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.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers’ comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

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<th>TITLE (PROVISIONAL)</th>
<th>Differences in acute ischemic stroke in-hospital mortality across referral stroke hospitals in Spain: a retrospective, longitudinal observational study</th>
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<td>AUTHORS</td>
<td>Estupiñán-Romero, Francisco; Pinilla Dominguez, Jaime; Bernal-Delgado, Enrique; AtlasVPM consortium, on behalf of the ...</td>
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VERSION 1 – REVIEW

<table>
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<th>REVIEWER</th>
<th>Lindmark, Anita</th>
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<td>REVIEW RETURNED</td>
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GENERAL COMMENTS

Thank you for the opportunity to read your study on the important topic of trends in in-hospital mortality. The paper has potential but I feel that there are quite a few clarifications that need to be made, see itemized list below.
1) Title: should read “Trends in in-hospital mortality...”. Also, the study design should be included in the title.
2) Throughout you use different words for the hospitals included in the study: “referral”, “reference”, “high-profile”. There is also a brief mention of “tertiary hospitals” on p. 8. This is unnecessarily confusing for the reader. Also you do not give the definition of such hospitals until the Discussion on p. 15. You should give a clear definition early on and be consistent in the terminology used.
3) There are several instances of undefined acronyms, for example AHRQ, AIS, COPD. Look through the text and make sure that acronyms are defined upon first use.
4) Introduction:
   a) The aim of the study is not strongly motivated and few references to previous studies are given.
   b) Is there a reference for the statement that effective reperfusion therapies have been unevenly implemented across healthcare systems and care providers? Is this a
general statement or specific to Spain?
c) You mention the National Stroke Care Strategy as being important for the widespread adoption of reperfusion therapies. Why was that, were there new guidelines implemented?
5) Methods:
a) I think this section would benefit from subheadings, e.g. “Data” and “Statistical Methods”.
b) Please provide the appropriate checklist (e.g. STROBE) for the study (see the section on Reporting guidelines at https://bmjopen.bmj.com/pages/authors/#submission_guidelines)
c) Why only hospital stays <31 days? Did you exclude patients who lived > 30 days but were hospitalized > 30 days?
d) Table S3 is not very clear. Also, the tables and figures in the Online Appendix should be in the order that they are referred to in the text.
e) AtlasVPM should be briefly introduced
f) I would like to see a definition of and motivation for using Elixhauser comorbidities. Also, why is only a subset of these used in the analysis? Is there a specific subset for stroke?
g) If in-hospital mortality is the outcome of interest (p. 8), why are patients dying before arrival relevant?
h) Is “coding practice” a well-known term? If not it should be briefly explained.
i) Why are the references for ICC, MOR only included in the footnote under Table 2?
j) As I understand it there are considerations to be made both when estimating and interpreting the ICC with a binomial outcome. How have you dealt with this?
k) AIC (and BIC) are useful for model comparisons but not on their own as measures of goodness of fit.
6) Results:
a) Is there a typo on p. 10 where it says “five percentage points decrease from roughly 13%... to 10,46% in 2015” since the percentages given do not match the decrease stated?
b) Proofread the second paragraph on p. 10, there appear to be words missing in a few places.
c) I can't find a description of the missing values and their potential impact on the results anywhere.
d) It is not clear that the OR in the first paragraph on p. 12 are from the estimated model in Table S1. Also, is this model adjusted for any additional covariates beside those in the table?
e) On p. 10 you write that you use Type 1 error rate 0,001 for tests. What is the
motivation for using 95% CIs for ORs? There is not necessarily an exact correspondence between hypothesis testing and interval estimation but it would be nice to see a motivation. Also you write that lymphoma is “significantly related” to in-hospital mortality but p > 0.001. It is also unclear why you give CIs for some variables but p-values for others.
f) Is it not paradoxical that patients receiving reperfusion therapy had an increased mortality risk? Do you think this is due to unobserved confounding? I don’t see anything in the Discussion about this.
g) Consider changing “enduring” on p. 12 to a more neutral word, eg. “with”.
h) You write on p. 12 that “No differences were found in the rest of the variables (see Table S1 and S2 in the online appendix).” Do you mean that there were no statistically significant differences? All coefficients in Table 52 are statistically significant, for example. Please clarify.
i) Are the results in Tables S1 and S2 from same model? This is not clear. Also the notation used in Table S2 is not defined.
j) It is not clear if the results in Fig. 1 are from the same model as those in the first paragraph on p. 12.
k) What is the interpretation of the ICC here? Why do you only report the ICC for patients not undergoing reperfusion therapy?
l) What is the interpretation of the MOR?
m) Proofread the second sentence on p. 13. Also Prob. > χ² should be P(χ² > 0.13).

7) Discussion:
a) For clarity it would be preferable that you report all results in the Results section rather than introducing new results in the Discussion.
b) Where does the 1,5% in the 2nd paragraph on p. 14 come from?
c) 3rd paragraph on p. 14: Rather than writing “such an outcome” you should write which outcome(s) are covered in the studies referenced.
d) The 2nd paragraph on p. 15 needs to be proofread.
e) I don’t understand where I can see the results of the sensitivity analysis including travelling distance in Table S2 (p. 16)
f) In the 2nd paragraph on p. 16, do you mean to refer to figure S4 rather than S2?

8) Author contributions: There is some Spanish mixed in here.
9) “Key points” should be “Strengths and limitations of this study” (see https://bmjopen.bmj.com/pages/authors/#submission_guidelines)
GENERAL COMMENTS

1) pag 7, 25-26 ... The date given by the authors as the approval date of the National Stroke Strategy is wrong. It was approved by the Interterritorial Council of the National Health System (CISNS) on November 26, 2008, not in 2018. It was evaluated in 2013 and 2020 (we attach the latest evaluation). It is well referenced in the bibliography, page 22, 51-53

2) pag 8, 16-18 ....at least 2000 episodes, more than 15 episodes/month.... o both criteria?

3) pag 8, 57-60 y 3-10 ... "we included hospitals with stroke units defined as units with endovascular hybrid operating rooms"...

4) pag 11, 51-52 ... lymphoma is irrelevant by its low prevalence...of much more interest is AF or neoplasia under treatment and, from another point of view, bleeding as a history or complication of reperfusion therapies.

