PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association of body temperature with in-hospital mortality among paediatric trauma patients: an analysis of a nationwide observational trauma database in Japan
AUTHORS	OKADA, ASAMI; OKADA, YOHEI; NARUMIYA, HIROMICHI; Ishii, Wataru; Kitamura, Tetsuhisa; OSAMURA, TOSHIO; IIDUKA, RYOJI

VERSION 1 – REVIEW

REVIEWER	Andrew Kiragu Children's of Minnesota and Hennepin Healthcare
REVIEW RETURNED	11-Dec-2019

GENERAL COMMENTS	An interesting study of pediatric trauma patients in Japan. The findings, for the most part, are not unexpected-there is a significant body of evidence linking hypothermia with increased mortality. However, this study is unique in the large number of patients and the setting in Japan. I have a few concerns. The authors do not quantify the degree of hypothermia for the patients less than 36 degrees Celsius which is a little problematic since there is likely a difference in mortality with lower temperatures. It would be helpful if the authors were able to show the range of temperatures below 36 and what temperature mortality was greatest. Another confounding factor not addressed is the variability in modalities in obtaining temperature. Most patients have axillary temperature and others tympanic and others yet rectal. What effect does this variability in temperature monitoring have? The finding of no increase in mortality at temperatures greater than 37 degrees Celsius regardless of the severity of ISS/AIS head is certainly novel and these patients should also be described a little better. I suspect given the relatively low average ISS of these patients that the number of severely injured patients in this group may not be enough to come to this particular conclusion. Again further elucidation of this group of patients would be helpful.

REVIEWER	Asim Alam North York General Hospital
REVIEW RETURNED	15-Feb-2020

GENERAL COMMENTS	Review - bmjopen-2019-033822

	Overall Comments: There is a dearth of literature on the association of hypothermia with pediatric patients as this population is often missed or forgotten from trauma studies. This is mostly because severe trauma leading to mortality is essentially much more uncommon in this population. There are concerns with the ethical framework used to conduct the study as mentioned below. I would be careful about discussing the hypothermia and isolated head trauma – this probably needs more discussion as there is a whole slew of researchers who believe that hypothermia is neuroprotective for trauma. Otherwise, I believe this is an important and welcomed addition to this literature. Title: Would add “The..” before Association, and “an” = The association of body temperature with in-hospital mortality among paediatric trauma patients: an analysis of a nationwide observational trauma database in Japan. Abstract: P2, L32 – admission body temperature? P2, L34 – Confusing about design: It is a retrospective cohort study no a retrospective and prospective cohort study. P2, L44 – Another statement about baseline demographics required. Introduction: P4,L65 – No reference for this statement Methods: P5, L48 – Just because the trauma association approved the database creation, does not essentially mean this particulary retrospective review has gone through proper ethics approval. I would suggest discussing how this particulary retrospective analysis obtained ethics approval to conduct this study. This is a research study involving human data and should have a specific REB number attached to it, even if it uses a known database. P5, L81 – Add (STROBE) in brackets. P7, L137 – Why would you expect a trauma patient from the field to have a temperature above 37 degrees? P7, L146 – This is not adequate enough as written above. Proper ethical approval must be obtained for this specific study prior to conducting analysis and publication. P8, L157 – Talking about sample size is not necessary here. Results: Discussion: P11, 196 – In any nation or just Japanese? P11, LN 203 – This sentence is worded awkwardly, both studies show an increase in mortality. Interpretation: - For years, the treatment of TBI and intracranial hypertension in adults post-trauma, has been proposed based on laboratory and animal data, to be hypothermia. However, in a recent large

	randomized controlled trial it was not proven to be true amongst single head injury patients.(N Engl J Med 2015; 373:2403-2412) If your explanation was correct, we would have seen similar coagulopathic issues amongst this population in this study. So the explanation provided here needs to be flushed out a little more. - Ibid point – P13 – Line 254

REVIEWER	Alexander Leichtle Inselspital - Bern University Hospital Insel Data Science Center Bern Switzerland
REVIEW RETURNED	15-Mar-2020

