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Dear Editor,

We wish to re-submit our manuscript entitled “Prognostic factors associated with hospital survival in comatose survivors of cardiac arrest” for your consideration.

Thank you for your review of our previous submission and for your recommendations for improvement. We have addressed your comments below (numbered), with our responses as dot-points.

1. This is an interesting an article describing the experience of a single center on the outcomes of cardiac arrest patients admitted to the intensive care unit. The paper addresses an important issue and its major strength is the large population.
    - Thank you.
2. However, I do have some comments/questions: a) How was comatose defined. Was it a GCS and if so what was the cut-off. Could they have been comatose as a result of medications administered during or right after the arrest
    - Unfortunately, this was poorly defined, but unlikely to be the result of medications.
    - Although there was no definition of ‘comatose’ in Bernard’s original two publications (Bernard et al., 2002, Bernard et al., 1997), we allocated a GCS of 7 or less as being classified as being comatose (either in the paramedic documentation, or in the hospital records).
    - We classified someone as comatose if:
        i. Highest documented GCS was 7 or less
        ii. Stated as ‘comatose’ (or similar) in documentation
        iii. Intubated and ventilated WITHOUT requirement for anesthesia or medications
3. The introduction mostly refers to hypothermia in cardiac arrest. However, this is not the aim of the paper and the introduction should reflect this

4. You are correct. Our aim was to identify patient, cardiac arrest and management factors that influenced outcome. Of these the patient and cardiac arrest factors were pre-defined, which left management factors. During the study period the ‘in vogue’ management factor was

therapeutic hypothermia, and thus our look at management focused on that. Our introduction has been modified to suit this.

5. The methods section should be clear about which versions of the APACHE score was used and in what circumstances

    - APACHED II & III data were obtained from the ICU database for patients admitted from July 1999. Our methods section has been modified.

6. The study included patients from 1993 but APACHE scores were only available post 1999. Does this mean that the multivariate analyses did not include APACHE scores or was it restricted to post 1999.
    - Multivariate analyses involving APACHE data were restricted to patients admitted from July 1999 onward. About 73% of the patients included in the study had APACHE data.
    - All other analyses NOT involving APACHE data covered the entire period.
7. What variables were included in the model. Was admission before/after 2002 used as a variable in the model.
    - The before and after 2002 dichotomy was NOT included in the model
    - Included variables were: Time to return of spontaneous circulation, rhythm, APACHE II score, institution of therapeutic hypothermia and gender. A new table is presented showing all the variables with their odds ratio in the final model.
8. How was the possibility of temporal trends n survival accounted for in the model.
    - The second group had 'sicker' patients, as indicated by a higher mean APACHE II score, which has previously been associated with worse outcomes following cardiac arrest. (Donnino et al., 2013)
    - There was also an increase in non-shockable rhythms and a higher mean time to return of spontaneous circulation (ROSC), both of which have also been associated with lower survival. (Bernard, 2009, Herlitz et al., 2005)
9. A minor point: Capitalize trade names (ex Bair Hugger and Arctic Sun) as well as APACHE scores consistently
    - Corrected
10. The medial LOS for hospital seems very short (5 days). Did it include mortalities as well?
    - Yes, LOS was time from admission to either discharge or death (whichever occurred first)
11. The study addressed a scientifically sound question and it is clinically relevant for prognostication of ICU patients with cardiac arrest. The sample size is very large. There are several comments I would like to raise for the improvement of the manuscript. 1. "Therapeutic hypothermia, regardless of method used (e.g., rapid infusion of ice cold fluids, topical ice, 'arctic sun', passive rewarming, 'bair hugger') and location initiated (e.g., pre-hospital,

emergency department, intensive care) was associated with increased survival."-------this statement should be clarified in the abstract whether it is concluded from univariate or multivariable analysis. As this can be influenced by other potential confounders.

- The effect of therapeutic hypothermia on survival was significant in univariate, but not multivariate. This has been corrected in both the abstract and main results sections.

12. In the method section, I did not found more detailed description of therapeutic hypothermia, its time frame relative to the occurrence of cardiac arrest, the target temperature. The performance of hypothermia should be described in method for aid judgment by readers.
    - Our study period overlapped with many therapeutic hypothermia studies,(Bernard et al., 2010, Bernard et al., 2002)' (Deasy et al., 2011) resulting in changes to therapeutic hypothermia protocols. Hence we did not describe any specific protocol in the methods section. We however collected and presented data on therapeutic hypothermia plan, decision to institute cooling, location of initial cooling, method of initiating cooling, method of maintaining cooling, targeted temperature, time taken to achieve target temperature, time at target temperature (both planned and actual), method of rewarming and the maximum temperature reached in the first 72 hours following cardiac arrest (MAX-TEMP) for readers to judge our results.
13. In table 2, there is an interesting finding that patients with rapid cooling (time to temp) are more likely to die. Is this an incidental finding resulting from random error or there are some underlying mechanisms? This can be discussed further.
    - We do not believe this is random.
    - We have added this to the discussion.
    - We have also added to the discussion the association between a higher maximum temperature and survival.
14. It is also strange time to target temp is shorter before 2002, the year of the publication of the landmark study. Shorter time indicates more rapid response and initiation of cooling. Why after strong evidence supporting the use of hypothermia the response slowed down? The proportion receiving HT increased, which is expected, after 2002.
    - There are a number of possibilities, however all are speculative:
        i. During the original trial period (1996-1999) there was a rigid research focus on this group of patients, and thus staff awareness, research staff funding and rigid trial protocols may have influenced timely management.
        ii. In addition, more labour intensive measures (eg., ice cold IV fluids, topical ice (scalp, neck, axilla, groin) may have allowed for more rapid cooling, in comparison to the Arctic Sun, which was more popular after 2002.
        iii. Arctic Sun's pads are applied to thorax and thighs, and NOT to the highly vascular areas such as axilla, groins, etc. Thus although allowing for greater control, may not have provided a rapidity in cooling as compared to previous methods.
15. I suggest presentation of the result of multivariable analysis in tables.

- Presented a table (table 4) for multivariable analysis as per your suggestion.

16. The primary end point is survival. However, I am also interested in the GCS score at discharge. In my experience, many cardiac arrest patients will end with normal vital signs but also poor GCS, or some of them are in vegetate states. Thus, I suggest the report of coma scales on survivors.
    - We agree that beyond survival, 'meaningful survival' may have been a more appropriate end point. Unfortunately, we did not collect data on Glasgow Coma Score, Glasgow Outcome Score or other neurological data on survivors.
17. Since the work in focus on risk factors of survival, some other factors merit reporting. Those include some universe risk factors such as lactate, use of vasopressors, serial organ functions. Or some of them need to be discussed if data are not available. Some literature may be relevant (e.g. J Thorac Dis. 2014 Jul;6(7):995-1003. BMJ Open. 2014 May 23;4(5):e004752.). one shortcoming is lack of some important risk factors.
    - We agree that markers of hypoperfusion (lactate, markers of organ dysfunction, etc) and the need for organ supports (vasopressors, ventilation, CRRT, etc) are important to exclude as confounding factors. Unfortunately, the documentation of these data was very poor and were largely missing. We therefore did not include them in our analysis. This is an inherent limitation of retrospective studies.

Thank you for your consideration of this manuscript.

Yours sincerely,

Ravindranath Tiruvoipati

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