	0.275
Baseline diastolic blood pressure (mmHg), mean±SD	86.5±12.6	80.8±13.0	t=1.141	0.259
Baseline serum glucose (mmol/L) , mean±SD	8.9±4.0	7.9±2.9	t=0.879	0.383
Baseline ASPECT score, median (IQR)	7 (4.5-8)	8 (7-9)	Z=0.138	0.154
Cardiogenic stroke, n (%)	4 (50.0)	23 (52.3)	□²=0.014	0.906
SMCV-, n (%)	6 (75.0)	15 (34.1)	□□□□□□□□	0.03
Poor collaterals, n (%)	4 (50.0)	14 (31.8)	□²=0.989	0.32
Intravenous thrombolysis, n (%)	3 (37.5)	15 (34.1)	□²=0.035	0.852
Times of thrombectomy passes	3.5 (2-4)	2 (2-3)	□=0.158	0.187



Tirofiban, n (%)	0 (0)	4 (9.1)	□²=0.788	0.375
Recanalization, n (%)	4 (50.0)	41 (93.2)	□□□□□□□□□	0.001
24-72h NIHSS, median (IQR)	37 (26.5-37)	16 (8.3-30.5)	□□□□□□□	0.002
Decompressive craniectomy, n (%)	3 (37.5)	7 (15.9)	□²=2.032	0.154
Midline shift, n (%)	3 (37.5)	11 (25.0)	□²=0.538	0.463
Poor outcome, n (%)	6 (75.0)	21 (47.7)	□²=2.017	0.156

PH, parenchymal hematoma; SD, standard deviation; IQR, interquartile range; OIT: onset to imaging time; NIHSS, national institute of health stroke scale; SMCV-, absent filling of ipsilateral superficial middle cerebral vein.

Minor:

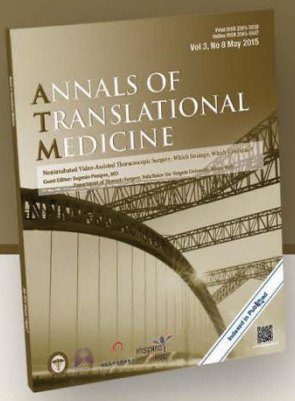
1) there are severe language and grammar problems at this point, some minor but some also of substance, making it very hard to almost impossible to understand the intention of the authors. There needs to be a rigorous native-speaker review of the manuscript.

Reply: Thanks for your suggestions. We have invited a native English speaker to review the manuscript. Language and grammar problems have been corrected.

2) what was the variable selection process for the multivariate analysis described in the results (paragraph starting at line 182)? It reads valid, as I would recommend including all predictors with a univariate p<0.1 into the analysis - but I would recommend explaining the process in the methods section

Reply: Thanks for your suggestion. The variable selection process is that all variables showed $P<0.1$ in univariate analysis were enrolled into multivariate analysis (poor collaterals, $P=0.014$; SMCV-, $P=0.066$; intravenous thrombolysis, $P=0.04$) (see table 1). We also have described this section in Method: “Variables identified by univariate analysis ($P < 0.1$) were included in binary logistic regression model.” (see page 11, line 203).

3) The section the relationship. Between smcv-, reperfusion and PH is repeating its results in the first two paragraphs. Of course, that cross tab leads to the same statistics, no matter which



direction you draw it. Right now, this double mention leads to confusion, asking whether there was secondary imaging, for which this statistical testing happened.

Reply: Thanks for your question. We've rearranged the whole section as you advised (see page 13, line 237-249).

Changes in the text:

There was no difference in rate of SMCV- between recanalization and no recanalization group (37.8% vs 57.1%, χ^2=0.944, *P*=0.331), while there was a significantly lower rate of SMCV- in reperfusion group, compared with no reperfusion group (34.1% vs 75.0%, χ^2=4.705, *P*=0.039) (see table 2). Binary logistic regression analysis showed that SMCV- was an independent risk factor for reperfusion (OR=0.172, 95%CI=0.031-0.960, *P*=0.045).

In reperfusion group, patients with SMCV- had a higher rate of PH than patients with SMCV+ (40% vs 13.8%, χ^2=3.866, *P*=0.049) (see table 2). In patients with SMCV-, the rates of PH were similar between no reperfusion and reperfusion group (50% vs 40%, χ^2=0.175, *P*=0.676). While in patients with SMCV+. The rate of PH was significantly lower in reperfusion group than that in no reperfusion group (13.8% vs 100%, □^{2}=8.908, *P*=0.032).