5) pag 13, 33-35 ... For a clinical neurologist, the explanation is clear: large and small vessel infarcts are put in the same bag; those with small vessels are not treated with reperfusion therapy and have very low mortality.

6) pag 15, 3-8 ... The reason, not mentioned, is that as hospital networks were organized, referral hospitals began to receive patients with large-vessel infarction from other hospitals, which are more serious and have higher mortality.

7) pag 15, 13-14 ... there is no mention of the role of the Stroke Units, which were extended and at the same period and carry a better prognosis.

In my opinion: To establish some kind of relationship between treatment in the acute phase and the outcome in terms of mortality, it would possibly have been more correct to use mortality on the first admission and not just 30-day in-hospital mortality.

Finally, the increase and extension of the use of reperfusion therapies have coincided in time with the increase in Stroke Units, stroke code, telestroke, hierarchization of referrals between hospitals. We must be very careful and not establish a cause-effect relationship between a greater number of reperusions and a decrease in mortality in that period. Other improvements in stroke care could explain part of the observed data. This should be reflected both in the conclusions and in the description of the limitations of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 [PLEASE SEE ATTACHED FILE ‘Review comments 221024’ FOR COMMENTS FROM REVIEWER 1]

Dr. Anita Lindmark, Umea Universitet Handelshogskolan

Comments to the Author:
Response: Thank you for the opportunity to read your study on the important topic of trends in in-hospital mortality. The paper has potential but I feel that there are quite a few clarifications that need to be made, see itemized list below.

Comment: Title: should read “Trends in in-hospital mortality...”. Also, the study design should be included in the title.
Response: Thank you for your comment. We have changed as Differences in acute ischemic stroke in-hospital mortality across referral stroke hospitals in Spain: an observational retrospective longitudinal study

Comment: Throughout you use different words for the hospitals included in the study: “referral”, "reference", “high-profile”. There is also a brief mention of "tertiary hospitals" on p. 8. This is unnecessarily confusing for the reader.
Response: Thank you for your comment. We have harmonized all terms regarding the hospitals studied as ‘referral stroke hospitals’ following a comment from Reviewer 2.

Comment: Also, you do not give the definition of such hospitals until the Discussion on p. 15. You should give a clear definition early on and be consistent in the terminology used.
Response: Thank you for your comment. We realized that the definition of hospitals considered for the analysis was scattered in different parts of the methodology leading to confusion. We have updated the Methods section to provide a clearer definition of what we considered a referral stroke hospital in the specification of the study population.

Population and setting
From all the hospital admissions in the study period, we first selected those episodes with an admission diagnosis of acute ischemic stroke (662,997 episodes). Then, we defined referral stroke hospitals as those capable of performing EMT, confirmed through the identification of EMT procedures performed in the last year of analysis (2015).

From those episodes treated in hospitals identified as referral stroke hospitals, we kept only the episodes with a stay shorter than 30 days, restricting the observation of case-fatalities to those more likely to be associated to the medical intervention on stroke (i.e., deaths in longer stays are more likely associated with nosocomial infections or the underlying health status of the patient). Finally, to reduce extra-heterogeneity, which may end up producing an overestimation of the intra-class coefficient, we restricted the study to those referral stroke hospitals with at least 2,000 ischemic stroke episodes recorded throughout the study period. The final study population included 196,099 episodes from 37 referral stroke hospitals (see flowchart as Figure S1 in the online appendix).

Comment: There are several instances of undefined acronyms, for example AHRQ, AIS, COPD. Look through the text and make sure that acronyms are defined upon first use.
Response: Thank you for your comment. We have reviewed the manuscript and the supplements and defined the acronyms upon first use as suggested.

Agency for Healthcare Research and Quality’s (AHRQ) (page 7)
Acute ischemic stroke (AIS) (page 3)
Chronic obstructive pulmonary disease (COPD) (page 10)

Comment: Introduction: a) The aim of the study is not strongly motivated and few references to previous studies are given.
Response: Thank you for your comment. We have review and updated the Introduction further clarifying the aim of the study adding several relevant references.
Comment: Introduction: b) Is there a reference for the statement that effective reperfusion therapies have been unevenly implemented across healthcare systems and care providers? Is this a general statement or specific to Spain?
Response: Thank you for your comment. We have reviewed the statement and added relevant references to the uneven implementation of reperfusion therapies across healthcare systems. However, since their introduction, effective reperfusion therapies, such as intravenous fibrinolysis (IVF) or endovascular mechanical thrombectomy (EMT) [2][3] have been unevenly implemented across health systems and healthcare providers depending on effective access to fibrinolysis drugs, lack of specialized resources (e.g., stroke units, endovascular operating theatres), effective access to urgent CT-scan imaging, or limited coverage of neurointerventional surgeons.

Comment: Introduction: c) You mention the National Stroke Care Strategy as being important for the widespread adoption of reperfusion therapies. Why was that, were there new guidelines implemented?
Response: We have added a brief paragraph explaining why the National Stroke Care Strategy lead the widespread adoption of reperfusion therapies. The National Stroke Care Strategy aimed to harmonized stroke care across Autonomous Communities (ACs), covering all the services to be provided in the stroke patients’ life-cycle (primary and secondary prevention of stroke, care in the acute phase, rehabilitation and return to normal life, as well as training and research). Notably, in acute care, the Strategy incepted the Stroke Code, which is common to all the AC, including clinical practice guidelines and protocols, the organization of care pathways, the required resources for effective coverage and provision (tele-stroke programs, stroke units, neurosonology resources, diffusion and perfusion magnetic resonance and neurovascular interventions). The Stroke Code set up a hierarchy of stroke hospitals, with a smaller group of them acting as referral stroke hospitals for endovascular interventions [X].


Comment: Methods: a) I think this section would benefit from subheadings, e.g. “Data” and “Statistical Methods”.
Response: Thank you for your comment. We have added subheadings to the Methods section (i.e., Design, Population and setting, Main endpoints, Variables, Sources of data, Bias control, Analysis, and Patient and public involvement).

Comment: Methods: b) Please provide the appropriate checklist (e.g. STROBE) for the study (see the section on Reporting guidelines)
Response: The STROBE checklist was initially provided as supplementary materials upon manuscript submission. We have resubmitted a STROBE checklist with updated references to the revised manuscript as supplementary materials.

