PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Predicting mortality in acute ischemic stroke treated with mechanical thrombectomy: Analysis of a multicenter prospective registry
AUTHORS	Li, Hao; Ye, Shisheng; Wu, Yuan-Ling; Huang, Sheng-Ming; Li, Yong-Xin; Lu, Kui; Huang, Jing-Bo; Chen, Lve; Li, Hong-Zhuang; Wu, Wen-Jun; Wu, Zhi-Lin; Wu, Jian-Zhou; Zhong, Wang-Tao; Xian, Wen-Chuan; Liao, Feng; Tung, Tao-Hsin; Wu, Qiao-ling; Chen, Hai; Yuan, Li; Yang, Zhi; Huang, Li-an

VERSION 1 – REVIEW

REVIEWER	Panagiotis Papanagiotou Dept. of Neuroradiology, Hospital Bremen-Mitte, Germany & National and Kapodistrian University of Athens, Greece
REVIEW RETURNED	10-Sep-2020

GENERAL COMMENTS	The study presents the development of a score for predicting mortality after thrombectomy in acute ischemic score. The paper is well written and gives a clear presentation of the results. Strengths of the study are the multicenter and prospective design. However, as the authors showed, the accuracy of the score is moderate, which limits its use in the clinical setting. This was also discussed appropriately. This study is a useful addition to the literature.

REVIEWER	Giovanni Merlino Stroke Unit, University of Udine, Italy
REVIEW RETURNED	16-Sep-2020

GENERAL COMMENTS	In this paper the authors investigated the pre-procedure variables associated with 90-days mortality in AIS patients undergoing MT. Moreover, they developed a new score in order to predict mortality in these patients. Although the manuscript is well written, it doesn't provide any new insight on MT treatment. In addition, it suffers from several relevant limitations. 1) A major problem in results interpretation is that this study was based on a retrospective analysis of a prospective observational registry. The authors should recognize this main limitation and include it in the text. 2) Collateral status represents an important predictor of outcome in AIS patients treated with MT. Please, include and analyze these data. 3) In addition to data on 90-days mortality, the authors collected information on hemorrhagic transformation and 90-days functional outcome. Thus, I ask the authors to perform a multivariate analysis in order to recognize predictors of SICH and functional dependence. 4) Since the developed PRACTICE score shows only a moderate predictive power, I suggest the authors to not perform this analysis and to delete this information from the text.

REVIEWER	GIANCARLO SALSANO
	Ospedale Policlinico San Martino, Italy
REVIEW RETURNED	09-Oct-2020

| GENERAL COMMENTS | We think you have an interesting data set here. However, the presentation of the findings and the expositional writing needs to be significantly better in all regards.
1. Authors state: " Our study aimed to determine pre-procedure predictors of mortality within 90 days ...". However study variables included not only pre-procedure clinical characteristics (sex, gender ...) and imaging (ASPECT, site of occlusion...) but also procedural details (endovascular technique, type of anesthesia...) and outcomes (TICI, ICH...), so I propose to delete the term pre-procedure from title, abstract and introduction.
2. Study variables and outcomes definition have to be better defined maybe in a supplementary material section. I would like to know if the variable "hypertension" indicates a history of hypertension or hypertension on presentation. I assume history of hypertension but I would like to see this spelled out.
3. As in #2 above for atrial fibrillation.
4. Again define endovascular procedure. What do you mean for routine embolectomy and mixed scheme?
5. Better explain also complications definition. For example SAH caused by arterial perforation was considered as contrast material extravasation during endovascular treatment or blood suffusion in sub-arachnoid spaces at CT follow-up? Moreover what kind of ICH classification do you follow (ECASS, SITS-MOST or NINDS criteria)?
6. Attention to these details will improve the impact of this paper.
7. The authors report 303 patients in 6 stroke centers in China. On average, this makes 50 MT per center per year. You can add the patient stratification for hospitals to underline the volume activity of the single center. Include also your definition for low, medium and high volume center.
8. Time from onset to arrival at the stroke center, time from onset to recanalization and time from groin puncture and recanalization are cited in the Study variables section. However I can't see that in table 1. Are that variable included in the bivariate analysis?
9. Authors cited HIAT, SAD score and THRIVE score that have only clinical variables. I would suggest adding the iSCORE, PLAN score (a) and POST score (b). Comparison AUC of PRACTICE with these score may be useful to understand the discriminative power of these tools.
a) Xiaopeng Chu et al. Validation of iScore and PLAN Score for Death in Thrombectomy in Acute Stroke Due to Anterior Circulation Large Artery Occlusion. J Stroke Cerebrovasc Dis. 2018 Nov;27(11):3261-3265. DOI: 10.1016/j.jstrokecerebrovasdis.2018.07.023.
b) Srikant Rangaraju et al. Pittsburgh outcomes after stroke thrombectomy score predicts outcomes after endovascular therapy for anterior circulation large vessel occlusions. Stroke.2014 Aug;45(8):2298-304. doi: 10.1161/STROKEAHA.114.005595.
10. "This population was not only exactly representative of the whole general population, but it was also difficult to estimate the mortality of a matched total population sample in China...". Add Hosmer-Lemeshow goodness-of-fit analysis in the statistical section to assess model calibration.
11. Explain acronyms under your tables. |

