PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute ischemic stroke outcomes following mechanical thrombectomy in the elderly versus their younger counterpart: a retrospective cohort study
AUTHORS	Villwock, Mark; Singla, Amit; Padalino, David; Deshaies, Eric

VERSION 1 - REVIEW

REVIEWER	Dr Yanzhong Wang King's College London, London, UK.
REVIEW RETURNED	30-Dec-2013

GENERAL COMMENTS	This is an interesting study with major strength in its large sample size. However, there are many issues with the study. The important ones are: 1) The dataset are not designed for detailed stroke research. Many important stroke phenotypes/variables are not available such as case mix variables (NIHSS, Barthel index, Glasgow coma scale and etc.), ischemic stroke subtypes (OCSP or TOAST subtypes), functional outcomes, risk factors and co-morbidities. Without these variables, the study is very much restricted, partial and mainly descriptive. 2) Many issues with statistics, and mainly the survival analyses is not properly done. Mortality rates are not clear. Is it 1-year or 2-year survival? If it is overall survival, when it is censored? It is inappropriate to use logistic regression for overall survival. Cox proportional hazards model should be used instead. Logistic regression could be used for analysis of survival at a fixed time point such as 1 or 2 years. 3) when doing multivariate analyses, all the confounding factors should be included and detailed in the tables (tab 2 and 3) with odd ratios and etc. Again, without adjusting for appropriate confounders, the results would be doubtful and subject to many questions. 4) Double check the distribution of continuous variables. For example, length of stay is a classical skewed variable and we can't use mean and SD with it. Median and IQR should be used instead, and different stats tests and models should be used for skewed variables. 5) Stats methods could be written more clearly and properly. To have stats support from a statistician or include a professional statistician in the study would be very helpful. 6) The title of paper didn't reflect the content as it's not only about old patients over 80 years old. 7) As there are many limitation in the study, the discussion section should be improved and more comprehensive.

REVIEWER	Sharon Yeatts Department of Public Health Sciences Medical University of South Carolina Charleston, SC USA

	Statistician for the referenced IMS III trial
REVIEW RETURNED	15-Jan-2014

GENERAL COMMENTS	This manuscript describes a retrospective cohort study conducted using the Nationwide Inpatient Sample in order to assess the effect of increased age (>80 years) on outcomes following ischemic stroke treatment treated with mechanical thrombectomy. Despite the recent completion of several high-profile endovascular trials, data on this particular population is somewhat scarce, since few patients in this age range are enrolled in clinical trials. While the information contained within the manuscript is potentially important, I found the manuscript somewhat confusing with regard to its primary objective, and which results pertain to which objective. Consider these specific examples: • Abstract line 20 specifies that the hypothesis concerns the comparison of elderly subjects (>80) to their younger counterparts. But more focus is given to the effect of EMT among the elderly subset of subjects. • Page 7, line 13 specifies the comparison of subjects receiving pharmacological thrombolysis with those receiving EMT, among the subset of patients >80. The Methods section does not address the hypothesis specified in the abstract (that of those >80 to <=80, among those receiving EMT). But Table 1 is designed to facilitate the latter comparison. • Page 10, line 37 focuses on the effect of EMT in the elderly subgroup, rather than on the effect of age among those receiving EMT. • Table 2: Title refers to the "effect of mechanical thrombectomy" (which would imply a comparison of mechanical thrombectomy to something else), but it seems to refer in fact to the age comparison among those subjects receiving mechanical thrombectomy? Please clarify the manuscript with regard to what comparison is being made in what subset of the population. Statistical concerns: • The analysis model specified includes both patient and hospital level variables. Patients treated within the same hospital would share these hospital-level characteristics, and so it would seem that the independence assumption would be violated. The methods section does not specify whether this potential correlation was considered or accounted for in the model. • Length of stay was analyzed via generalized linear model. How were deaths handled in this analysis? Would a time-to-event analysis be more appropriate, since it would allow for the censoring of subjects who died in-hospital?

