Author's response to reviews

Title: Does Interhospital Transfer Improve Outcome of Acute Myocardial Infarction? A Propensity Score Analysis from the Cooperative Cardiovascular Study

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Author's response to reviews: see over
Dear Dr. Marlee,

Thank you for continued thorough and thoughtful review. Attached is our revised manuscript, “Does Interhospital Transfer Improve Outcome of Acute Myocardial Infarction? A Propensity Score Analysis from the Cooperative Cardiovascular Study”.

We have made significant revisions per the comments of the 3 reviewers. We will address each comment below (responses are underlined). All reviewers raised concerns about Table 5. We used the methods described by Frolkis et al in their analysis of ventricular arrhythmias, (N Engl J Med 2003;348:781-90.) Given the continued confusion and concerns over Table 5, we have decided to delete Table 5 from the manuscript.

Thank you for the opportunity to resubmit our manuscript. We believe it is a valid addition to the literature on care of patients with acute myocardial infarction.

We look forward to hearing from you.

Sincerely

John M. Westfall, MD,MPH
Associate Dean for Rural Health
University of Colorado Denver
#1
The manuscript is of potential interest to the readers of your Journal, because it contributes to the debate about the outcome of inter-hospital transfer in acute myocardial infarction.

Major Compulsory Revisions

The methods continue to be not completely clear to me. I suggest the authors to outline a sequence of steps in the Statistical Methods section and presenting the results of each step separately. This will help the reader and reviewer. The methods we use are modeled after a study in the New England Journal of Medicine on ventricular tachycardia. We describe these methods in a similar manner. We have added several short sections to better describe and define our methods. It is really beyond the scope of this paper to thoroughly describe propensity score analysis. Propensity score analysis is a post-hoc analysis that attempts to simultaneously control for the patient factors that might be related to the outcome of interest (in this case transfer). We have added several short sections and believe that we have provided a stepwise approach that describes each method in order.

I think that the proper analysis for table 5 is a multivariable approach in each pre-specified subgroup, e.g. logistic regression analysis in the subgroup of diabetic patients with 30-day mortality as outcome variable, with transfer (OR to be reported in table), age, gender etc as explanatory variables. This analysis obviously differs from analysis of table 4. Table 5 has been troubling for several reviews. While we feel it adds some new information to the manuscript in terms of the differential benefit of transfer among various subpopulations, it probably does not add sufficiently to the manuscript to include. We have deleted Table 5 and portions of the results and discussion related to subgroup analysis. We plan to consider Table 5 and the analysis as a separate manuscript.

In conclusion, the methods continue to be unclear to me, but it could be a lack of my statistic preparation, therefore I suggest to sent this manuscript to an expert statistician for review.
Review #2

The revised version is improved and easier to follow.

I have 2 remaining concerns. The most important deals with the subgroup analysis provided in Table 5. The authors establish that transferred and non-transferred patients are very different and hence the value of propensity scoring. Yet their subgroup analysis is based on the complete, unbalanced population. Any association between the subgroup variables and other confounders will lead to a biased result. I feel that the question of interaction can only be reliably addressed by including interaction terms in the restricted study population of propensity score matched individuals. Table 5 has been troubling for several reviews. While we feel it adds some new information to the manuscript in terms of the differential benefit of transfer among various subpopulations, it probably does not add sufficiently to the manuscript to include. We have deleted Table 5 and portions of the results and discussion related to subgroup analysis.

I also that discussion of why lower risk patients are transferred, when multiple trials have shown (cf SHOCK) that it is the high risk patient who benefits from transfert and increased interventionalism. While the research may show that high risk patients are more likely to benefit, the data reveal that younger, lower risk patients are more likely to be transferred. We agree this is puzzling, however, we have found this in previous studies, and others have found this as well. (as a part-time rural physician, I am often faced with an elderly patient that refuses to be transferred. And our rural critical access hospital never keeps any acute MI (STEMI or NSTEMI) unless the patient refuses transfer.
Review #3

General
In general, I am satisfied with the statistical analyses. I do have some questions and comments geared toward presentation.

