

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China: Findings from a Nationwide Registry Study in China
AUTHORS	Wang, HaiYan; Gu, Hongqiu; Zhou, Qi; Jiang, YingYu; Yang, Xin; Wang, Chunjuan; Zhao, Xingquan; Wang, Yilong; Liu, Liping; Meng, Xia; Li, Hao; Liu, Chelsea; Li, Zixiao; Wang, Yongjun; Jiang, Yong

VERSION 1 – REVIEW

REVIEWER	Van den Berg-Vos, RM OLVG West, Amsterdam
REVIEW RETURNED	31-Aug-2021

GENERAL COMMENTS	<p>In general: I considered to advise a rejection as I do not agree with the hypothesis and find parts of the results section not really breaking news. On the other hand, it concerns an impressive number of patients and hospitals and I am an advocate of using data out of real time quality registers and therefore my advise is to give the authors the possibility to revise the manuscript.</p> <p>Per section I have the following comments :</p> <p>Strengths and limitations As a reviewer I do not understand the explanation in point 2 , "the data have a stronger level of evidence": than what or who? :and I do not understand the argument mentioned under point 3</p> <p>Introduction: I do not understand and do not fully agree with the hypothesis that young acute ischemic stroke patients would be treated more frequently with IV tPA and have shorter treatment times. In general practice a diagnosis of stroke in young patients often asks more of the treating physicians as more rare causes should be considerend and sometimes more diagnostic modalities are necessary. In the Dutch Acute Stroke Audit indeed treatment times are (non-significantly) longer for patients < 50 years than > 50 years. It is my experience that the fear of complications (which may be bigger in older patients) does not lengthen treatment times in clinical practice. On the contrary I fully agree with the hypotheisis that younger patients have better in-hospital outcomes compared to older adults, but wonder whether this needs further research.</p> <p>Methods: Study population: Weakness: I do not see the rationale of the definition of young stroke < 50. We know that the incidence of vascular risk factors is growing so a substantial part of pats < 50 years will have atherosclerotic disease. Why not incorporate the absence of vascular risk factors into the definition?</p>
-------------------------	---

	<p>Strength : this study comprises an impressive number of patients and hospitals!</p> <p>Outcomes: For me the rationale of excluding patients with an onset-to-door time > 3.5h is not clear? If maintained in the manuscript then it should be mentioned in the ainea of the Study Population</p> <p>Results: I find the tables too extensive, consider making them shorter and more compact</p> <p>Discussion: The definition of young patients and the explanation of it in the Discussion (why is the definition of < 50 years more applicable in China than a lower cut-off of eg 40 years) needs further explanation.</p> <p>In the discussion the authors extensively discuss their findings of a higher rate of sICH and in-hospital mortality among older adults treated with IV tPA, but these findings are not so relevant because the differences were not significant adjusted for NIHSS scores and in general practice these findings are intuitive and no breaking news.</p> <p>I found the sentence "this may also reflect, in part, that physicians in China are more conservative in selecting patients for intravenous thrombolysis (IVT) because of possible complications" a little woriesome: IVT is nowadays a cornerstone of the acute treatment and possibly this is not always the case in some parts of China but I advise to put this somewhat different in the Discussion.</p>
--	--

REVIEWER	Tan, KS University of Malaya, Dept of Medicine
REVIEW RETURNED	31-Aug-2021

GENERAL COMMENTS	<p>The incidence of stroke is rising among adults worldwide and the data is particularly important from China which has the largest population as contributed by data from China Stroke Centre Alliance. However, as the current data represents only about 18 percent of 9000 public hospitals in China, (Wang Y, et al. Stroke and Vascular Neurology 2018;3:e000154. doi:10.1136/svn-2018-000154), it will be useful to add more information on the distribution and numerical contributions of the relevant centres participating in the study. One suggestion is to put in a schematic map and/or table to describe the centres by city and province. In this way, the reader can understand which regions in China are represented. The paper is excellent and technically well written.</p>
-------------------------	--

REVIEWER	Wang, Yanzhong Kings College London, School of Population Health and Environmental Sciences
REVIEW RETURNED	05-Dec-2021

GENERAL COMMENTS	<p>This is a useful study on Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China. The study design, datasets, statistical methods and analyses, and presentation and interpretation of the results are mostly adequate. The paper focused mainly on differences in outcomes between young and old stroke patients but didn't go further to use the data to explain reasons of these differences or no difference, which makes the paper a bit superficial and therefore need to at least address this in the limitation.</p>
-------------------------	--