Minor concerns:

- In the abstract, the term "outcome measure" generally refers to a data point (mortality) than to the statistic used to describe it (odds-ratio).
- A Bonferroni correction is specified to account for multiplicity associated with four tests (presumably for four outcomes). But many more than four hypothesis tests were conducted. Table 1 alone contains 15 p-values. Perhaps it would be reasonable to use a simple 0.01 (for example) in order to nominally control the Type I error.
- Table 1: the pvalue for age is not meaningful. The age categories were determined based on age, so the average age is necessarily different.
- Tables 2 and 3: the footnote defines the OR, but "OR" is not in the table.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Dr Yanzhong Wang
This is an interesting study with major strength in its large sample size. However, there are many issues with the study. The important ones are:
1) The dataset are not designed for detailed stroke research. Many important stroke phenotypes/variables are not available such as case mix variables (NIHSS, Barthel index, Glasgow coma scale and etc.), ischemic stroke subtypes (OCSP or TOAST subtypes), functional outcomes, risk factors and co-morbidities. Without these variables, the study is very much restricted, partial and mainly descriptive.

Thank you for taking the time to review this manuscript. We agree that this is a major limitation of the database. The last paragraph of the discussion lists these limitations. Yet, the benefit of a large database study is that we can examine medical practice in a very large population without selection bias. So while the study is limited, we believe it does add value and can indicate areas worth further prospective examination.

2) Many issues with statistics, and mainly the survival analyses is not properly done. Mortality rates are not clear. Is it 1-year or 2-year survival? If it is overall survival, when it is censored? It is inappropriate to use logistic regression for overall survival. Cox proportional hazards model should be used instead. Logistic regression could be used for analysis of survival at a fixed time point such as 1 or 2 years.

Thank you for highlighting this ambiguity. Mortality in this study is limited to the acute in-patient stay. The database is anonymized and does not allow any follow-up information. As such, there is no censored mortality data. It is analyzed at a fixed time point – hospital discharge. Mortality has been changed to "inpatient mortality" throughout the manuscript to clarify this point.

3) when doing multivariate analyses, all the confounding factors should be included and detailed in the tables (tab 2 and 3) with odd ratios and etc. Again, without adjusting for appropriate confounders, the results would be doubtful and subject to many questions.

Thank you for this suggestion. The multivariate analysis has been redone. We are now only considering categorical variables associated with mortality based on the literature. The five selected variables are: elderly (> 80 yrs), thrombolysis administration, presentation to a "high-volume" stroke center, gender, and severity of illness (based on 3M's APR-DRG). All of the factors are now presented in the newly created Figure 1 (a modification of Table 2). Table 3 has been eliminated, as the focus of the paper is now solely on the comparison of the elderly and their younger counterpart.

4) Double check the distribution of continuous variables. For example, length of stay is a classical skewed variable and we can't use mean and SD with it. Median and IQR should be used instead, and different stats tests and models should be used for skewed variables.

Thank you. Table 1 has been updated to reflect this. The logistic regression and generalized linear models did not use any continuous variables. The variables were all categorical. The independent samples t-tests have been modified to Mann-Whitney U-tests.

5) Stats methods could be written more clearly and properly. To have stats support from a statistician or include a professional statistician in the study would be very helpful.

The statistics section of the Methods has been edited to be clearer in our approach. The lead author has a masters degree in mechanical engineering with training in biostatistics.

6) The title of paper didn't reflect the content as it's not only about old patients over 80 years old.

The title has been amended to better reflect the hypotheses.

7) As there are many limitation in the study, the discussion section should be improved and more comprehensive.

After rerunning the analysis, the discussion has been greatly expanded and includes three new paragraphs to provide a more comprehensive review.

Reviewer Name Sharon Yeatts

This manuscript describes a retrospective cohort study conducted using the Nationwide Inpatient Sample in order to assess the effect of increased age (>80 years) on outcomes following ischemic stroke treatment treated with mechanical thrombectomy. Despite the recent completion of several high-profile endovascular trials, data on this particular population is somewhat scarce, since few patients in this age range are enrolled in clinical trials.