Comment: Methods: c) Why only hospital stays <31 days? Did you exclude patients who lived > 30 days but were hospitalized > 30 days?
Response: Yes, although there is no a rule on a particular timeframe, studies on hospital performance and mortality use stays shorter than 30 days to focus on deaths that are more likely related to medical intervention or acute inpatient care. Deaths in longer stays are more likely associated with nosocomial infections or the underlying health status of the patient. We added a paragraph to the ‘Population and setting’ subheading within Methods to clarify this point. From those episodes treated in hospitals identified as referral stroke hospitals, we kept only the episodes with a stay shorter than 30 days, restricting the observation of case-fatalties to those more likely to be associated to the medical intervention on stroke (i.e., deaths in longer stays are more likely associated with nosocomial infections or the underlying health status of the patient).
Comment: Methods: d) Table S3 is not very clear. Also, the tables and figures in the Online Appendix should be in the order that they are referred to in the text.
Response: Thank you for your noticing. This was not a table indeed. We have completely redone Table S3. We have taken advantage and reordered tables and figures in the Online Appendix to follow the order in which they are referred in the text.

Comment: Methods: e) AtlasVPM should be briefly introduced
Response: We have added a paragraph briefly introducing Atlas VPM in the ‘Sources of data’ subheading in Methods.

Atlas VPM reuses routine data mainly from electronic records from hospital admissions and primary care visits for the identification and selection of cases (e.g. surgical procedures of interest, specific diseases, quality and safety events), the analysis of clinical attributes of the patient (e.g. comorbidities, concurrent surgery), the analysis of administrative features worth to collect (e.g. admission and discharge data, date of surgery), and for the identification of the place of residence (i.e. primary, health care or grand area where the patient resides). Atlas VPM implies a linkage and exchange process with the 17 Departments of Health of the Spanish regions sharing a research agenda assessing unwarranted variations in medical practice and translating research outcomes into profiling and benchmarking tools meant to facilitate clinical and policy decision-making. Atlas VPM [X].

https://doi.org/10.1007/s43999-022-00005-3

Comment: Methods: f) I would like to see a definition of and motivation for using Elixhauser comorbidities. Also why is only a subset of these used in the analysis? Is there a specific subset for stroke?
Response: We used the list of Elixhauser comorbidities as a fairly used list of patient comorbidities with standardized definitions that are used to characterize patients underlying burden of disease and provide risk-adjusted estimates when comparing care providers. It may be used as an index (providing an overarching measure) or as an independent list, then, selecting those comorbidities that are shown to be associated with the outcome of interest. This is the approach that we followed – as suggested here Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998; 36:8–27 pmid:9431328

So, the list of variables comes out of the modelling of the association of each of the Elixhauser’s comorbidities and the 30-day mortality along the study period. Those retained in the model (significantly associated for an alfa error of 5%) are the ones that appear in the results of the paper. We may have misled the reviewer with the statement that we had used a stroke-specific Elixhauser’s approach (as we have used in other projects). On the contrary, in this case, we have used a data-driven approach.

With a view to elicit the potential effect of the hospital of treatment in the risk of death regardless the differences in the patients attended, patients’ age, sex, and the list of Elixhauser’s comorbidities were used in the risk-adjustment modeling. [X] [X].


Comment: Methods: g) If in-hospital mortality is the outcome of interest (p. 8), why are patients dying before arrival relevant?
Response: Thank you for your question. Our main aim with this study is measuring differences in adjusted in-hospital mortality due to ischemic stroke between referral stroke hospitals during the study period.

However, we have to recognize alternative explanation to our main finding, which is the between hospitals differences in mortality. One of the reasons, for a priori worse health outcome may be a
differential access to reperfusion therapies due to access barriers, implying higher outpatient mortality and increasing the risk of selection bias (those arriving are less likely to die). In order to make more robust the hospital comparison we need to estimate whether access was different across hospital. We assessed it using a complementary model considering the travelling distance from the centroid of the patients’ location of residence to the nearest referral stroke hospital as a sensitivity analysis. We have discussed this sensitivity analysis in the Discussion section. This comment has not translated in any change in the main text.

Comment: Methods: h) Is “coding practice” a well-known term? If not it should be briefly explained.
Response: Thank you for your comment. “Coding practice(s)” is a well-known and commonly using term in the area of Health Services research using administrative data or claims data as the codification of diagnoses and procedures using international standards (i.e., ICD-10) might be driven by incentives (i.e., in case of claims with a reimbursement purpose), lack of resources for codification or even healthcare provider culture. A brief search in Pubmed with the string “coding practices” directly renders 220 mentions in articles since 2010. This comment has not translated in any change in the main text.

Comment: Methods: i) Why are the references for ICC, MOR only included in the footnote under Table 2?
Response: Thank you for noting the error. We have included the references when explaining the use of the ICC and MOR in the ‘Analysis’ subheading in Methods.

Comment: Methods: j) As I understand it, there are considerations to be made both when estimating and interpreting the ICC with a binomial outcome. How have you dealt with this?
Response: We use ICC as a measure of the variance explained by hospital as independent random effects, after adjusting by all patient-level covariates, and complemented by the MORs calculated for the interaction between the hospital and having received reperfusion therapy. In our case, ICC provides a magnitude of the variance explained by the hospital but more importantly an instrument to test whether the hospital random effect is statistically significant thus pointing at significant differences in hospital performance. We wonder if your considerations on the interpretation of the ICC with binomial outcomes derive from its use in sample size calculation in clustered trials designs. In this case, ICC is known to be associated with the prevalence of the binary outcome, which discourages its use. Please, if we have not replied properly to this point, just let us know.

Comment: Methods: k) AIC (and BIC) are useful for model comparisons but not on their own as measures of goodness of fit.
Response: Thank you for noting this inconsistency. As you point out, we used AIC to select the final model whose results are shown in the paper, and the area under the receiver operating characteristic (ROC) curve to assess the goodness of fit of this model. We have clarified this in the text accordingly. Finally, we considered the receiver operating characteristic (ROC) curve for the estimation of the goodness of fit of the model. The decision on the final model presented in the results was taken according to the Akaike information criteria (AIC)

Comment: Results: a) Is there a typo on p. 10 where it says “five percentage points decrease from roughly 13% ... to 10,46% in 2015” since the percentages given do not match the decrease stated?
Response: Thank you for commenting on the typo. We had dragged the number from a previous version where we used a relative proportional (to the population) reduction. We have corrected the sentence. Nevertheless, in-hospital mortality rates observed an overall decrease from roughly 13% of in-hospital mortality in 2003 to 10.46% in 2015 (see figure S2 in the online appendix).
Comment: Results: b) Proofread the second paragraph on p. 10, there appear to be words missing in a few places.
Response: Thank you for your comment. We have proofread the paragraph to maintain consistency. Regarding patients' profiles, the age and sex kept somewhat similar, with patients 74 years old and 46% female, and an increased number of comorbidities registered, notably renal failure, metastatic cancers, coagulopathy and electrolytic disorders.