	The other issue is about summary statistics. In table 1, all the continuous variables were summarised in both mean/SD and median/IQR, which is very inadequate. Depending on the distribution of the data, continuous variables with normal distribution should be summarised as mean and SD, while those with skewed/non-normal distribution need to be summarised as median and IQR. Also, parametric or non-parametric tests should follow accordingly. Can authors please check the distributions of all the continuous variables in table 1 and then decide appropriate summary stats and stats tests?
--	---

REVIEWER	Turc, Guillaume GHU Paris
REVIEW RETURNED	08-Dec-2021

GENERAL COMMENTS	<p>Statistical review :</p> <p>The statistical methods are generally sound. However, the following points need to be addressed :</p> <ol style="list-style-type: none"> 1) Consider using propensity score matching (PSM) for the primary analysis, which would lead to better control of potential confounders. The very large sample would be optimal for PSM. The dependent variable for the calculation of the propensity score would be age (<50 years vs. >= 50 years). Please present in a table or figure the ASD of each variable before and after PSM. 2) The sentence « An ASD larger than 10 was considered statistically significant » is incorrect. An ASD larger than 10% suggests meaningful imbalance, not statistical significance (Austin, Stat Med 2009). In the tables, please mention « ASD (%) » instead of « ASD », wherever appropriate. 3) How was potential multicollinearity assessed in multivariable models? It is likely that some of the variables included in the models are highly collinear (e.g., SBP and DBP). 4) How did the authors deal with potential interactions between variable included in the logistic models ? 5) The rate of missing data is very high for some key variables such a in-hospital NIHSS score. Please ensure that the results would remain stable after multiple imputations for missing data (sensitivity analysis). 6) At the bottom of page 19, the authors mention « non-significantly higher odds of independent ambulation at discharge », but the point estimate clearly suggests a neutral association (aOR 1.00, 95%CI 0.93-1.08) 7) Please replace « multivariate » by « multivariable » throughout the manuscript (see PMID 19000286 for explanation) 8) 'Statistical analysis' section : please mention that you also used mean and SD for descriptive statistics. Specify which non-parametric tests were used. 9) Regarding the onset-to-door time, the cutoff (3.5hrs) is rather unusual. Why did you make this choice? 10) Page 15, the authors report that « young adults had a significantly higher mean BMI than older adults », but the medians are 24.2 and. 23.7, respectively. It is very uncertain whether that statistical difference is clinically meaningful. This should be mentioned. 11) In the abstract, please write « 793 175 » instead of « 79 3175 » <p>Additional suggestion : please consider citing both US (Powers et al, Stroke 2019) and European (Berge et al, Eur Stroke J 2021) guidelines on intravenous thrombolysis in the introduction.</p>
-------------------------	--

--	--

VERSION 1 – AUTHOR RESPONSE

2. Reviewer: 1

Dr. RM Van den Berg-Vos, OLVG West, Amsterdam

Comments to the Author:

In general: I considered to advise a rejection as I do not agree with the hypothesis and find parts of the results section not really breaking news. On the other hand, it concerns an impressive number of patients and hospitals and I am an advocate of using data out of real time quality registers and therefore my advise is to give the authors the possibility to revise the manuscript.

Per section I have the following comments :

Strengths and limitations

1) As a reviewer I do not understand the explanation in point 2 , "the data have a stronger level of evidence": than what or who? :and I do not understand the argument mentioned under point 3
Response: Thank you for your question. We rewrote the Strengths and limitations section. The new section reads:

- We used data from a large-scale, nationwide, hospital-based, multicenter quality improvement initiative.
- Multiple regression models adjusted for different levels of covariates were used to check the robustness of the results ;
- Data on intra-arterial therapies, puncture times, door-to-imaging, and follow-up outcomes after discharge were not collected and reported.

2) Introduction: I do not understand and do not fully agree with the hypothesis that young acute ischemic stroke patients would be treated more frequently with IV tPA and have shorter treatment times. In general practice a diagnosis of stroke in young patients often asks more of the treating physicians as more rare causes should be considered and sometimes more diagnostic modalities are necessary. In the Dutch Acute Stroke Audit indeed treatment times are (non-significantly) longer for patients < 50 years than > 50 years. It is my experience that the fear of complications (which may be bigger in older patients) does not lengthen treatment times in clinical practice. On the contrary I fully agree with the hypothesis that younger patients have better in-hospital outcomes compared to older adults, but wonder whether this needs further research.