Reviewer 1:

1.Response to comment:(Please state any competing interests or state "None declared": None declared)

Response: We have made correction according to the Reviewer's comments. Please check and revise.

2.Response to comment:(The study presents the development of a score for predicting mortality after thrombectomy in acute ischemic score. The paper is well written and gives a clear presentation of the results. Strengths of the study are the multicenter and prospective design. However, as the authors showed, the accuracy of the score is moderate, which limits its use in the clinical setting. This was also discussed appropriately. This study is a useful addition to the literature.)

Response: We're very thankful for Reviewer's comments.

Reviewer 2:

1.Response to comment:(Please state any competing interests or state 'None declared': None declared)

Response: We have made correction according to the Reviewer's comments. Please check and revise.

2.Response to comment:(In this paper the authors investigated the pre-procedure variables associated with 90-days mortality in AIS patients undergoing MT. Moreover, they developed a new score in order to predict mortality in these patients. Although the manuscript is well written, it doesn't provide any new insight on MT treatment. In addition, it suffers from several relevant limitations. 1) A major problem in results interpretation is that this study was based on a retrospective analysis of a prospective observational registry. The authors should recognize this main limitation and include it in the text.)

Response: We're very thankful for Reviewer's comments, and we have added the main limitation at Page 7 lines 7-9. Please check and revise.

3.Response to comment:(2) Collateral status represents an important predictor of outcome in AIS patients treated with MT. Please, include and analyze these data.)

Response: We're very thankful for Reviewer's suggestion. Disappointingly, in the our registry the collateral status assessment was not performed systematically so the variable, although of great interest, were not available on all patients and are not therefore included in the analysis.

4.Response to comment:(3)In addition to data on 90-days mortality, the authors collected information on hemorrhagic transformation and 90-days functional outcome. Thus, I ask the authors to perform a multivariate analysis in order to recognize predictors of SICH and functional dependence.)

Response: Considering the Reviewer's good suggestion, we have tried to perform a multivariate analysis to recognize predictors of SICH and functional dependence. Disappointingly, only eighth (3.6%) patients suffered from SICH, therefore we can not get the reliable analysis results about predictors of SICH (The number of positive cases is too small to perform logistics regression analysis). In the multivariate analysis of functional dependence (MRS score 3-6), age≥80, male, admission NIHSS score≥18, sedation under local anesthesia, general anesthesia, and stenting implantation associated with a higher risk of functional dependence (Table1 in revised letter). However, our study aimed to determine predictors of mortality, and therefore we did not included the contents in our paper. But this will be our further study.

5.Response to comment:(4) Since the developed PRACTICE score shows only a moderate predictive power, I suggest the authors to not perform this analysis and to delete this information from the text.)

Response: We're very thankful for Reviewer's good suggestion. Currently, the prognostic scoring system related to mortality of patients with MT remain lacking, and such knowledge would impact on family members decision-making before mechanical thrombectomy and neurologists management

decisions after MT. Beside, our study would be a useful addition to the literature. Therefore, after careful consideration, we decide to keep the content of developing PRACTICE score.