Comment: Results: c) I can't find a description of the missing values and their potential impact on the results anywhere.
Response: Thank you for your comment. We did not include an analysis of the missing data within the scope of the study. As we used administrative data produced by the Departments of Health of the Regional governments upon the mandate of the Ministry of Health via national law, missing data although possible is usually negligible.
Our study mainly relies on the identification of the ischemic stroke admission as registered in the diagnosis of admission, age, sex and death and dates. All of them are mandatory fields, so they have to be properly filled out. Health Departments performed quality checks to reduce information losses. In addition, Atlas VPM has in addition a quality assurance process for processing these data including feedback to the Health Authorities producing the original data.
We have included a reference of this quality checks in the methods section as:
Notably, as part of its data quality assurance methodology, Atlas VPM conducts regular (once a year) quality checks to, for example, avoid over time coding variations, correct semantic and syntactic inconsistencies in the variables, or reallocate admission episodes to the place of residence if there are changes in geolocation of administrative areas or hospital providers.

Comment: Results: d) It is not clear that the OR in the first paragraph on p. 12 are from the estimated model in Table S1. Also, is this model adjusted for any additional covariates beside those in the table?
Response: Thank you for your comments. We have reordered the tables to follow the order of presentation in the manuscript. Table S2 presents the actual output of the model -estimates and standard deviation of the estimates for each covariate, as well as p-value < 0.001.
In turn, we use OR in the main text as it provides a more intuitive interpretation of the results in terms of risk. OR derives directly from the exponentiation of the beta coefficients (estimates) in the Table S2.

Comment: Results: e) On p. 10 you write that you use Type 1 error rate 0,001 for tests. What is the motivation for using 95% CIs for ORs? There is not necessarily an exact correspondence between hypothesis testing and interval estimation but it would be nice to see a motivation.
Response: Thank you for raising this point. The rationale behind using p<0.001 as the threshold in the model in Table S2 and Confidence Interval 95% lays on the different use of the information provided. We may agree that it is rather confusing though.
In the case of the p values 0.001, given the large numbers in our study, it is likely to find spurious associations between the co-variates and the outcome. To reduce the risk of spurious association we required our model to be more restrictive in the acceptance of association. So, just those variables with such a level of association were accepted as predictors.
However, when informing about the risks (ORs), we just used those variables observed to be strongly associated; in this case, providing CI using the same standard error for a less restrictive alfa error.
Given the large numbers in this study, we performed all hypothesis tests using a Type 1 error rate of 0.001

Comment: Also you write that lymphoma is “significantly related” to in-hospital mortality but p> 0.001. It is also unclear why you give CIs for some variables but p-values for others.
Response: Thank you for noticing this is actually a mistake. As explained in the previous comment just those showing significance at 0.001 were included in the description of the results.

Comment: Results: f) Is it not paradoxical that patients receiving reperfusion therapy had an increased mortality risk? Do you think this is due to unobserved confounding? I don't see anything in the Discussion about this.
Response: Thank you for your insightful comment.
It may seem paradoxical but it is consistent with the criteria of indication of the reperfusion therapy (larger vessels vs. smaller vessels) and also with the adjustment of indications over the years. There is also an expected differential effect over the years depending on learning curves, services reorganization and the implementation new technologies.
Our hypothesis is that those patients more likely to receive therapy are also those more likely to have a higher baseline risk of death. The OR estimate confirms this statement when reperfusion status is introduced in the model as a fixed effect. In addition, when including the interaction term, between the utilization trend of reperfusion and the hospital of treatment (as a random slope) the difference in MOR between those non-treated and those treated became non-statistically significant reflecting that the context (hospital) where the patient is treated also matters.
We have not made any change with regard to this question in the text. However, as per another comment by reviewer 2, we have included a general comment in the discussion that may partially address you concern on unobserved confounding in this study. If you feel that we have not adequately address your question, please let us know.
The results of our study are conditioned to the information registered in the administrative records. This issue may entail a limitation as we may have not been able to adjust for some residual differences in patients’ severity across hospitals. Limiting the comparison to those referral stroke hospitals, likely to be treating similar case-mix of patients, as well as the large numbers in this study, reduces the risk of residual confounding.

Comment: Results: g) Consider changing "enduring" on p. 12 to a more neutral word, e.g. “with”.
Response: Thank you for your thoughtful comment. We have changed the term ‘enduring’ for a more neutral ‘with’.
Likewise, patients with metastatic cancer (OR=5.10, CI95% 4.66 to 5.58), fluid and electrolyte disorders (OR 2.43; CI95% 2.25 to 2.62), (…)

Comment: Results: h) You write on p. 12 that "No differences were found in the rest of the variables (see Table S1 and S2 in the online appendix)." Do you mean that there were no statistically significant differences? All coefficients in Table S2 are statistically significant, for example. Please clarify.
Response: Thank you for this comment. The reference to Table S1 is a mistake dragged on from a previous draft. Sorry for that.
In page 12, we do refer to variables in Table S2. In Table S2, we provide the information on the fitted smooth terms, which are not variables as such. We have corrected accordingly.
No differences were found in the rest of the variables (see Table S2 in the online appendix). All fitted smooth terms, including the interaction terms, introduced in the model were statistically significant (see Table S2 in the online appendix).