Response: Thank you for bringing this up. The cut-off age of this study is 50 years old. At present, stroke under the age of 50 is becoming more and more common, but these people tend to be less complicated with underlying diseases; In addition, doctors in China tend to actively offer thrombolysis for young people, even if it is stroke mimics because the benefits of thrombolysis may outweigh the disadvantages. Therefore, we hypothesized that young acute ischemic stroke patients would be treated more frequently with IV tPA and have shorter treatment times.

3) Methods: Study population:

Weakness: I do not see the rationale of the definition of young stroke < 50. We know that the incidence of vascular risk factors is growing so a substantial part of pats < 50 years will have atherosclerotic disease. Why not incorporate the absence of vascular risk factors into the definition?

Response: We agree that a substantial part of pats < 50 years have atherosclerotic disease. We chose 50 as the cut-off age because several important international studies on thrombolytic therapy in young people also set the cut-off age at 50(1. Toni D, Ahmed N, Anzini A, et al. Intravenous thrombolysis in young stroke patients: results from the SITS-ISTR. *Neurology* 2012;78:880-7. doi: 10.1212/WNL.0b013e31824d966b. 2.Poppe AY, Buchan AM, Hill MD. Intravenous thrombolysis for

acute ischaemic stroke in young adult patients. *Can J Neurol Sci* 2009;36:161-7. doi: 10.1017/s031716710012027x). Using the same cut-off age value would benefit the comparison with other studies and also have advantages for potential systematic review and meta-analysis.

4) Strength : this study comprises an impressive number of patients and hospitals!

Response: Thank you for your comments.

5) Outcomes: For me the rationale of excluding patients with an onset-to-door time > 3.5h is not clear? If maintained in the manuscript then it should be mentioned in the ainea of the Study Population

Response: Thank you for bringing this up. The classic time windows for IV-tPA is 4.5hrs, we leave one hour out for door-to-needle time; that why we used 3.5hrs as the cutoff for onset-to-door time. This is also in line with our previous report (Gu HQ, Yang X, Wang CJ, Zhao XQ, Wang YL, Liu LP, Meng X, Jiang Y, Li H, Liu C, Wangqin R, Fonarow GC, Schwamm LH, Xian Y, Li ZX, Wang YJ. Clinical characteristics, management, and in-hospital outcomes in patients with stroke or transient ischemic attack in china. *JAMA Netw Open*. 2021; 4 (8):e2120745; doi:10.1001/jamanetworkopen.2021.20745;2021/08/14).

6) Results: I find the tables too extensive, consider making them shorter and more compact

Response: Thank you for this suggestion. We have revised the tables accordingly.

7) Discussion:

The definition of young patients and the explanation of it in the Discussion (why is the definition of < 50 years more applicable in China than a lower cut-off of eg 40 years) needs further explanation.

Response: Thank you for your suggestion. We have added more discussion for clarification.

8) In the discussion the authors extensively discuss their findings of a higher rate of sICH and in-hospital mortality among older adults treated with IV tPA, but these findings are not so relevant because the differences were not significant adjusted for NIHSS scores and in general practice these findings are intuitive and no breaking news.

Response: Thank you for your comments. We agree with you on this point. We have shorten the discussion accordingly.

9) I found the sentence "this may also reflect, in part, that physicians in China are more conservative in selecting patients for intravenous thrombolysis (IVT) because of possible complications" a little woriesome: IVT is nowadays a cornerstone of the acute treatment and possibly this is not always the case in some parts of China but I advise to put this somewhat different in the Discussion.

Response: Thanks for your concern. We have shorten the discussion part for higher rate of sICH among older adults as suggested, therefore, this sentence has been moved out.

3、Reviewer: 2

Prof. KS Tan, University of Malaya

Comments to the Author:

The incidence of stroke is rising among adults worldwide and the data is particularly important from China which has the largest population as contributed by data from China Stroke Centre Alliance. However, as the current data represents only about 18 percent of 9000 public hospitals in China, (Wang Y, et al. *Stroke and Vascular Neurology* 2018;3:e000154. doi:10.1136/svn-2018-000154), it will be useful to add more information on the distribution and numerical contributions of the relevant centres participating in the study. One suggestion is to put in a schematic map and/or table to describe the centres by city and province. In this way, the reader can understand which regions in China are represented. The paper is excellent and technically well written.