GENERAL COMMENTS	General Comments: 1. The topic is important, and the usage of a large national register seems to be an adequate way to address the questions. The results seem reasonable in terms of path-mechanisms and published literature. 2. Has the study been recorded in a large international trial database? 3. How was consent evaluated, as the children might not speak for themselves. Specific comments: 1. Is there a specific association with specific diagnoses or mechanisms, that in turn might lead to hypothermia, so that hypothermia might only be a proxy for the underlying mechanism's mortality. 2. I would like to see the reasons for excluding some patient groups (e.g. helicopter usage) 3. Did the mortality rate differ from just generally hospitalized patients without trauma? 4. Was mortality also associated to other, latent variables, that might explain the outcomes (e.g. long time without treatment, that also might lead to hypothermia)? 5. Has coagulopathy bee measured? 6. How is the data available for replications studies?

REVIEWER	Kristien Verdonck Institute of Tropical Medicine Antwerp, Belgium
REVIEW RETURNED	16-Mar-2020

GENERAL COMMENTS	The present peer review focuses on the statistical analysis. The authors describe the statistical methods quite clearly. I recomputed some of the crude statistics in the manuscript and obtained the same results as those presented in the paper. However, I do have concerns about the following issues: - The fact that there are missing data in this retrospective nationwide study is understandable. The authors recognize this as a limitation which is good. However, in the analysis, they use a complete-case approach while there are better ways to deal with missingness. The following references (among others) describe the issue and propose alternative approaches that deserve to be considered in this study: Richter S et al. Handling of Missing Outcome Data in Traumatic Brain Injury Research: A Systematic Review. J Neurotrauma. 2019;36(19):2743-2752; Pedersen et al. Missing data and multiple

	imputation in clinical epidemiological research. Clin Epidemiol. 2017;9:157-166; Lee KJ et al. Introduction to multiple imputation for dealing with missing data. Respirology. 2014;19(2):162-167. - As this is a multi-centre study, I assume the data may be clustered per centre or per region (i.e. correlated data). Although I do not expect a major impact of clustering in this particular study, it would anyway be appropriate to account for it, for example by using generalized estimating equations. - There are several quantitative variables in this study (e.g. body temperature and age). These are categorised for the analysis (data reduction, see also item 11 of the STROBE checklist). The reason for this choice is not entirely clear. Why were quantitative variables categorised even if this leads to a loss of information (e.g. possible "dose effect" of (low) temperature cannot be evaluated anymore)? Were the definitions of the subgroups defined before the start of the analysis? Different cut-offs could lead to different findings. - In the presentation and the discussion of the study strengths, the authors imply that thanks to the large sample size, it was possible to adjust for confounding. I would like to highlight that large sample sizes are no guarantee against confounding. If relevant information on possible confounders is not collected accurately or goes missing, the risk of confounding and other types of bias remains high. - In this study, there is considerable confounding with regard to the main outcome: the crude odds ratio for the association between low body temperature and dying is 7.8 and after adjustment, this goes down to a 2.8. Which variables were included in the regression models that produced the adjusted odds ratios? Which of those variables are the most important confounders? Overall, the fact that the confounding is so pronounced and that the strength of association differs across subgroups (according to type of trauma) complicates the interpretation – and particularly the generalisation- of the findings. In addition, I have a few minor comments: - Limitations: "uncoordinated confounding". What does this mean, or is it a typo? This term appears twice in the manuscript. - Statistical methods: "and each outcome as an objective variable". What is meant with this expression? - Outcome. "The overall in-hospital mortality value was 2.5%". The word "value" does not seem appropriate in this context. - Previous literature and strength. The use of words such as "while" and "however" suggests that the findings from this study go against those of previously published studies. But that does not seem to be the case here, because if I understood it correctly, all cited literature suggests that low body temperature is associated with a higher risk of dying? I found this somewhat confusing.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Andrew Kiragu
Institution and Country: Children's of Minnesota and Hennepin Healthcare
Please state any competing interests or state 'None declared': None declared

-An interesting study of pediatric trauma patients in Japan. The findings, for the most part, are not unexpected-there is a significant body of evidence linking hypothermia with increased mortality. However, this study is unique in the large number of patients and the setting in Japan.