Reviewer C:

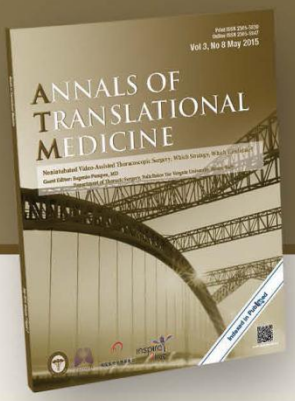
The authors have attempted to correlate the absence of venous filling with hemorrhage and repercussion.

What was the criteria for thrombectomy used in their institution?

Reply: Thanks for your question. We have corrected our patients' selection criteria for mechanical thrombectomy. In our study, we only enrolled acute LAO patients who admitted within 6 hours after stroke onset based on 2018 AHA/ASA guideline[1]. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (i) prestrike mRS score of 0-1; (ii) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (iii) age ≥18 years; (iv) NIHSS score of ≥6; (v) ASPECTS of ≥6; and (vi) treatment can be initiated (groin puncture) within 6 hours of symptom onset.

Reference

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, 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

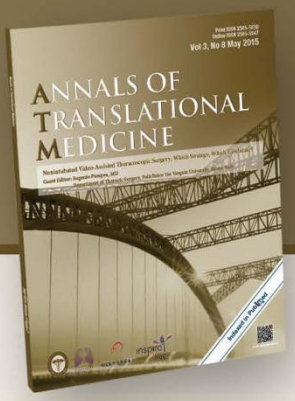
We have modified our text into “Patients exhibiting no clinical improvement after thrombolysis and patients who arrived at 4.5-6 hours after stroke onset were thrombectomy candidates. According to 2018 AHA/ASA guideline, these candidates were selected for thrombectomy if they meet all the following criteria: (1) prestrike mRS score of 0-1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset. Patients with any contraindication for thrombolysis who were eligible for thrombectomy also received thrombectomy directly.” (see page 7, line 111-116)

Reviewer D:

The authors identified the associations of SMCV to reperfusion, recanalization, PH after undergoing thrombectomy. The negative SMCV indicates low reperfusion rate and further predicts higher PH rate in the patients with reperfusion. Although this is a retrospective study, it provides a novel imaging marker that can be used as a predictor for the poor reperfusion. The topic and results of this study is interesting. However, some minor revisions are needed.

1. In the ‘Introduction’ section the author should review more literature regarding the reperfusion or recanalization associated factors, which may be more in agreement with the topics and the title.
Reply: Thanks for your suggestion. To better follow our topics for readers, we have added the description for the relation between SMCV- and reperfusion in Introduction (see page 6, line 82-85).
Changes in the text: It was also reported that abnormal venous outflow may hinder the reperfusion of ischemic brain tissue in LAO even after successful recanalization. There is no study yet to clarify the relationship between SMCV and PH when cerebral blood perfusion restored through thrombectomy in patients with acute LAO.

2. The baseline description should be detailed. For example, how many patients were performed with the bridging therapy, and how many were with thrombectomy alone; The num. of SMCV+, SMCV-, reperfusion, non-reperfusion, recanalization, non-recanalization should also be presented.



Reply: Thanks for your suggestion. We have supplied more detailed description in our revised manuscript this time (see page 12, line 211-215).

Changes in the text: SMCV- was presented in 21 patients (40.4%). 18 patients (34.6%) were performed with the bridging therapy, and 34 (65.4%) were with thrombectomy alone. After thrombectomy, 44 patients achieved reperfusion (84.6%), and 15 (28.8%) had PH within 48h after thrombectomy.

3. What's the meaning for 'The rates of PH were similarly high between no reperfusion and reperfusion group in SMCV- patients', if it is of essential, why the author did not present the PH rates between non- and reperfusion group in SMCV+ patients. Meanwhile, what about the patients with and without recanalization, maybe also presented in this section.

Reply: Thanks for your questions. As to your first question, in SMCV+ patients, PH rate was significantly lower in reperfusion group, compared with that in non-reperfusion group (13.8% vs 100%, χ^2=8.908, *P*=0.032). We've added this part into the result section (see page 13, line 246-248).

As to your second question, in SMCV+ patients, there was no significant difference in PH rate between patients with and without recanalization (17.9% vs 33.3%, χ^2=0.416, *P*=0.519). However, this part was not very correlated with our topic, we did not add it into the result section.

4. The definition of the SMCV should be detailed and imaging figures should be presented in the paper.

Reply: Thanks for your suggestion. According to your suggestion, the definition of SMCV- have been detailed in manuscript, and we've added an imaging figure to reveal SMCV-.