Comment: Results: i) Are the results in Tables S1 and S2 from same model? This is not clear. Also the notation used in Table S2 is not defined.
Response: Yes, results on both former tables S1 and S2 are direct outputs of the model. Differences in the specification of the results are due to the different nature of the covariates within the GAMM. Those variables traditionally introduced as categorical or binary variables can produce an OR ratio via exponentiation of the resulting beta coefficients (estimates), whether additive terms introduced as fitted smooth functions can only produce information on their effective degrees of freedom accounting for the grade of the polynomial used to fit the interaction of that term with the estimated outcome.
We have updated the numeration of the table as S2 (A) and (B) and added this note in the Online Supplementary Material as note after Table S2. Tables S2 (A) and (B) are direct outputs of the final GAMM model. Table S2 (A) shows the results for the parametric coefficients, while Table S2 (B) shows the outputs for those fitted smooth terms introduced in the same model. While parametric coefficients (variables traditionally introduced as categorical or binary variables in a regression) are reported using their beta coefficients (and standard errors), fitted smooth terms can only be reported using their effective degrees of freedom for the polynomial grade used to fit their interaction with the estimated outcome (Edf | Ref.df).

Comment: Results: j) It is not clear if the results in Fig. 1 are from the same model as those in the first paragraph on p. 12.
Response: Thank you for your comment. Figure 1 is produced from the same model as results in the first paragraph. Figure 1 corresponds to the result of the fitted smoothed function for the in-hospital mortality associated with having received reperfusion therapy or not along the study period. Fitted smoothed functions are produced for those covariates fitted in the GAMM using thin-plate splines. For those variables, an OR only can be produced as a measure of the difference in log(RR) across the fitted smooth function, for instance, before and after the year 2008, thus we do only present the figure with a note facilitating its interpretation.

Comment: Results: k) What is the interpretation of the ICC here? Why do you only report the ICC for patients not undergoing reperfusion therapy?
Response: The ICC informs of the proportion of total variation in the outcome that can be explained by the hospital. We have included a paragraph explaining ICC and MOR in the methods (see below). Thank you for noticing. We unintentionally omitted the reference to ICC in patients undergoing reperfusion therapy. In this version, it has been included in the abstract and in the results section.

Comment: Results: l) What is the interpretation of the MOR?
Response: The MOR is defined as the median value of the distribution of odds ratios (OR) obtained when randomly picking two patients with the same covariate values from two hospitals with a different underlying risk of an event of interest, and comparing the one from the hospital with the highest risk to the one from the hospital with the lowest risk. In simple terms, the MOR can be interpreted as the median increased odds of reporting the outcome if a similar patient (i.e. receiving reperfusion therapy or not) is treated in another hospital with a higher risk.

Comment: Results: m) Proofread the second sentence on p. 13. Also Prob. > \chi^2 should be (\chi^2 > 0.13).
Response: Thank you for noting and commenting on the typo. We have changed the sentence to provide only the Prob. > \chi^2 = 0.7178 or p-value 0.7178.

Comment: Discussion: a) For clarity it would be preferable that you report all results in the Results section rather than introducing new results in the Discussion.
Response: Thank you for your comment. We just highlighted the MOR figures in a way that is consistent with new drafting of the results section. Except in the discussion of the alternative explanations provided in the sensitivity analysis no new results are provided. We have redrafted as followed:

Our study shows that referral stroke hospitals explained part of the variation in AIS adjusted in-hospital mortality, after patients' differences and time effects were adjusted, in both patients underlying reperfusion therapy and those who did not. The risk of dying is estimated to be 31% lower in the best-performing hospitals in patients not receiving reperfusion therapies, and 46% lower in those patients receiving reperfusion therapies.

Comment: Discussion: b) Where does the 1.5% in the 2nd paragraph on p. 14 come from?
Response: This figure interpreted the ICC provided in the results. In the new drafting we just had held the interpretation of the MOR. See redrafting in previous comment.

Comment: Discussion: c) 3rd paragraph on p. 14: Rather than writing "such an outcome" you should write which outcome(s) are covered in the studies referenced.
Response: Thank you for your comment. We have changed the expression "such an outcome" for "the evolution of acute ischemic stroke mortality rates".

The overall reduction in the rates observed in our study is consistent with the evolution of acute ischemic stroke hospital mortality rates in different international studies on the matter, such as the global stroke statistics at the national level [16], (…)

Comment: Discussion: d) The 2nd paragraph on p. 15 needs to be proofread.
Response: We have redrafted as follows:
In turn, the statistically significant differences in adjusted AIS in-hospital mortality rates across hospitals (Figure 2) may be explained by the uneven adoption of intravenous fibrinolysis across hospitals, the early adoption of endovascular mechanical thrombectomy in a very small set of referral hospitals [22], different learning curves and organizational factors that affected differentially the implementation of the Stroke Code.

Comment: Discussion: e) I don’t understand where I can see the results of the sensitivity analysis including travelling distance in Table S2 (p. 16)
Response: The results of the sensitivity analysis are presented only as box plots in Figure S2. Although we have not included any estimate as in Table S2 – the figure includes the estimation of the difference. We have added an explanation of this difference as a note. See below:

N.B. Figure S2 offers direct comparison between the distributions of the hospital level random effects parameters. The difference is tested using a paired T-test on the means of both distributions. Figure S2 (A) compares the final model used to estimate AIS 30-day in-hospital mortality (Model.without.distance) with the same model adding a parameter considering the traveling distance from patients' location to the nearest stroke referral hospital (Model.with.distance). Figure S2 (B) compares the final model (Full.model) with the same model without introducing the Elixhauser variables (Model.without.Elixhauser.variables). The comparison of the distribution of the hospital level random effect parameters is shown segmented between those patients not receiving reperfusion therapy (left) and those receiving reperfusion therapy (right) to facilitate the interpretation of the interaction term between hospital of treatment and the trend of utilization of reperfusion therapy.

If the reviewer requires further details of the models, please just let us know.

Comment: Discussion: f) In the 2nd paragraph on p. 16, do you mean to refer to figure S4 rather than S2?
Response: Thank you for noticing. This is mistake. We did indeed refer to the former figure S4, now figure S2.
Comment: Author contributions: There is some Spanish mixed in here.
Response: Thank you for noting the typo.
EBD y FER conceptualization and design. FER prepared the dataset. JP implemented the analytical scripts and run the analyses. FER and EBD drafted the paper. All authors approved the manuscript.

Comment: “Key points” should be “Strengths and limitations of this study”.
Response: Thank you for your comment. We have deleted the ‘Key points’ and added the ‘Strengths and limitations of the study’ immediately below the abstract as instructed by the editor.

