Author's response to reviews

Title: Prehospital transportation to therapeutic hypothermia centers and survival from out-of-hospital cardiac arrest

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Author's response to reviews: see over
Dear Mr. Giray,

Thank you for the opportunity to revise and resubmit our manuscript “Prehospital transportation to therapeutic hypothermia centers and survival from out-of-hospital cardiac arrest”. Below my coauthors and I have provided direct responses in bold to each reviewer’s specific critiques.

Sincerely,
Derek DeLia

**REVIEWER 1**
1. Although there is precedent for it, the combined endpoint of death/hospice/SNF placement vs. home/rehab/transfer/other as a surrogate for neurologically "intact" survival is problematic. Rehab vs. SNF placement is often driven by economic or geographical considerations rather than functional status, and the misclassification of a modest number of patients as "good" or "poor" neurological outcome could result in significant changes to the study results. This weakness should be acknowledged, and cited in the study limitations. Although the inclusion of insurance status in the model may correct for this on some level, that correction is incomplete. This should be acknowledged as a minor essential revision.

   We have described this issue more fully in the discussion/limitations section. There we point out that our findings are not sensitive to insurance status or poverty rates in hospital service areas. We also mention that our findings do not change under additional sensitivity analyses that we conducted in response to comment #5 below.

2. The rates of survival with good and poor outcomes after discharge alive from the hospital seem very uncharacteristic to me - corroborating my concern described above. In the TTM trial and others, hospital survivors typically are described as 70-85% CPC 1-2 at 6 months post-discharge. This makes me worry that your discharge destination scheme has misclassified patients. This should be addressed in the Discussion as a minor essential revision.

   We do not have sufficient data to compare 6-month survival rates. However, we note in the discussion on page 19 lines 418-421 that our rates of survival to hospital discharge are consistent with national epidemiologic data. We believe that the rates cited by the reviewer (Nielson, et al., NEJM 2014) are not comparable to our study. Neilson’s study was a clinical trial that enrolled only the subset of patients who survived long enough to have initiation of TH. Our analysis reflects the survival of all OHCA patients – not just those receiving TH.

3. Inability to include "down time" (from arrest to ROSC) in the model is a weakness that should be recognized. Down time is strongly associated with the severity of brain injury and overall survival after CA, and would help to determine
if the severity of illness is truly comparable between the groups, and help correct other biases in the regression model. This is a discretionary revision.

We agree that this is an important point and have included it in our description of limitations on pages 17-18 lines 390-392.

4. The inclusion of PCI in your model - one of the factors in post-resuscitation care that is most consistently associated with improved outcomes, would make the study stronger. This should be considered and if not included, described as a methodological weakness - a minor essential revision.

We agree that inclusion of PCI would improve the analysis. Given a number of constraints, including the deadline for resubmission, we are unable to build PCI into our modeling. We have discussed this issue as a study limitation in the discussion section of the paper on page 17 lines 386-390.

5. If after your internal discussion you agree that the combined endpoint variable is problematic, it would be reasonable to simply look at survival at 30 days. The argument for this is that most survivors are in good neurological condition, and you don't have to worry about unmeasured economic, social, and geographical influences on the endpoint - discretionary revision.

We understand the reviewer's concern and have decided to conduct sensitivity analyses using survival to discharge and 30-day survival without any adjustment for neurological status. We found no fundamental differences in the results. We briefly mention this in the last sentence of the results section and provide full model estimates in the appendix.

6. Finally, I would suggest you replace at least some of the references to therapeutic hypothermia with targeted temperature management. Even if you were evaluating centers that utilize TH, the current discussion is (appropriately) framed as one of TTM, since the best target temperature is very much in question.

We agree with this suggestion to make terminology more consistent with the current dialogue in the field. We have used TTM instead of TH in parts of the introduction and discussion. We have retained the TH terminology throughout the methods and results sections to ensure that technical aspects of the study are clear and consistently described.

Additional point raised by Reviewer 1

Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Yes, though referencing the manuscripts that describe associations between hospital size, teaching status, location, volume, and outcomes after cardiac
arrest should be cited. Look for Brandon Carr’s work.

Although several articles examine these issues, we felt the 2009 publication by Carr et al. was most relevant to our work. In both cases, OHCA arrest outcomes were better at larger hospitals but no significant associations were found between teaching and non-teaching hospitals. This work is referenced on page 17 lines 381-383 of the discussion section.

REVIEWER 2
1. Page 7, line 150 sentence that starts with although a recent trial has raised....it’s quite long and it doesn’t flow well. I would recommend splitting it into two sentences.

We have divided the sentence as suggested.

2. Page 8 under setting. It might be good to include the number of BLS units, if possible.

Although we agree that this would be useful, counting BLS units in NJ is challenging due to the use of volunteer and professional BLS units throughout the state. We are not aware of any comprehensive or up-to-date BLS census in the state, and therefore, we are not able to provide a clear number as we have done for ALS units.

3. Is there any data available on the number of OHCA calls attended by BLS units only?

In our database, every OHCA call involves an ALS unit. Although it is theoretically possible for a BLS-only response to take place, we expect such responses to be very rare.

4. I just want to confirm how data on 30-day neurologically intact survival is being captured? Is it also through NJDDCS?

This is captured through a combination of NJDDCS and mortality records. NJDDHS provides the discharge information needed to proxy neurological status and mortality records give the information needed to determine whether the patient survived within the 30-day observation window. This is clarified on page 10 lines 226-233 of the revised manuscript.

5. Page 11, Analysis section, under incident characteristics, location of OHCA and bystander CPR were not included in multiple log reg models. What was the reason? Multicollinearity?
Although we do not have a clear classification for location of OHCA available, we have looked more carefully at bystander CPR. We found that inclusion of bystander CPR does not affect any of the odds ratios related to TH and the bystander CPR variable never produced a large or statistically significant relationship to the outcome variables. Therefore, following our methodology for all model covariates (described on pages 14 lines 324-327), we included bystander CPR in our descriptive table (Table 1) but did not include bystander CPR in the final reported models.

6. Page 13, Results section it seems that authors could not link data for 737 patients (almost 13%) and what is more worrisome, out of 832 patients that survived to hospital discharge they did not have 30-day outcome available for 166 patients, which is 19.95%. I would like to see where these 166 patients were treated (TH or non-TH centers). Also text in the Results section describing Figure 1 could be a bit more precise to reflect it better, especially with the missing data on the transferred patients.

We have tabulated original transport destination for the 166 patients who were later transferred. We found that these patients were taken to TH hospitals in roughly the same proportion as those included in the modeling. This is pointed out in the first paragraph of the results section. More detail about Figure 1 is also included in this paragraph.

7. Discussion is good, though I would like to see stronger discussion on missing data and its impact.

We have enhanced various parts of the discussion section with more attention to how missing data may have affected the results. This includes discussion about the need for a proxy measure of neurological status and discussion about observations that were lost during data linkage.

8. Analyses were well done; like the part on instrumental variable.

We appreciate the comment and have retained the overall analytic approach.