Authors' Response:
We appreciate you for taking out time to review our manuscript and giving these favourable comments. We agree with all your comments and revised the manuscript based on your suggestions. Here are our point-by-point responses to your comments.

-I have a few concerns. The authors do not quantify the degree of hypothermia for the patients less than 36 degrees Celsius which is a little problematic since there is likely a difference in mortality with lower temperatures. It would be helpful if the authors were able to show the range of temperatures below 36 and what temperature mortality was greatest.
Authors' Response:
Thank you for this query and important suggestion. We agree with the idea. We considered that there might be temperature-dependent variations in outcomes in the lower temperature ranges (lower temperature would result in higher mortality); thus, we added the cubic spline curve to describe this (Fig. 2). Accordingly, we have revised the manuscript to reflect this as follows:

(Results, page 9, lines 191 – 193, revised manuscript)
'Furthermore, the restricted cubic spline between BT and the estimated adjusted odds ratio of in-hospital mortality is shown in Figure 2, which indicates the dose-response relationship between BT and in-hospital mortality in the patients with BT <36.0 ºC'.

-Another confounding factor not addressed is the variability in modalities in obtaining temperature. Most patients have axillary temperature and others tympanic and others yet rectal. What effect does this variability in temperature monitoring have?
Authors' Response:
Thank you for your comment. We considered that the accuracy of the measuring method might vary and lead to a measurement bias (we believe that this may not be confounding because various methods seem not to be associated with mortality. If an association exists, it might be as a result of severity). Unfortunately, we had no detailed information on the temperature measuring methods. Thus, we discussed this point as part of the study limitations.

(Limitations, page 14, lines 285 – 288, revised manuscript)
'Secondly, the JTDB does not present unified information on the BT measurement methods used (e.g. measuring device used or the measurement timing). Moreover, the accuracy of all the measurements could not be validated. These factors might have led to measurement bias'.

-The finding of no increase in mortality at temperatures greater than 37 degrees Celsius regardless of the severity of ISS/AIS head is certainly novel and these patients should also be described a little better.
Authors' Response:
Thank you for the constructive advice.
Based on the comment, we revised the discussion to reflect this point in the manuscript as follows:

(Discussion, page 13, lines 277 – 279, revised manuscript)
'Furthermore, according to the results on higher BT values (≥37.0), aggressive warming among paediatric trauma patients in pre-hospital settings may be justified and preferable to hypothermia, even if the presence of severe head trauma is still an assumption'.

- I suspect given the relatively low average ISS of these patients that the number of severely injured patients in this group may not be enough to come to this particular conclusion. Again further elucidation of this group of patients would be helpful.

Authors' Response:
Thank you for pointing this out. We agree with you, and we revised the conclusion in the manuscript as follows:

(Conclusion, page 14, lines 297 – 299, revised manuscript)
'In our study, we observed a clear association between hypothermia (BT <36.0 ºC) on hospital arrival and in-hospital mortality; no such association was observed between higher BT values (≥37.0 ºC) and outcomes. Further research is necessary to eliminate potential biases associated with this study and validate the results'.

Once more, we appreciate you for taking out time to review our manuscript and giving us these important pieces of advice.
We look forward to your response.

Reviewer: 2
Reviewer Name: Asim Alam
Institution and Country: North York General Hospital
Please state any competing interests or state 'None declared': None declared

Overall Comments:
-There is a dearth of literature on the association of hypothermia with pediatric patients as this population is often missed or forgotten from trauma studies. This is mostly because severe trauma leading to mortality is essentially much more uncommon in this population.
There are concerns with the ethical framework used to conduct the study as mentioned below. I would be careful about discussing the hypothermia and isolated head trauma – this probably needs more discussion as there is a whole slew of researchers who believe that hypothermia is neuroprotective for trauma. Otherwise, I believe this is an important and welcomed addition to this literature.
Authors' Response:
We appreciate you for taking out time to review our manuscript and giving us favourable comments. We agree with all your comments and have revised the manuscript based on your suggestions. Here are our point-by-point responses to your comments.