Dr. Javier Marta Moreno, Hospital Universitario Miguel Servet, Hospital Universitario Miguel Servet

Comments to the Author:
1) pag 7, 25-26 ... The date given by the authors as the approval date of the National Stroke Strategy is wrong. It was approved by the Interterritorial Council of the National Health System (CISNS) on November 26, 2008, not in 2018. It was evaluated in 2013 and 2020 (we attach the latest evaluation). It is well referenced in the bibliography, page 22, 51-53
Response: Thank you for noting – the reviewer is correct. 2018 was a typo that is already fixed.

2) pag 8, 16-18 ....at least 2000 episodes, more than 15 episodes/month.... o both criteria?
Response: Thank you for the comment. We have redrafted the whole population and setting subsection as per a comment by the other reviewer. The current reads this way
Finally, to reduce extra-heterogeneity, which may end up producing an overestimation of the intra-class coefficient, we restricted the study to those referral stroke hospitals with at least 2,000 ischemic stroke episodes recorded throughout the study period.

3) pag 8, 57-60 y 3-10 ... “we included hospitals with stroke units defined as units with endovascular hybrid operating rooms”... Stroke Units is a well-defined facility: A specialized ward designated for acute stroke patients with continuous monitoring of vital parameters, with a multidisciplinary team approach including a trained neurologist and specialized nursing staff. An endovascular operating room is not included in the definition. It is probably more correct to speak of hospitals capable of performing thrombectomies in acute strokes, comprehensive stroke centers (American Heart-Stroke Association, term), Stroke Center (European Stroke Organization, term), or probably the most correct in this period (2008-15 ) is to call them referral stroke hospitals.
Response: Thank you for the suggestion of using referral stroke hospitals all across the text.
We have redrafted in several places to address your comment and the other reviewer’s comment, to provide a better sense of the National Strategy. So

In the introduction, we have added
The National Stroke Care Strategy aimed to harmonized stroke care across Autonomous Communities (ACs), covering all the services to be provided in the stroke patients’ life-cycle (primary and secondary prevention of stroke, care in the acute phase, rehabilitation and return to normal life, as well as training and research). Notably, in acute care, the Strategy incepted the Stroke Code, which is common to all the AC, including clinical practice guidelines and protocols, the organization of care pathways, the required resources for effective coverage and provision (tele-stroke programs, stroke units, neurosonology resources, diffusion and perfusion magnetic resonance and
neurovascular interventions). The Stroke Code set up a hierarchy of stroke hospitals, with a smaller group of them acting as referral stroke hospitals for endovascular interventions. In the methods section, we have clarified the operational definition of a referral stroke hospital, as here:

From all the hospital admissions in the study period, we first selected those episodes with an admission diagnosis of acute ischemic stroke (662,997 episodes). Then, we defined referral stroke hospitals as those capable of performing EMT, confirmed through the identification of EMT procedures performed in the last year of analysis (2015).

4) pag 11, 51-52 ... lymphoma is irrelevant by its low prevalence...of much more interest is AF or neoplasia under treatment and, from another point of view, bleeding as a history or complication of reperfusion therapies.

Response: We used the list of Elixhauser comorbidities as a fairly used list of patient comorbidities with standardized definitions that are used to characterize patients underlying burden of disease and provide risk-adjusted estimates when comparing care providers. It may be used as an index (providing an overarching measure) or as an independent list, then, selecting those comorbidities that are shown to be associated with the outcome of interest. This is the approach that we followed – as suggested here Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998; 36:8–27 pmid:9431328

So, the list of variables comes out of the modelling of the association of each of the Elixhauser’s comorbidities and the 30-day mortality along the study period. Those retained in the model (significantly associated for an alfa error of 5%) are the ones that appear in the results of the paper. We may have misled the reviewer with the statement that we have used when explaining the Elixhauser’s approach (as we have used in other projects) as it was explained as disease-specific in reference to the selection of comorbidities. On the contrary, in this case, we have used a data-driven approach.

We agree with the reviewer of the negligible relevance of lymphoma as a predictor of death. Also agree on the fact that there may be other predictor factors not included in the modelling that may lead to some residual confounding -this is pointed out as one of the limitations as follows:

The results of our study are conditioned to the information registered in the administrative records. This may entail a limitation as we may have not been able to adjust for some residual differences in patients’ severity across hospitals. Although, limiting the comparison to the referral stroke hospitals that are likely treating similar case-mix of patients may have reduced the risk of residual confounding, we may have not entirely ruled out some differences in patients’ severity. However, we have also to recognize that having used the universe of admissions from hospitals that admit more than 2,000 patients a year, the patients’ risk will tend to distribute homogeneously – similar number of patients with AF, neoplasia in treatment, etc. or mix of small vs large vessels in the assisted population etc. So, even though residual confounding may exist, after adjusting for age, sex and a number of comorbidities, it is unlikely that this explains the variation observed between hospitals.

5) pag 13, 33-35 ... For a clinical neurologist, the explanation is clear: large and small vessel infarcts are put in the same bag; those with small vessels are not treated with reperfusion therapy and have very low mortality.

Response: We do agree with the reviewer. This is consistent with what we have found - We add here the response to reviewer 1 with regard to may be a paradoxical effect.

Our hypothesis is that those patients more likely to receive therapy are also those more likely to have a higher baseline risk of death. The OR estimate confirms this statement when reperfusion status is introduced in the model as a fixed effect. In addition, when including the interaction term, between the
utilization trend of reperfusion and the hospital of treatment (as a random slope) the difference in MOR between is also greater in those treated reflecting that the context (hospital) where the patient is treated also matters.

We have not made any change in the text as our inference is on the hospitals of treatment, and we do expect, having a similar case-mix in those referral stroke hospitals, particularly with large numbers.

6) pag 15, 3-8 ...The reason, not mentioned, is that as hospital networks were organized, referral hospitals began to receive patients with large-vessel infarction from other hospitals, which are more serious and have higher mortality.

Response: This is true, but the underlying question is on whether this phenomenon, transfers out for mechanical reperfusion is different across referral hospitals. We do not this information as such, but we do have as a proxy the way we have modelled the hospital effect – being a random effect, we are covering unobserved latent factors – for example whether there is a stroke unit and for how long, or whether the distribution of hospitals in the area matter in term of the care pathways.