Changes in the text:

Absent filling of ipsilateral SMCV (SMCV-)

We assessed the SMCV on 4D-CTA reconstructed from CTP by Vitrea® fX (Version 1.0, Vital images, Minnetonka, MN, USA). Images were analyzed using maximum intensity projection (MIP). SMCV was defined negative (SMCV-) if no ipsilateral SMCV vein signal was seen until the late venous phase. Otherwise, it is defined as positive (SMCV+) (see Figure 2). Absent SMCV only presented in contralateral side was also ascribed to SMCV+ group (see page 9, line 160-164).

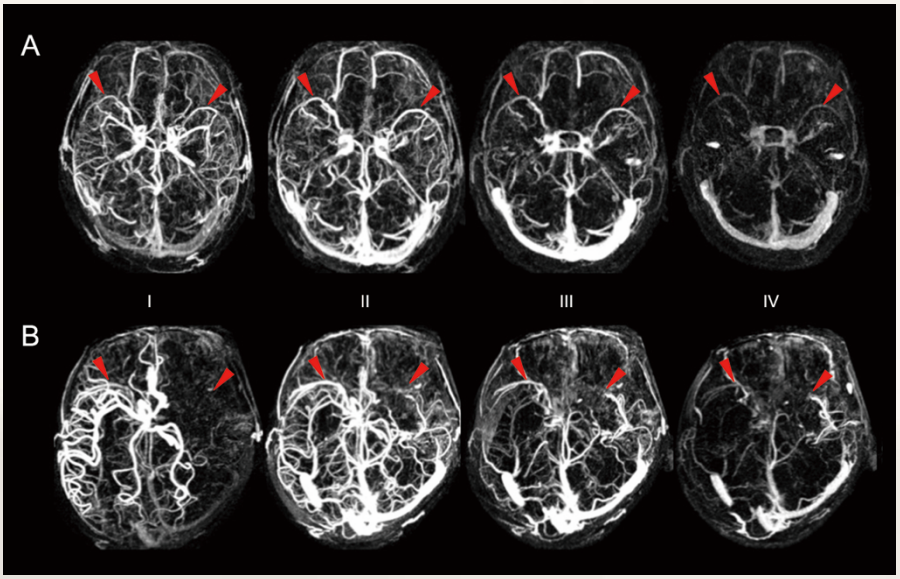
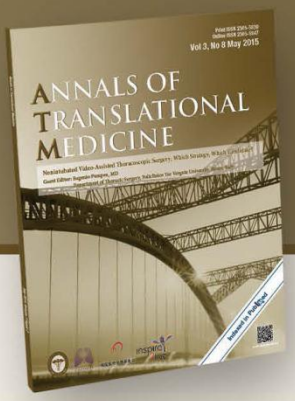


Figure 2. Examples of opacification of SMCV on dCTA in healthy and acute LAO patients. It's known that cerebral veins are opacified in sequence. As surface cortical veins are opacified early in the venous phase, SMCV can be well seen in this phase (I). Mid-venous phase (II and III) is always the best phase to view overall picture of cerebral veins as more down stream venous channels can be visualized. While in late venous phase (IV), the contrast within SMCV can be almost cleared out as most superficial veins are no longer visualized in this phase. Bilateral symmetrical SMCV opacification (red triangular arrow) can be seen in the healthy control subject from early to late phase (see patient A, I-IV). According to this regularity, SMCV was defined as negative (SMCV-) if no contrast filling of SMCV across the whole venous phase in the ischemic hemisphere. Otherwise, it was defined as positive (SMCV+). In patient B with acute left intracarotid artery occlusion, the ipsilateral SMCV (see the left red triangular arrow) that did not present on dCTA from early to late venous phase was marked as SMCV-. SMCV, superficial middle cerebral vein; dCTA, dynamic computed tomography angiography; LAO, large artery occlusion.

Reviewer E:

Thank you for giving me the opportunity to review this manuscript. The manuscript relates to a study which investigates the relationship among SMCV, PH and reperfusion, and has been demonstrated that SMCV- was a risk factor for reperfusion, but not for PH, in those LVO patients



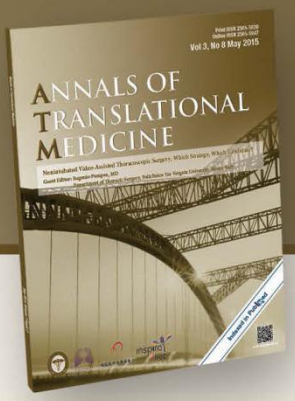
underwent thrombectomy. Totally, it is a well-written and organized manuscript which make a concise and novel conclusion for an important area of research, as predicting stroke recovery could have widespread influence. I have some minor concerns about the manuscript in its present forms:

1, How did you determine this sample size? If you did not evaluate sample size calculation, you should disclose at limitation part. The number of samples were relatively small, and results of subgroup analysis base on the small sample size should be interpreted with caution.
Reply: Thanks for your suggestion. We've disclosed it at limitation part as you advised.
Changes in the text: In addition, the results based on our small sample study should be interpreted with caution.

