## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Predictors of mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion: subgroup analysis of a multicenter randomized clinical Trial |
| **AUTHORS** | Li, Hao; Huang, Jinbo; Cao, Jie; Ye, Shisheng; Chen, Hai; Liao, Geng; Du, Weijie; Li, Chaomao; Yuan, Li; Fang, Ling; Yang, Pengfei; Zhang, Yongwei; Xing, Pengfei; Zhang, Xiaoxi; Ye, Xiaofei; Peng, Ya; Liu, Sheng; Zhang, Liyong; Yang, Zhi; Liu, Jianmin |

## VERSION 1 – REVIEW

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| **REVIEWER** | Bivard, Andrew<br>Melbourne Brain Centre |
| **REVIEW RETURNED** | 23-Jul-2021 |

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| **GENERAL COMMENTS** | The authors present a secondary statistical analysis from the DirectMT trial identifying risk factors for mortality after EVT. The present analysis is well presented with minimal room for comment given the purely statistical nature of the project.<br><br>Further comment should be given in the discussion to the results and limitations of the DirectMT trial. These are highly relevant to the current study, such as the degree of patient cross over as well as the outcome of the trial. |

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| **REVIEWER** | Merlino, Giovanni<br>Universita degli Studi di Udine Polo Medico Medicina e Chirurgia, Stroke Unit, Department of Neurosciences |
| **REVIEW RETURNED** | 27-Sep-2021 |

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| **GENERAL COMMENTS** | This study is a subgroup analysis of the DIRECT trial including 622 affected by acute ischemic stroke (AIS) due to large vessel occlusion (LVO) and undergoing mechanical thrombectomy (MT) with or without intravenous thrombolysis. The aim of this study was to recognize the predictors of mortality despite a successful recanalization (TICI>2b). After controlling for confounders, symptomatic ICH, NIHSS score > 17 at baseline, glucose levels at admission > 130 mg/dl were associated with higher mortality, whereas smoking seemed to be a protective factor.<br>Although the study is very interesting, I think that it might be improved.<br>In particular, the authors should consider the following comments:<br>1) In addition to mortality, the authors should include “poor outcome”, i.e. mRS 3-6, as primary endpoint.<br>2) Please, use the TOAST for classifying AIS etiology. |

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| | 3) Regarding baseline NIHSS score, the authors reported the following sentence in the Conclusion section: "…This indicates that it is difficult to reverse the outcome of stroke with severe neurological deficit (as indicated by a high NIHSS score) despite successful reperfusion". Although I agree that baseline NIHSS score represents a risk factor for mortality, I suggest the authors to collect information on post-thrombectomy NIHSS and to check a possible association between post-thrombectomy NIHSS and their primary endpoints, "poor outcome" and mortality. At which time NIHSS will be a stronger predictor of impaired outcome?<br>4) Regarding hyperglycemia, the authors should report not only data on admission glucose, but also information on glucose levels within 24 h after MT. In fact, recent studies (Yong et al. Stroke 2008, 39, 2749–2755. Putaala et al. Cerebrovasc. Dis. 2011, 31, 83–92. Yoo et al PLoS ONE 2014, 9, e94364. Merlino et al. J Clin Med 2020 20;9:1932) demonstrated that dynamic hyperglycemic pattern is able to predict outcomes in AIS treated with recanalization therapy. If the authors did not collect this information, they should include this issue among their limitations.<br>5) Tables should be reformatted appropriately, e.g. subheading in bold, Chinese words to delete/translate (table 1).<br>6) The authors should report in table 2 ORs and p-values for ALL the variables included in the multivariate models, both associated and not associated with the outcome measures. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1(Prof. Andrew Bivard):
1.Response to comment:(The authors present a secondary statistical analysis from the DirectMT trial identifying risk factors for mortality after EVT. The present analysis is well presented with minimal room for comment given the purely statistical nature of the project.)
Response: We're very thankful for Reviewer's comments.