We have redrafted the paragraph to accommodate this suggestion, as

In turn, the statistically significant differences in adjusted AIS in-hospital mortality rates across hospitals (Figure 2) may be explained by the uneven adoption of intravenous fibrinolysis across hospitals, the early adoption of endovascular mechanical thrombectomy in a very small set of referral hospitals [22], different learning curves. organizational factors that affected differentially the implementation of the Stroke Code (for example, the existence of stroke units) and finally, some unobserved latent factors as uneven patterns of patients’ transfers from secondary hospitals to the referral stroke hospitals.

7) pag 15, 13-14 ... there is no mention of the role of the Stroke Units, which were extended and at the same period and carry a better prognosis.

Response: Please, see our previous reply.

In my opinion: To establish some kind of relationship between treatment in the acute phase and the outcome in terms of mortality, it would possibly have been more correct to use mortality on the first admission and not just 30-day in-hospital mortality.

Response: What we have used is a normative definition by ARQH. What this definition means is exactly what the reviewer suggest.

Finally, the increase and extension of the use of reperfusion therapies have coincided in time with the increase in Stroke Units, stroke code, telestroke, hierarchization of referrals between hospitals. We must be very careful and not establish a cause-effect relationship between a greater number of reperusions and a decrease in mortality in that period. Other improvements in stroke care could explain part of the observed data.

This should be reflected both in the conclusions and in the description of the limitations of the study.

Response: We do fully agree with the reviewer’s comment. We have double-checked the text just in case an expression on causality was inadvertently used.

The type of study and the type of inference that we aim was not causal. Consequently, any message conveyed in the results and discussion provides a sense of association not causation.

We have redrafted the conclusion as follows

Overall in-hospital mortality rates within 30-days after admission decreased between 2003 and 2015, coincidently with the widespread adoption of reperfusion therapies within referral hospitals in Spain. However, over the years, between-hospital variations in mortality persisted beyond differences in the patients’ treated.
COI statements:

Reviewer: 1
Competing interests of Reviewer: No competing interests.

Reviewer: 2
Competing interests of Reviewer: No.

VERSION 2 – REVIEW

| REVIEWER | Lindmark, Anita  
|          | Umea Universitet Handelshogskolan, Department of Statistics |
| REVIEW RETURNED | 06-Mar-2023 |

GENERAL COMMENTS

Thank you for addressing many of my questions and concerns. There are however remaining concerns, mainly related to statistical methods, reproducibility of your results and language. Below I have outlined the remaining concerns in relation to my previous points:

Methods:

f) I asked “I would like to see a definition of and motivation for using Elixhauser comorbidities. Also, why is only a subset of these used in the analysis? Is there a specific subset for stroke?”
The other reviewer also had questions about this and in your reply to both of us you wrote that you had used a data driven approach to select which of the Elixhauser comorbidities to include in the analyses. This is very much relevant information, why do you not mention this anywhere in the article?

g) I asked “If in-hospital mortality is the outcome of interest (p. 8), why are patients dying before arrival relevant?”
I think I better understand why patients dying before arrival are relevant. However, you write on p. 10 that “To estimate potential losses, we compared our in-hospital mortality with the case fatality rates for ischemic stroke in Spain, as reported by the Spanish Ministry of Health in the OECD Health Statistics 2020 [19]”. The only reference I can find to this is in the discussion where you write that “following the OECD report on case fatality due to AIS in Spain [19], most case fatalities due to AIS were reported in-hospital and within the first days of admission.” It is unclear to me if this is the comparison and what the results were?
i) I asked “As I understand it there are considerations to be made both when
estimating and interpreting the ICC with a binomial outcome. How have you dealt with this?"

You replied that you interpret the ICC as “a measure of the variance measured by the variance explained by hospital…” and that the concerns about ICC with a binary outcome are when using the ICC to calculate sample size in cluster trials. However, in the paper by Merlo et al. (2006) http://dx.doi.org/10.1136/jech.2004.029454 (which you also cite) issues are raised about the ICC with precisely the interpretation that you use. So, my question remains.

Results:

h) I asked “You write on p. 12 that "No differences were found in the rest of the variables (see Table S1 and S2 in the online appendix)." Do you mean that there were no statistically significant differences? All coefficients in Table S2 are statistically significant, for example. Please clarify.” In your reply you missed my point which is that the statement “No differences were found in the rest of the variables” is very imprecise. What do you mean by “no differences”? Do you mean no statistically significant differences? Or no differences whatsoever? Table S2 only contains statistically significant differences so you must either use a different definition of “no differences” or be referring to information not seen in the table. This needs to be clarified.

i) I asked “What is the interpretation of the MOR?” In your reply to me you give a correct interpretation of the MOR, however in all the places in the text where you define the MOR you write that it is estimated as the median value of the odds ratio between the hospital with the highest risk and the hospital with the lowest risk, which is not correct. Since this is one of the main measures used in your study this needs to be addressed!

m) I wrote “Proofread the second sentence on p. 13. Also Prob. > χ^2 should be P(χ^2 > 0.13).” You removed the Prob. > χ^2 and only write the p-value. It is unclear which test the p-value is from, is it a test of the interaction parameter?

Author contributions: There is still some Spanish mixed in here. Overall, I would recommend that you consider using a language editing service to proofread your text as there are still incomplete sentences in some places.

Additional comment:
• The phrasing “AIS adjusted in-hospital mortality” used in the Results section is unclear. It
sounds as if it is in-hospital mortality adjusted for AIS, rather than in-hospital mortality after AIS adjusted for covariates.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1 [PLEASE SEE ATTACHED FILE ‘Review comments 221024’ FOR COMMENTS FROM REVIEWER 1]

Dr. Anita Lindmark, Umea Universitet Handelshogskolan

Comments to the Author:

Please see comments in the attached file.

Comment: Methods:

f) I asked “I would like to see a definition of and motivation for using Elixhauser comorbidities. Also, why is only a subset of these used in the analysis? Is there a specific subset for stroke?”

The other reviewer also had questions about this and in your reply to both of us you wrote that you had used a data driven approach to select which of the Elixhauser comorbidities to include in the analyses. This is very much relevant information, why do you not mention this anywhere in the article?

Response: Thank you for your comment. We updated the Methods section as below:

Eliciting the potential effect of the hospital of treatment on the risk of death regardless the differences in the patients attended, required risk adjustment. Patients’ age, sex, and the list of Elixhauser comorbidities were used in the risk-adjustment following a data-driven approach, thus, retaining in the model only those comorbidities statistically associated with the outcome (significantly associated for an alpha error of 5%) [14] [15].