While the information contained within the manuscript is potentially important, I found the manuscript somewhat confusing with regard to its primary objective, and which results pertain to which objective. Consider these specific examples:
• Abstract line 20 specifies that the hypothesis concerns the comparison of elderly subjects (>80) to their younger counterparts. But more focus is given to the effect of EMT among the elderly subset of subjects.
• Page 7, line 13 specifies the comparison of subjects receiving pharmacological thrombolysis with those receiving EMT, among the subset of patients >80. The Methods section does not address the hypothesis specified in the abstract (that of those >80 to <=80, among those receiving EMT). But Table 1 is designed to facilitate the latter comparison.
• Page 10, line 37 focuses on the effect of EMT in the elderly subgroup, rather than on the effect of age among those receiving EMT.
• Table 2: Title refers to the "effect of mechanical thrombectomy" (which would imply a comparison of mechanical thrombectomy to something else), but it seems to refer in fact to the age comparison among those subjects receiving mechanical thrombectomy?
Please clarify the manuscript with regard to what comparison is being made in what subset of the population.

Thank you for highlighting this concern. To better focus the paper and eliminate confusion, we have simplified the objectives to address only one hypothesis, dealing with the comparison of elderly subjects (>80) to their younger counterparts. Additionally, we've modified table 2 into Figure 1 and reworded the title to better reflect the contents. The primary and secondary objectives now focus on 'hard end-points' in the NIS database – mortality, charges, and length of stay. These measures are not subject to coding errors or misdocumentation. We removed discharge home as a primary objective as it is not a "hard end point". It may be influenced by the payor status and social factors, rather than a true assessment of independence and self-care. We left it in Table 1 and commented on the univariate statistics. But address the limitation in the last paragraph of the discussion.

Statistical concerns:
• The analysis model specified includes both patient and hospital level variables. Patients treated within the same hospital would share these hospital-level characteristics, and so it would seem that the independence assumption would be violated. The methods section does not specify whether this potential correlation was considered or accounted for in the model.

The multivariate analysis has been redone. We are now only considering categorical variables associated with mortality based on the literature. The five selected variables are: elderly (> 80 yrs), thrombolysis administration, presentation to a "high-volume" stroke center, gender, and severity of illness (based on 3M's APR-DRG). All variables were checked for multicollinearity and all had variation inflation factors from OLS just over 1 indicating no correlation. The generalized linear models used generalized estimating equations to produce estimators of the regression parameters and their variances (empirical variance estimation method).

• Length of stay was analyzed via generalized linear model. How were deaths handled in this analysis? Would a time-to-event analysis be more appropriate, since it would allow for the censoring of subjects who died in-hospital?

The length of hospital stay and associated hospital charges were only calculated for patients who did not die during their hospital course. This was done to eliminate the artificial shortening of these variables in cases involving a withdrawal of care. This information has been added to the second paragraph of the Methods Section.

Minor concerns:
• In the abstract, the term "outcome measure" generally refers to a data point (mortality) than to the statistic used to describe it (odds-ratio).

Thank you for this clarification. This has been edited.

• A Bonferroni correction is specified to account for multiplicity associated with four tests (presumably for four outcomes). But many more than four hypothesis tests were conducted. Table 1 alone contains 15 p-values. Perhaps it would be reasonable to use a simple 0.01 (for example) in order to nominally control the Type I error.

Thank you for this suggestion. This has been incorporated into the final sentence of the methods section.

• Table 1: the pvalue for age is not meaningful. The age categories were determined based on age, so the average age is necessarily different.

The median age is presented for each group, along with the interquartile range, to give the reader an idea of the age composition of each group. But yes, we agree that an associated P-value is not meaningful and this has been removed.

• Tables 2 and 3: the footnote defines the OR, but "OR" is not in the table.

Table 3 has been removed as the paper now focuses only on the defined primary and secondary objectives. Table 2 has been converted into Figure 1. The abbreviation for odds-ratio has been removed from the footnote.

VERSION 2 – REVIEW

REVIEWER	Dr Yanzhong Wang Division of Health and Social Care Research, King's College London, London, UK
REVIEW RETURNED	06-Feb-2014

GENERAL COMMENTS	The authors have answered all the questions to my satisfaction. The paper has been substantially improved with clear and focused research questions/outcomes, adequate statistical analyses, good presentation of study results, and comprehensive discussion of the findings. Well done and many thanks!