Major Compulsory Revisions
1. Relative risk. I agree with the authors about the interpretation of confidence intervals. But why relative risk rather than risk difference or odds ratios? The justification for relative risk needs to be clear, or another estimate used. Table 5 has been troubling for several reviews. While we feel it adds some new information to the manuscript in terms of the differential benefit of transfer among various subpopulations, it probably does not add sufficiently to the manuscript to include. We have deleted Table 5 and portions of the results and discussion related to subgroup analysis.

2. C statistic. If you use this statistic, it is important to provide some kind of framework for its interpretation. Will a reader wonder if C is equivalent to R^2 from regression? You need to decide if reporting this statistic is worth the potential cost of explaining it. We have added a sentence to provide a short definition of the c statistic.
3. Statistical analyses, sentence with Kruskal-Wallis test and ref 27. I do not have page numbers in my copy of the manuscript. You write: Difference between groups were tested using the chi-square or Kruskal-Wallis test. What things were tested? We compared the means for patient characteristics listed in Table 1.
4. Propensity score analysis. Because this appears to be a major component of your statistical analysis, I believe a summary of this approach is warranted within the manuscript. You provide a reference, but you need the summary in your paper. We have added a very brief summary of propensity score analysis. Coupled with the reference we believe this is adequate given the scope of the paper.
5. Table 1. In table 1 you raise the issue of multiple comparisons. Please address this issue. We raise the issue that due to the large number of cases in the CCP, clinically insignificant difference may be statistically significant, for example, a White blood count of 10.9 is not clinically different than one of 10.8, but because there are 200,000 patients, this difference is statistically significant. We have changed the footnote on table 1. We do not discuss the problem of multiple comparisons and feel it is not significant to our analysis and is well beyond the scope of this paper.

Minor Essential Revisions
1. Nonparsimonious logistic regression. Why do you need the adjective
nonparsimonious? This is the standard method we have found reported in the literature and implies that the initial analysis does not restrict the variables included in the model.

2. P values. Please report precise P values rather than $P < 0.05$. Precise P values are more informative than simple cutoffs. P values can be rounded to 2 decimal places if greater than 0.01, otherwise 3 decimal places will suffice. $P < 0.001$ is the lowest P value you really need to report. **We are deleting table 5. We have reported precise p values, changed others to reflect the above comments**

3. Percentages. Throughout the manuscript and Tables, please report percentages to the nearest integer. Is 0.1% all that meaningful? The values will be easier to read as integers, and you want your manuscript to be as easy to read as possible. **We have changed percentages to integers**

Discretionary Revisions

None
Dear Dr. Marlee,

Thank you for the thorough and thoughtful review. Attached is our revised manuscript, “Does Interhospital Transfer Improve Outcome of Acute Myocardial Infarction? A Propensity Score Analysis from the Cooperative Cardiovascular Study”. We have made significant revisions per the comments of the 2 reviewers. We will address each comment below (responses are underlined). Both reviewers raised concerns about Table 5. We used the methods described by Frolkis et al in their analysis of ventricular arrhythmias, (N Engl J Med 2003;348:781-90.) We believe that Table 5 adds information to the literature on transfer and raises the important question, “Which patient is most likely to benefit from transfer?” We continue to study this question and hope others will see this as an opportunity to study transfer more intensely. If the editor feels that Table 5 is too confusing for folks, or does not add important information we will consider deleting this table and the accompanying text from the manuscript.

Thank you for the opportunity to resubmit our manuscript. We believe it is a valid addition to the literature on care of patients with acute myocardial infarction

We look forward to hearing from you.

Sincerely

John M. Westfall, MD,MPH
Associate Dean for Rural Health
University of Colorado Denver
Review #1

Major Compulsory Revisions

Methods.
The classification of therapy reported in table 4 is not defined in the method section: there is only a reference (24) but it is not explained what is the difference among the five treatments reported. We have added a paragraph to explain these treatment classifications.

The methods used for results reported in table 5 are not described: are crude measures or OR from multiple logistic regressions? We have added a section in the methods to further describe Table 5.

Results.