Comment: Methods:

g) I asked “If in-hospital mortality is the outcome of interest (p. 8), why are patients dying before arrival relevant?”

I think I better understand why patients dying before arrival are relevant. However, you write on p. 10 that “To estimate potential losses, we compared our in-hospital mortality with the case fatality rates for ischemic stroke in Spain, as reported by the Spanish Ministry of Health in the OECD Health Statistics 2020 [19].” The only reference I can find to this is in the discussion where you write that “following the OECD report on case fatality due to AIS in Spain [19], most case fatalities due to AIS were reported in-hospital and within the first days of admission.” It is unclear to me if this is the comparison and what the results were?

Response: Reviewing the drafting of the text we realized that we may have misled the reviewer as there is no transition between the potential source of bias regarding death before arrival and a second potential source of bias that we also considered as it was how well we had captured all the deaths after AIS produced in the hospitals in our sample. This is why we looked for an external source, in this case the OECD Health Statistics. The text has been modified accordingly in the methods section as In the Methods section:

Another potential source of bias could be the accuracy of our data source to capture all deaths after AIS within the hospitals in our sample. We checked conditions for in-hospital mortality for ischemic stroke in Spain, as reported by the Spanish Ministry of Health in the OECD Health Statistics 2020 [19].

Additionally, in the Discussion section we have consistently added a new text including the figures of comparison as follows:

Thirdly, it is unlikely that we may have failed in capturing in-hospital deaths after AIS provided that the dataset used for this study is part of the mandatory national statistics. In addition, our figures are comparable with those in the 2011 OECD report [19] - 11.0 case fatalities per 100 stroke patients in the OECD report versus 11.4 case fatalities per 100 stroke patients in our sample.
Comment: Methods:
i) I asked “As I understand it there are considerations to be made both when estimating and interpreting the ICC with a binomial outcome. How have you dealt with this?”
You replied that you interpret the ICC as “a measure of the variance measured by the variance explained by hospital…” and that the concerns about ICC with a binary outcome are when using the ICC to calculate sample size in cluster trials. However, in the paper by Merlo et al. (2006) http://dx.doi.org/10.1136/jech.2004.029454 (which you also cite) issues are raised about the ICC with precisely the interpretation that you use. So, my question remains.
Response: Thank you for coming back on this. From the two methods described by Merlo et al. (2006), we have used the second one, the linear threshold model method or latent variable method. In his words, “the method assumes that the propensity for visiting a private physician is a continuous latent variable underlying our binary response. In other words, every person has a certain propensity for visiting a private physician but only persons whose propensity crosses a certain threshold actually does it. The unobserved individual variable follows a logistic distribution with individual level variance equal to \( \pi^2/3 \) (that is, 3.29). On this basis, the ICC is calculated as \( VA / VA + 3.29 \).
Using this method, the ICC is only a function of the area level variance and does not directly depend on the prevalence of the outcome as in the simulation method”. Accordingly, we have referred explicitly to the latent variable method in the methods section in Page 11.
The ICC was calculated using the linear threshold model method that is just a function of the area-level variance and consequently independent of the prevalence of the outcome. ICC informs of the proportion of total variation in the outcome that can be explained by the hospital.

Comment: Results:
h) I asked “You write on p. 12 that "No differences were found in the rest of the variables (see Table S1 and S2 in the online appendix)." Do you mean that there were no statistically significant differences? All coefficients in Table 52 are statistically significant, for example. Please clarify.”
In your reply you missed my point which is that the statement “No differences were found in the rest of the variables” is very imprecise. What do you mean by “no differences”? Do you mean no statistically significant differences? Or no differences whatsoever? Table S2 only contains statistically significant differences so you must either use a different definition of “no differences” or be referring to information not seen in the table. This needs to be clarified.
Response: Yes, we meant that there were no statistically significant differences. Table S2 only contains those variables that were found to be statistically associated with the outcome. We have updated the text to clarify this point, as follows:
No statistically significant differences were found in the rest of the variables (see all statistically significant variables associated with the outcome in Table S2 in the online appendix). All fitted smooth terms, including the interaction terms, introduced in the model were found as statistically significant (see Table S2 in the online appendix).

Comments: Results:
l) I asked “What is the interpretation of the MOR?”
In your reply to me you give a correct interpretation of the MOR, however in all the places in the text where you define the MOR you write that it is estimated as the median value of the odds ratio between the hospital with the highest risk and the hospital with the lowest risk, which is not correct. Since this is one of the main measures used in your study this needs to be addressed!
Response: Thank you for noting. You are correct we provided you with a version that it is not accurate enough. We have now changed the text including the proper explanation, the one provided to you in our previous reply. As
The MOR is defined as the median value of the distribution of odds ratios (OR) obtained when randomly picking two patients with the same covariate values from two hospitals with a different
underlying risk of an event of interest and comparing the one from the hospital with the highest risk to the one from the hospital with the lowest risk. In simple terms, the MOR can be interpreted as the median increased odds of reporting the outcome if a similar patient (i.e., receiving reperfusion therapy or not) is treated in another hospital with a higher risk.

Comment: Results:
m) I wrote "Proofread the second sentence on p. 13. Also Prob. > $\chi^2$ should be ($\chi^2 > 0.13$)." You removed the Prob. > $\chi^2$ and only write the p-value. It is unclear which test the p-value is from, is it a test of the interaction parameter?
Response: We clarified the test used to check the difference on the MOR in those that underwent reperfusion therapies versus those who did not in the test. As follows: This MOR difference between the two groups of patients was not statistically significant for a $\chi^2$ test of differences ($\chi^2 > 0.13; p$ value= 0.7178).

Comment: Author contributions: There is still some Spanish mixed in here. Overall, I would recommend that you consider using a language editing service to proofread your text as there are still incomplete sentences in some places.
Response: Thank you for your comment. We reviewed and deleted the Spanish in the Author contributions. We asked for the assistance of a native English-speaking colleague in copy-editing the manuscript.

Comment: Additional comment:
• The phrasing “AIS adjusted in-hospital mortality” used in the Results section is unclear. It sounds as if it is in-hospital mortality adjusted for AIS, rather than in-hospital mortality after AIS adjusted for covariates.
Response: Thank you for your comment. We changed the phrasing to “adjusted in-hospital mortality after AIS” along the text.