2, The clinical study, even retrospectively, would be better register on website of clinicaltrials.gov.
Reply: Thanks for your suggestion. We are already preparing for the registration on website of clinicaltrials.gov， but we cannot provide the number of clinical trial this time as it will take time to get the approval. We've mentioned this in our limitation part (see page 18, line 337-339)
Changes in the text: Further validations should be extended in larger sample and multicenter clinical trials in future.

3, How about the long-time outcome at 3 months for those LVO patients underwent thrombectomy in different SMCV groups?
Reply: Thanks for your question. We did not supply this result as we only focused on short-outcome in this study. As SMCV- closely associated with 3-months poor outcome has been illustrated in our previous study, we did not repeat the analysis of relationship between SMCV- and long term outcome in this study. However, future studies should include both short- and long-term outcomes in order to provide a more comprehensive judgment to the predictive value of SMCV- in LAO patients. We've mentioned this in our limitation part (see page 17-18, line 327-335).

Changes in the text: Thirdly, we did not provide long-term follow-up data as we focused on observing fast change of clinical manifestation in acute LAO patients in this study. As in acute LAO, patients may suffer rapid deterioration of neurological deficit, which even led to death within several days after stroke onset. Therefore, short-term outcome might be more reflective of



prognosis than 3-months long-term outcome in acute LAO patients. Our future studies will include both short- and long- term outcomes in order to comprehensively judge the predictive value of SMCV- in LAO patients received thrombectomy.

Reviewer F:

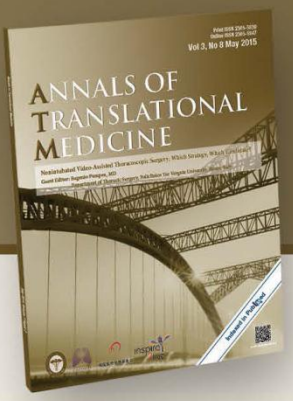
In this study, investigators evaluated the correlations among SMCV, PH and reperfusion, and the association between SMCV and PH in patients when reperfusion was achieved. This is an interesting study that provides novel insights into the association between SMCV and PH in reperfusion patients.

Major comments
Imaging analysis
1. Please report inter-rater variability results.
Reply: Thanks for your suggestion. We've reported this results in Statistical analysis -Method (Please see Page 11, Line 191-195),

Changes in the text: Cohen's kappa coefficient was used to assess the level of inter- and intra-observer agreement for detecting the presence of SMCV-, poor collaterals, midline shift, and PH. Excellent inter- and intra-observer agreement was seen in distinguishing the SMCV- (κ=0.918 and 0.879), poor collaterals (κ=0.912 and 0.824), midline shift (κ=0.906 and 0.803) and PH (κ=0.924 and 0.954).

2. Please detail the numbers for those excluded patients.
Reply: Thanks for your suggestion. We've corrected our inclusion and exclusion criteria, and we've added a study flowchart as figure 1 to detail numbers of included and excluded patients.

ANNALS OF TRANSLATIONAL MEDICINE



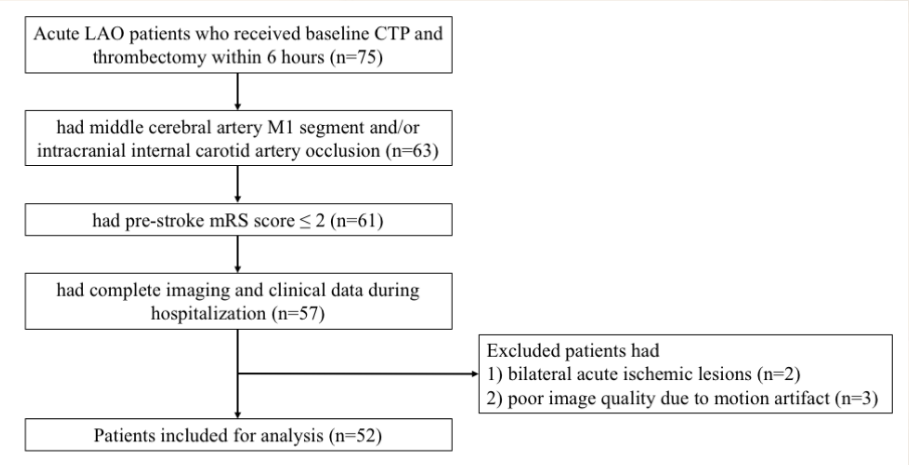


Figure 1. Study flowchart. LAO, large artery occlusion; CTP, computed tomography perfusion; mRS, modified Rankin Scale.