Response: Thank you for your suggestion. We have added an online supplemental table to show the distribution of hospitals by province in this study.

4. Reviewer: 3

Dr. Yanzhong Wang, Kings College London

Comments to the Author:

1) This is a useful study on Thrombolysis, Time-to-Treatment and In-Hospital Outcomes Among Young Adults with Ischemic Stroke in China. The study design, datasets, statistical methods and analyses, and presentation and interpretation of the results are mostly adequate. The paper focused mainly on differences in outcomes between young and old stroke patients but didn't go further to use the data to explain reasons of these differences or no difference, which makes the paper a bit superficial and therefore need to at least address this in the limitation.

Response: Thank you for bringing this up. We have add this limitation in discussion section.

The other issue is about summary statistics.

2) In table 1, all the continuous variables were summarised in both mean/SD and median/IQR, which is very inadequate. Depending on the distribution of the data, continuous variables with normal distribution should be summarised as mean and SD, while those with skewed/non-normal distribution need to be summarised as median and IQR. Also, parametric or non-parametric tests should follow accordingly. Can authors please check the distributions of all the continuous variables in table 1 and then decide appropriate summary stats and stats tests?

Response: Thank you for your comments. We presented both mean/SD and median/IQR for all continuous variables in table 1, because these statistics could provide more comprehensive information. However, we'd like to choose mean/SD or median/IQR based on the distribution of these variables to reduce table 1 as you suggested. In addition, based on the distribution of the variable, the absolute standard difference (ASD) or Hodges–Lehmann estimator would be used to assess differences between groups, instead of p values from traditional t-tests or Wilcoxon-rank sum tests.

Reviewer: 4

Dr. Guillaume Turc, GHU Paris

Statistical review :

The statistical methods are generally sound. However, the following points need to be addressed :
1) Consider using propensity score matching (PSM) for the primary analysis, which would lead to better control of potential confounders. The very large sample would be optimal for PSM. The dependent variable for the calculation of the propensity score would be age (<50 years vs. ≥ 50 years). Please present in a table or figure the ASD of each variable before and after PSM.

Response: Thank you for your suggestion. We did not prefer PSM because propensity scores are usually estimated in situations where a patient has some propensity to receive an intervention (e.g., prescribing a drug, receiving a procedure), not has some property (e.g., sex, age). Another reason is that PSM would increase imbalance, inefficiency, model dependence, and bias (more discussion in King G, Nielsen R. Why propensity scores should not be used for matching. *Political Analysis*. 2019; 27 (4):435-454; doi:10.1017/pan.2019.11;). In addition, we performed a series of sensitivity analyses to assess the robustness of our multiple regression analysis.

2) The sentence « An ASD larger than 10 was considered statistically significant » is incorrect. An ASD larger than 10% suggests meaningful imbalance, not statistical significance (Austin, *Stat Med* 2009). In the tables, please mention « ASD (%) » instead of « ASD », wherever appropriate.

Response: Thank you for your suggestion. We improved the manuscript accordingly.

3) How was potential multicollinearity assessed in multivariable models? It is likely that some of the variables included in the models are highly collinear (e.g., SBP and DBP).

Response: Thank you for your concern. We checked the multicollinearity by the variance inflation factor (VIF), and all VIFs were less than 10, indicating the collinearity is acceptable.

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > t	Tolerance	Variance Inflation
Intercept	1	76.83936	0.48421	158.69	<.0001	.0	
BMI	1	-0.46901	0.01243	-37.72	<.0001	0.98341	1.01687
HGBn	1	0.18821	0.03396	5.54	<.0001	0.99055	1.00954
SBP	1	0.15252	0.00274	55.72	<.0001	0.63089	1.58506
DBP	1	-0.28496	0.00451	-63.15	<.0001	0.62711	1.59463

4)How did the authors deal with potential interactions between variable included in the logistic models?

Response: Thanks. For simplicity of the model, we did not consider interactions in the logistic model. And we believe this strategy is in line with the literature.

5)The rate of missing data is very high for some key variables such a in-hospital NIHSS score. Please ensure that the results would remain stable after multiple imputations for missing data (sensitivity analysis).

Response: Thank you for your suggestion. We have provided multiple imputation analyses in Table 2 and 4, and the results were largely consistent with previous analyses.