-Title: Would add "The.." before Association, and "an" = The association of body temperature with in-hospital mortality among paediatric trauma patients: an analysis of a nationwide observational trauma database in Japan.
Authors' Response:
Thank you for this advice. We have modified the title.

(Title, page 1, lines 1 – 2, revised manuscript)
'Title: The association of body temperature with in-hospital mortality among paediatric trauma patients: an analysis of a nationwide observational trauma database in Japan'.

Abstract:
P2, L32 – admission body temperature?
Authors' Response:
Thank you for pointing this out. We have modified the term.

(Abstract, page 2, line 32, revised manuscript)
'…body temperature (BT) on hospital arrival…'

P2, L34 – Confusing about design: It is a retrospective cohort study no a retrospective and prospective cohort study.
Authors' Response:
Thank you for this query. We have revised the term.

(Abstract, page 2, line 34, revised manuscript)
'Design: A retrospective cohort study'.

P2, L44 – Another statement about baseline demographics required.
Authors' Response:
Thank you for this advice. We revised as follows:

(Abstract, page 2, lines 43 – 44, revised manuscript)
'Results: A total of 9,012 patients were included [median age: 9 years (interquartile range, 6.0-13.0 years), mortality: 2.5% (226/9,012)]'.

Introduction:
P4,L65 – No reference for this statement
Authors' Response:
Thank you for pointing this out. We have cited a reference as requested.

Methods:
P5, L48 – Just because the trauma association approved the database creation, does not essentially mean this particulary retrospective review has gone through proper ethics approval. I would suggest discussing how this particulary retrospective analysis obtained ethics approval to conduct this study. This is a research study involving human data and should have a specific REB number attached to it, even if it uses a known database.
Author's Response>
Thank you for this important constructive criticism. We have provided the ethical approval number by the research ethics committee of the Japanese Association for the Surgery of Trauma in the methods section (approval ID No 2548).
The ethics committee of the Japanese Association for the Surgery of Trauma and that of each institution approved the participation in the registry and retrospective analyses using anonymized data from the JTDB based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labor, and Welfare of Japan. Thus, we believe that our study is ethically sound.
We have added this information in the manuscript for clarity.

(Methods, page 5, lines 82 – 89, revised manuscript)
'The need for informed consent for registration in the JTDB, retrospective analysis of the anonymized data, and publication of the results was waived as approved by the ethics committee of the Japanese Association for the Surgery of Trauma and that of each institution; this was based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labor and Welfare of Japan.10 The approval documents from the Japanese Association for the Surgery of Trauma and the representative institution (National Defense Medical College Research Institute) are available on the JTDB website (https://www.jtcr-jatec.org/traumabank/dataroom/ethics2.htm). (The approval ID No 2548)'.

P5, L81 – Add (STROBE) in brackets.
Authors' Response:
Thank you for the advice. We have revised as recommended.

P7, L137 – Why would you expect a trauma patient from the field to have a temperature above 37 degrees?
Authors' Response:
Thank you for this important question. Although we do not know the exact reason, we believe that the high temperature is mainly as a result of exposure to hot environments such as outdoors in the summer or during exercise.

P7, L146 – This is not adequate enough as written above. Proper ethical approval must be obtained for this specific study prior to conducting analysis and publication.
Authors' Response:
Thank you for the important criticism. We have addressed this query in our response to your earlier comment (#P5, L48). Please, refer to it.

P8, L157 – Talking about sample size is not necessary here.
Authors Response:
Thank you for your advise. We have deleted this portion of the text in the revised manuscript.

Results:
Discussion:
P11, 196 – In any nation or just Japanese?
Authors' Response:
Thank you for the question. To the best of our knowledge, in any nation.

P11, LN 203 – This sentence is worded awkwardly, both studies show an increase in mortality.
Authors' Response:
Thank you for pointing this out. We have revised this portion of the text.