REVIEWER	Sharon D. Yeatts Department of Public Health Sciences Medical University of South Carolina Unblinded statistician for the referenced IMS III trial
REVIEW RETURNED	12-Feb-2014

GENERAL COMMENTS	This manuscript describes a retrospective cohort study conducted using the Nationwide Inpatient Sample in order to assess the effect of increased age (>80 years) on outcomes following ischemic stroke treatment treated with mechanical thrombectomy. Despite the recent completion of several high-profile endovascular trials, data on this particular population is somewhat scarce, since few patients in this age range are enrolled in clinical trials. The authors were responsive to previous concerns regarding the focus and flow of the manuscript. It is now clear that the manuscript aims to assess the impact of age on outcome among patients who were treated with EVM. Statistical concerns: • The analysis model now contains only patient-level characteristics, eliminating the previous concern over correlation among subjects. • The manuscript was clarified to indicate that length of hospital stay and associated hospital charges were analyzed only for patients who did not die during the hospital stay. The rationale for this is that subjects who die would have artificially shorter lengths of stay and charges. The comparison on these outcomes was not significant, which the authors note was surprising. While the rationale for excluding such cases seems reasonable, there is the potential for selection bias in this approach. Intuition suggests that the elderly are more likely to be excluded than the young, since increased age is associated with in-hospital mortality. In fact, the elderly who are not excluded may be likely to have a lesser disease severity, perhaps a lower comorbidity burden, etc than those who are excluded. This would bias the results toward the null hypothesis of no difference. This should be addressed. • In the revision, the specifics of the GEE models were made

a little more vague. What was the link function? Were the assumptions valid? How should the "exponential parameter estimates" resulting be interpreted? And why the need for the GEE model, rather than simply a generalized linear model? The outcomes are not repeated over time; since the center-level characteristics have been removed from the model, there is no dependence to account for…

Minor concerns:

- Page 9, lines 48-51: "Although …cost." is not a sentence

VERSION 2 – AUTHOR RESPONSE

Reviewer: The manuscript was clarified to indicate that length of hospital stay and associated hospital charges were analyzed only for patients who did not die during the hospital stay. The rationale for this is that subjects who die would have artificially shorter lengths of stay and charges. The comparison on these outcomes was not significant, which the authors note was surprising. While the rationale for excluding such cases seems reasonable, there is the potential for selection bias in this approach. Intuition suggests that the elderly are more likely to be excluded than the young, since increased age is associated with in-hospital mortality. In fact, the elderly who are not excluded may be likely to have a lesser disease severity, perhaps a lower comorbidity burden, etc than those who are excluded. This would bias the results toward the null hypothesis of no difference. This should be addressed.

Response: Thank you for highlighting this concern. Our intent was to eliminate the cases of comfort care with artificially low costs and length of stay. Including these cases we felt would bias the results towards a lower cost and length-of-stay for the population that receives the greatest percentage of comfort care – which in this case would be the elderly subpopulation. If we do not exclude in-hospital deaths, we observe statistically lower charges and length-of-stay for the elderly.

We have included the length-of-stay and charges for all patients (deaths included) in Table 1. The methods have been modified to reflect this additional analysis, and the discussion has been edited to reflect the impact of this bias.

Reviewer: In the revision, the specifics of the GEE models were made a little more vague. What was the link function? Were the assumptions valid? How should the "exponential parameter estimates" resulting be interpreted? And why the need for the GEE model, rather than simply a generalized linear model? The outcomes are not repeated over time; since the center-level characteristics have been removed from the model, there is no dependence to account for…

Response: Thank you for this clarification in wording. The log-link function was used along with the gamma distribution in a generalized linear model. The only assumption in this case is the independence of cases. The exponential parameter estimates are equivalent to the ratio of estimated marginal means. This has been added to the method section.

Reviewer: Page 9, lines 48-51: "Although …cost." is not a sentence

Response: Thank you, we have modified the wording of that sentence.