Table2
OUTCOME MODEL OR (95%CI) P value
TPA 4 1.19(1.15-1.22) <0.001
TPA 3.5H 4 1.23(1.19-1.28) <0.001

Table4
OUTCOME MODEL OR (95%CI) P value
sICH 4 0.79(0.52-1.20) 0.2664
In-hospital mortality 4 0.65(0.43-1.00) 0.0476
Independent ambulation at discharge 4 1.02(0.96-1.10) 0.4893

6)At the bottom of page 19, the authors mention « non-significantly higher odds of independent ambulation at discharge », but the point estimate clearly suggests a neutral association (aOR 1.00, 95%CI 0.93-1.08)

Response: Thank you for pointing it out. We have corrected this statement in the revised manuscript.

7)Please replace « multivariate » by « multivariable » throughout the manuscript (see PMID 19000286 for explanation)

Response: Thank you for pointing it out. We have corrected it accordingly.

8) 'Statistical analysis' section : please mention that you also used mean and SD for descriptive statistics. Specify which non-parametric tests were used.

Response: Thank you. We used absolute standard difference (ASD) or Hodges–Lehmann estimator for mean/SD and median/IQR, respectively.

9) Regarding the onset-to-door time, the cutoff (3.5hrs) is rather unusual. Why did you make this

choice?

Response: Thank you for pointing it out. The classic time windows for IV-tPA is 4.5hrs, we leave one hour out for in-hospital delay; that why we used 3.5hrs as the cutoff for onset-to-door time. This is also in line with our previous report (Gu HQ, Yang X, Wang CJ, Zhao XQ, Wang YL, Liu LP, Meng X, Jiang Y, Li H, Liu C, Wangqin R, Fonarow GC, Schwamm LH, Xian Y, Li ZX, Wang YJ. Clinical characteristics, management, and in-hospital outcomes in patients with stroke or transient ischemic attack in china. JAMA Netw Open. 2021; 4 (8):e2120745; doi:10.1001/jamanetworkopen.2021.20745;2021/08/14).

10) Page 15, the authors report that « young adults had a significantly higher mean BMI than older adults », but the medians are 24.2 and. 23.7, respectively. It is very uncertain whether that statistical difference is clinically meaningful. This should be mentioned.

Response: Thank you for your suggestion. We have improved the description accordingly.

11) In the abstract, please write « 793 175 » instead of « 79 3175 »

Response: Our apologies for this oversight. We have revised this sentence.

Additional suggestion : please consider both US (Powers et al, Stroke 2019) and European (Berge et al, Eur Stroke J 2021)

Response: Thank you for this suggestion. We have cited these guidelines on intravenous thrombolysis in the introduction.

VERSION 2 – REVIEW

REVIEWER	Van den Berg-Vos, RM OLVG West, Amsterdam
REVIEW RETURNED	30-Jan-2022
GENERAL COMMENTS	I find the revised version of the manuscript improved and my comments incorporated sufficiently.. The quality of the manuscript suffices now.
REVIEWER	Wang, Yanzhong Kings College London, School of Population Health and Environmental Sciences
REVIEW RETURNED	06-Feb-2022
GENERAL COMMENTS	Thanks authors for their great effort to improve the manuscript. I am mostly satisfied with the response and revision. Only one minor issue remaining: the NIHSS score in hospital in table 1 doesn't look like following a normal distribution therefore need to summarise with median and IQR instead of mean and SD. Mean±SD
REVIEWER	Turc, Guillaume GHU Paris
REVIEW RETURNED	25-Jan-2022
GENERAL COMMENTS	No further comments on the paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Dr. Guillaume Turc, GHU Paris

Comments to the Author:

No further comments on the paper.

Response: Thank you for your comments.

Reviewer: 1

Dr. RM Van den Berg-Vos, OLVG West, Amsterdam

Comments to the Author:

I find the revised version of the manuscript improved and my comments incorporated sufficiently.. The quality of the manuscript suffices now.

Response: Thank you for your comments.

Reviewer: 3

Dr. Yanzhong Wang, Kings College London

Comments to the Author:

Thanks authors for their great effort to improve the manuscript. I am mostly satisfied with the response and revision. Only one minor issue remaining: the NIHSS score in hospital in table 1 doesn't look like following a normal distribution therefore need to summarise with median and IQR instead of mean and SD.

Mean±SD

Response: Thank you for your comments. Following your suggestion, we used media(IQR) instead of mean and SD for NIHSS score in table 1.