2.Response to comment:(Further comment should be given in the discussion to the results and limitations of the DirectMT trial. These are highly relevant to the current study, such as the degree of patient cross over as well as the outcome of the trial. )
Response: (1)There were 4 patients (1.2% of subjects) in each group who crossed over to the alternative treatment, which is within the acceptable range. Therefore, no further discussion is necessary. (2) We have made further discussion of the results and limitations at Page 7 lines 9-17, Page 8 lines 3-8 and Page 9 lines 8-15. Please check and revise.

Reviewer 2(Dr. Giovanni Merlino):
1.Response to comment:( In addition to mortality, the authors should include "poor outcome", i.e. mRS 3-6, as primary endpoint.)
Response: We're very thankful for Reviewer's good suggestion, and we also think this will improve our article. However, this is beyond the scope of our study. The analysis of "poor outcome" is the research of other center of DIRECT-MT.

2.Response to comment:( Please, use the TOAST for classifying AIS etiology.)
Response: We have made correction according to the Reviewer's comments. Please check and revise at Page 4 lines 12-14 and Table 1.

3.Response to comment:( Regarding baseline NIHSS score, the authors reported the following sentence in the Conclusion section: "…This indicates that it is difficult to reverse the outcome of stroke with severe neurological deficit (as indicated by a high NIHSS score) despite successful reperfusion". Although I agree that baseline NIHSS score represents a risk factor for mortality, I suggest the authors to collect information on post-thrombectomy NIHSS and to check a possible association between post-thrombectomy NIHSS and their primary endpoints, "poor outcome" and mortality. At which time NIHSS will be a stronger predictor of impaired outcome?)
Response: We're very thankful for Reviewer's good suggestion. We have included the analysis of post-thrombectomy NIHSS to the study. In the study, post-thrombectomy NIHSS was a stronger predictor. Please check and revise at Page 6 lines 19-22.

4.Response to comment:( Regarding hyperglycemia, the authors should report not only data on admission glucose, but also information on glucose levels within 24 h after MT. In fact, recent studies (Yong et al. Stroke 2008, 39, 2749–2755. Putaala et al. Cerebrovasc. Dis. 2011, 31, 83–92. Yoo et al PLoS ONE 2014, 9, e94364. Merlino et al. J Clin Med 2020 20;9:1932) demonstrated that dynamic hyperglycemic pattern is able to predict outcomes in AIS treated with recanalization therapy. If the authors did not collect this information, they should include this issue among their limitations.)
Response: We're very thankful for Reviewer's good suggestion. In fact, our research only include the glucose levels on admission glucose, and we have added the limitation at Page 8 lines 3-8. Please check and revise.

5.Response to comment:( Tables should be reformatted appropriately, e.g. subheading in bold, Chinese words to delete/translate (table 1).)
Response: We're very thankful for Reviewer's careful review. We have made correction according to the Reviewer's comments. Please check and revise.

6.Response to comment:( The authors should report in table 2 ORs and p-values for ALL the variables included in the multivariate models, both associated and not associated with the outcome measures.)
Response: We're very thankful for Reviewer's good suggestion. But our multivariate models were built using forward/backward stepwise logistic regression with variables entered into the model at the 0.05 significance level. Therefore, only the statistically significant variables are obtained(Linfante I, et al. Journal of neurointerventional surgery. 2016;8:224-9. Raul G. Nogueira, et al. Stroke. 2009;40:3777-3783.).

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And we underlined in revised paper.
We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.

With kind regards,

**VERSION 2 – REVIEW**

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| **REVIEWER** | Merlino, Giovanni<br>Universita degli Studi di Udine Polo Medico Medicina e Chirurgia, Stroke Unit, Department of Neurosciences |
| **REVIEW RETURNED** | 21-Jan-2022 |

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| **GENERAL COMMENTS** | The authors addressed my concerns. |