Reviewer 3:
1.Response to comment:(1. Authors state: "Our study aimed to determine pre-procedure predictors of mortality within 90 days ...". However study variables included not only pre-procedure clinical characteristics (sex, gender ...) and imaging (ASPECT, site of occlusion...) but also procedural details (endovascular technique, type of anesthesia...) and outcomes (TICI, ICH...), so I propose to delete the term pre-procedure from title, abstract and introduction.)
Response: We're very thankful for Reviewer's careful review. Because the primary goal of the study was predicting mortality before the procedure. Although we included procedural details and outcome in the bivariate analysis, these variables were not used in the multivariate model, which had been explained in "Statistical Analysis and Score Development" section at Page 5 lines 5-7. And we corrected tittle as "Predicting mortality in acute ischemic stroke treated with mechanical thrombectomy: Analysis of a multicenter prospective registry". Please check and revise.
2.Response to comment:(2. Study variables and outcomes definition have to be better defined maybe in a supplementary material section. I would like to know if the variable "hypertension" indicates a history of hypertension or hypertension on presentation. I assume history of hypertension but I would like to see this spelled out. 3. As in #2 above for atrial fibrillation.)
Response: We have added a supplementary material section to define study variables and outcomes according to the Reviewer's comments. And added more detail information at Page 4 lines 4-7 and 19-21. Please check and revise.
3.Response to comment:(4. Again define endovascular procedure. What do you mean for routine embolectomy and mixed scheme?)
Response: We are very sorry for our confusing expression. In our study, routine embolectomy defined as stent thrombectomy alone, and mixed scheme defined as combining stent thrombectomy with balloon guiding catheter, direct-aspiration first-pass technique, solumbra, or stent retriever-mediated manual aspiration thrombectomy. Since the thrombectomy scheme did not contribute to our study, we decided to delete those variables.
4.Response to comment:(5. Better explain also complications definition. For example, SAH caused by arterial perforation was considered as contrast material extravasation during endovascular treatment or blood suffusion in sub-arachnoid spaces at CT follow-up? Moreover, what kind of ICH classification do you follow (ECASS, SITS-MOST or NINDS criteria)? 6. Attention to these details will improve the impact of this paper.)
Response: (1) SAH caused by vascular perforation defined as contrast material extravasation confirmed by angiogram during mechanical thrombectomy. Other complications definition was added at supplementary material section. (2) Intracranial hemorrhage defined by the Heidelberg Bleeding Classification. Symptomatic intracranial hemorrhage confirmed by the 24 hours follow-up head CT with a ≥4 points NIHSS score increase according to the Heidelberg criteria.
5.Response to comment:(7. The authors report 303 patients in 6 stroke centers in China. On average, this makes 50 MT per center per year. You can add the patient stratification for hospitals to underline the volume activity of the single center. Include also your definition for low, medium and high volume center.)
Response: We're very thankful for Reviewer's good suggestion. Stroke centers were divided into low (Zhongshan People's Hospital, Yunfu People's Hospital,Affiliated Hospital of Guangdong Medical University), medium (First Affiliated Hospital of Jinan University, Shunde Hospital of Southern Medical University)and high (Maoming People's Hospital)volume center (Figure1 in revised letter). Low, medium and high volume center were defined as including patients <50, 50≤ including patients <100, and including patients≥100. We added the content at Page 3 lines 37-43.
6.Response to comment:(8. Time from onset to arrival at the stroke center, time from onset to recanalization and time from groin puncture and recanalization are cited in the Study variables section. However I can't see that in table 1. Are that variable included in the bivariate analysis?)

Response: We're very thankful for Reviewer's careful review. We have deleted the content from the Study variables section. Please check and revise.

7.Response to comment:(9. Authors cited HIAT, SAD score and THRIVE score that have only clinical variables. I would suggest adding the iSCORE, PLAN score (a) and POST score (b). Comparison AUC of PRACTICE with these scores may be useful to understand the discriminative power of these tools.)

Response: We're very thankful for Reviewer's good suggestion. After reading the recommended articles carefully, we found that PLAN score and POST score can't be validated in our registry database, because of lacking of specific neurologic deficit (each item of NIHSS score)and final infarct volume respectively. Therefore, we added the iSCORE and PREMISE score (Gattringer T, Posekany A, Niederkorn K, et al. Predicting Early Mortality of Acute Ischemic Stroke. Stroke. 2019;50:349-56.) to compare with PRACTICE score(Figure1). The receiver operator curve analysis found that PRACTICE score (area under the curve[AUC] = 0.744, 95% confidence interval [CI] 0.669-0.820) was numerically better than iScore (AUC =0.661, 95% CI 0.577-0.745) and PREMISE score (AUC =0.638, 95% CI 0.551-0.725) for predicting 90-day mortality(Figure 1 in main document). The content was added at Page 4 lines 36-52, Page 5 lines 13-15, 44-46.

8.Response to comment:(10. "This population was not only exactly representative of the whole general population, but it was also difficult to estimate the mortality of a matched total population sample in China...". Add Hosmer-Lemeshow goodness-of-fit analysis in the statistical section to assess model calibration.)

Response: We're very thankful for Reviewer's comments, and we have added Hosmer-Lemeshow goodness-of-fit analysis in the statistical section. Calibration of the model was good (Hosmer-Lemeshow goodness-of-fit P=0.77). Please check and revise.

9.Response to comment:(11. Explain acronyms under your tables.)

Response: We're very thankful for Reviewer's comments, and we have explained acronyms under your tables. Please check and revise.