3. Your major factor was SMCV, please add in the characteristics.

Reply: Thanks for your question. We have added the detailed description of studying factors, including SMCV, in the first paragraph of our result (see page 12, line 211).

Changes in the text： SMCV- was presented in 21 patients (40.4%).

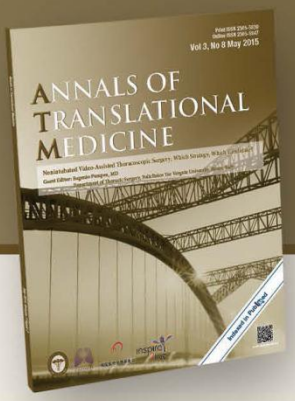
3. It is warranted to present another table to present the results of univariable and multivariable analysis. Multivariable logistic regression analysis is needed.

Reply: Thanks for your question. We've added the results of univariable and multivariable analysis as supplementary tables (two univariable analysis tables can be found in our reply of question 5-Reviewer B).

The multivariable logistic regression analysis is shown as below.

Supplementary table II. Multivariate analysis for factors associating with PH after thrombectomy

Model 1	OR	95%CI	*P value*
SMCV-	1.320	0.264-6.598	0.735
Poor collaterals	4.603	0.889-23.824	0.069
Intravenous thrombolysis	0.176	0.031-0.996	0.049
Model 2	OR	95%CI	*P value*
SMCV-	0.722	0.102=5.090	0.744



Poor collaterals	6.737	0.969-46.821	0.054
Intravenous thrombolysis	0.104	0.013-0.831	0.033
Reperfusion	0.110	0.013-0.913	0.041

PH, parenchymal hematoma; SMCV, superficial middle cerebral vein.

Discussion

1. “thrombolysis bridging” was mentioned in Line 263, please explain.

Reply: We feel sorry to make you confused. We guess you may not have read the sentence completely. The whole sentence is “Notably, we found that patients received intravenous thrombolysis bridging with thrombectomy (abbreviated as bridging therapy) had a significantly lower rate of PH”. In this sentence, bridging therapy means intravenous thrombolysis bridging with thrombectomy.

2. “a potential risk of selection bias” in Line 287. Please explain.

Reply: Thanks for your question. Small-sample size and retrospective study can draw a potential risk of selection bias. We’ve modified the text in limitation (see Page 17, line 321-322).

Changes in the text: This study had several limitations. First, it was a small-sample and retrospective study, which created a potential risk of selection bias.

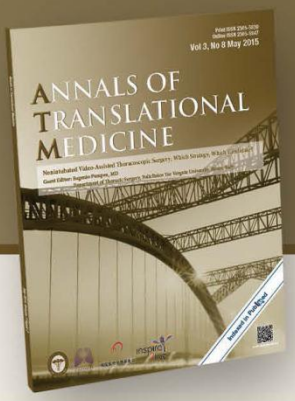
3. “Neurological outcome measures” in Line 131. Please discuss this in line with the results.

Reply: Thanks for your suggestion, but we’re not quite understand how you define the neurological outcome measures being discussed in line with our results. We think that it’s impossible to discuss all neurological outcomes in the discussion part because only PH and reperfusion were the focus of our research. In our present manuscript, we’ve already discussed our main findings about PH and reperfusion in our results. Therefore, we did not modify the content or the order of our discussion.

Minor comments

1. Line 51, the “Absent” should be “absent”. Line 52, what’s the meaning of “PH6”?

Reply: Thanks for your correction. 6 is the reference number, which should be superscript. We’ve modified the text as you advised (see Page 5, line 74).



Changes in the text: We have previously found that the absent filling of SMCV (marked as SMCV-) was associated with brain edema expansion and poor functional outcome in acute ischemic stroke, but not with PH[6].

2. Line 131, you write “Neurological Outcome measures”, which only two words have written in capitals, please correct it.

Reply: Thanks for your correction.

We’ve corrected it into “Neurological outcome measures” as you advised (see Page 10, line 166).