Characteristics associated with improved mortality among transferred patients

1) When we compare two relative risks we compare their confidence intervals: if they do not overlap, it is reasonable to conclude that the parameter value differs for the two populations. In this section the authors erroneously consider a different impact if the 95% confidence interval for the subgroup with a specific condition did not include the relative risk for the subgroup without that specific condition. We respectfully disagree with this reviewer. The reviewer’s comment that only when the 95% confidence intervals do not overlap are the ORs significantly different is too conservative. This would mean that the ORs are 4 standard deviations apart. (that is roughly equivalent to p<.01.) It is accepted standard to interpret differences in ORs as we have done. Payton et al. (ME Payton, JIS, October 2003) state that when comparing ORs and confidence interval overlap, it only requires confidence intervals equal to about 83% to achieve a statistically significant difference at p=.05. We believe our methods to be sound and valid.

2) If table 5 reports crude measures (as I suppose), I suggest to perform a multiple logistic approach in order to adjust the mortality risks for the other patient characteristics and the severity of illness. Multiple logistic regression models can be found in Table 4. The purpose of Table 5 is to see if there is a differential impact on mortality among transferred patients with different characteristics. The point is to show that while it appears nearly all patients benefit from transfer, some groups of patient benefit more than others. We have added a bit more explanation for this table in the methods. We used the methods described by Frolkis et al in their analysis of ventricular arrhythmias, (N Engl J Med 2003;348:781-90.)

Conclusions

The authors’ conclusions are justified by the results found in the study, except the conclusion that those who underwent transfer had generally higher quality of care. Is this conclusion based on odds ratios for different therapies presented in Table 4? The basis for this conclusion is in Table 2 where it shows that transferred patients were more likely to receive aspirin, beta blockers, and thrombolytics. We added a reference to Table 2 in this section of the results.

Table 5 should be shortened, it could report only the significant results derived
from the multiple logistic regressions. We included factors of clinical importance in Table 5. These are characteristics that have been implicated in previous literature and upon which clinical decisions are often made.

Minor Essential Revisions
Keywords : â##transfer â## is missing  added

Results.
â##Rural Hospital and mortality â##
- a duplication of data is found in the text (30-day crude mortality)  removed
â##Characteristics associated with improved mortality among transferred patientsâ##
-There is a â##contradictionâ## in the title which should be corrected.  ok

Tables
A legend is needed to provide a clear explanation that allows the tables to be understood.  Tables are explained in the text to avoid redundant material.

Discretionary Revisions
This is a large data-set, have the authors considered the opportunity to investigate the effect of â##transferâ## in patients firstly admitted to the rural hospitals?  We have considered this. it is actually part of this analysis as well. It shows up in the close association between technology index and and rural. And also in table 5 where there is really minimal difference in mortality improvement between patients transferred from a rural community or an urban community. The reviewer is absolutely correct in understanding how important it is to evaluate transfer in rural communities. This is and will be an ongoing analysis and research agenda for the corresponding author.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions.  We hope that our revisions and explanations are sufficient to warrant publication in BioMed Central. Thank you.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests
Review #2
This large observational study has several interesting findings. However, I do have a number of issues that the authors may want to consider. The provision of comments is complicated by the authors not having provided page numbers.
1. The paper never states what is the primary study hypothesis. Is this meant to be a purely descriptive study? This is acceptable but should be stated.  
2. A limitation, in my opinion, the authorsâ## over enthusiasm and misunderstanding of propensity methods which subtracts from the important substantive messages in this paper. While there may be infrequent situations where propensity scores out perform conventional regression techniques (such as with rare outcomes where conventional modeling of the outcome may give unstable estimates), neither approach can adjust for the major potential bias of observational research, namely unmeasured confounding or selection bias. Contrary to what the authors assert multivariable regression modeling will provide accurate adjustments in large datasets providing sufficient outcomes have occurred. Propensity scores are often over hyped and several publications exist demonstrating empirically the lack of improvement with propensity scores (cf Sturmer AJE 2005, Stukel JAMA 2007). In the present example, I doubt that propensity scores improves the analysis compared to regular repression techniques. It would be interesting if the authors would repeat their analysis using standard techniques to test this opinion. This is not to imply that their chosen analysis is wrong or inferior but only that the same limitations of residual confounding due to unmeasured covariates still exist.  
3. More details are required concerning the methods. What is a â##structured medical record reviewâ##? What was the random sampling process? What measures of validity exist in the assessment of aspirin and thrombolytic indications? The CCP is a well known database in the United States. There are dozens of publications on the CCP data. Due to space limitations we will refer readers unfamiliar with the CCP to these publications. 
4. Why do the numbers of excluded and retained patients in the methods not add up to the total number of patients? The same comment applies to the number of hospitals.  
5. The authorsâ## interpretation of the C statistic is overly optimistic; remember that chance alone gives a C statistic of 0.5. In my opinion 0.57 = weak and 0.68 fair ability. We have toned down our optimism. For this part of the paper, the C Statistic is fairly academic, not particularly relevant to the propensity score analysis and does not add much information. We would be happy to delete these sentences.
6. Why were only the variables in Table 2 used to construct the propensity score, or is this a simple typo? Why was diabetes and history of CABG not selected as covariates for the propensity score? The basic idea of propensity is to make the treatment groups as similar as possible, like randomization, in order to assess the main effect of transfer on mortality and why exclude these mortality confounders. Typo, from previous analysis. It should say Table 1. thanks.

7. The conclusion that transferred patients, even after adjustment, have a lower mortality may be true but the present analysis is not convincing. The mean time until transfer is not reported and it is well known that mortality following AMI is a function of time. Patients with a given propensity score should be matched not only on the score but also conditional on being alive at the time of transfer. Again thinking of propensity as a method of randomization, a patient with a propensity score X who dies at day 1 is not necessarily comparable to a patient with score X as determined when transferred on day 4,5,6or 7. We are unaware of convincing data on timing of transfer and mortality. There have been several studies that compare timing in transfer specific to primary angioplasty and/or reperfusion therapy. But there is no clear association between mortality and transfer on day one and transfer on later days. Patients who died on the day of admission were deleted because they did not have an equal opportunity to undergo transfer. All patients were alive at the time of transfer. If time is an important factor than our analysis would be conservative in it estimates on the benefit of transfer.

8. The authors mention the confusion as to how to attribute mortality for transferred patients but then do not state how they handled this situation in their urban versus rural analysis. We handled transferred patient by including them in the analysis. They are the primary study group of interest. We added a sentence to state this explicitly. Many previous studies have deleted them from analysis. And many previous studies have taken the next step and said that patients in X hospital or cared for by a particular type of physician had better outcomes. We describe the phenomenon of outcomes associated with a particular treatment (transfer) and with the initial place of presentation (rural or urban). We do not attempt to “assign responsibility” to an individual or an institution.

9. The analysis examining improved mortality as a function of subgroups (Table 5) seems incomplete. The proper analysis would have been to include multiple interactions terms in a multivariable model and to perform statistical testing. Table 4 includes our regression models using the propensity score matched patients. Table 5 provides an additional method for parsing out the impact of transfer on mortality among different groups of patients. It is clear that patients benefit from transfer. Table 5 shows that some patients benefit more that others, patients with comorbidities seem to have less benefit from transfer than those without comorbidities. 10. The authors could provide a more complete discussion of their results. For example, is there a transfer paradox whereby those at lower risk (younger, less comorbidities) are being transferred? This is exactly the finding. We comment on this phenomenon in the section on Transfer and Mortality. This finding that transferred patients are younger and healthier is one of the major findings. This is also the second sentence of the discussion. According to Table 5, patients transferred from low tech hospitals have only 55% the probability of dying of those not
transferred. Patients transferred from low tech hospitals have a mortality benefit. However, there were lots of patients transferred from high tech hospitals, and while they saw a benefit from transfer it was not as much. (OR 0.45 v 0.83) These are crude ORs and not adjusted. Table 4 includes the adjusted OR. Again, table 5 is to help sort out differential benefit to transfer. I have changed the title to reflect this.
This needs some discussion and comment. Also requiring comment is the essentially non-benefit of increased technology and the large benefits of applying evidence based medical therapies. Does this not raise the question as to why so many patients systematically receive invasive interventions following AMI? Finally some comment about the low rates of smoking counselling is required. We do not mention many of the treatments. Smoking cessation counseling has been discussed in previous papers on CCP and is beyond the scope of this paper.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions. We hope that our revisions and explanations are sufficient to warrant publication in BioMed Central. Thank you.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
'I declare that I have no competing interests'