Interpretation:
- For years, the treatment of TBI and intracranial hypertension in adults post-trauma, has been proposed based on laboratory and animal data, to be hypothermia. However, in a recent large randomized controlled trial it was not proven to be true amongst single head injury patients.(N Engl J Med 2015; 373:2403-2412) If your explanation was correct, we would have seen similar coagulopathic issues amongst this population in this study. So the explanation provided here needs to be flushed out a little more.
- Ibid point – P13 – Line 254
Authors' Response:
Thank you for this important criticism. Based on your suggestion, we have included the suggested RCT in our discussion.

(Discussion page 13, lines 261 – 267, revised manuscript)
'Furthermore, a multi-institutional randomized controlled trial reported that hypothermic management (32–35 ºC) for adult patients with a severe head injury worsened their functional outcome.34 Accordingly, we hypothesise that hypothermia in cases of a severe head injury might cause coagulopathy and lead to mortality. In our study, most of the patients who died had a severe head injury (Table 4). Additionally, subgroup analyses indicated that there is an association between hypothermia and mortality in patients with a severe head injury, but no apparent association was

observed in patients without a head injury. Thus, we believe that the mechanism we have suggested is reasonable'.

Again, we appreciate you for taking out time to review our manuscript and giving us these important pieces of advice.
We look forward to your response.
Reviewer: 3
Reviewer Name: Alexander Leichtle
Institution and Country:
Inselspital - Bern University Hospital
Insel Data Science Center, Bern, Switzerland
Please state any competing interests or state 'None declared': None declared

Authors' Response:
We appreciate you for taking out time to review our manuscript and giving us favourable comments. We agree with all your comments and have revised the manuscript based on your suggestions. Here are our point-by-point responses to your comments.

General Comments:
1. The topic is important, and the usage of a large national register seems to be an adequate way to address the questions. The results seem reasonable in terms of path-mechanisms and published literature.
Authors' Response:
Thank you for the favourable comments.

2. Has the study been recorded in a large international trial database?
Authors' Response:
Thank you for this question. This study has not been registered in any international trial register because this study is a retrospective analysis by secondary usage of a registry data; thus, we understand that it is not mandatory to register it.

3. How was consent evaluated, as the children might not speak for themselves.
Authors' Response:
Thank you for this important question. This study is a retrospective analysis by secondary usage of registry data. According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour, and Welfare of Japan, the ethics committee of the Japanese Association for the Surgery of Trauma and those of each participating institution approved for informed consent to be waived in this trauma registry. If there were patients who do not want to be registered, they could opt-out.

Cf. Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html
Ethical committee approval
https://www.jtcr-jatec.org/traumabank/dataroom/data/JAST_syounin.pdf

Specific comments:
1. Is there a specific association with specific diagnoses or mechanisms, that in turn might lead to hypothermia, so that hypothermia might only be a proxy for the underlying mechanism's mortality.
Authors' Response:

Thank you for this important criticism. We agree that hypothermia might only be a proxy for the underlying mechanism of mortality. We revised the limitation section of the manuscript to clarify this.

(Limitations, page 14, lines 289 – 291, revised manuscript)
'Moreover, unmeasured confounding factors such as an unknown underlying mechanism of mortality or coagulopathy might have influenced the results, and hypothermia might just be a proxy for these unknown factors'.

2. I would like to see the reasons for excluding some patient groups (e.g. helicopter usage)
Authors' Response:
Thank you for this important question.
We did not include patients with an unknown mechanism of injury, or injury due to burns because patients with burns or an unknown type of injury were not regarded as part of the general trauma population. Further, the patients not directly transferred from the scene by an ambulance (e.g. physician-staffed helicopter or transferred from other hospitals) might have received some medical interventions before hospital arrival. Thus, we did not include these categories of patients to ensure that the targeted patients were specifically general trauma patients managed by paramedics. We revised the manuscript to explain these points.

(Methods, page 6, lines 110 – 116, revised manuscript)
'We also excluded those for whom the primary mechanism of injury was a burn or unknown because they are not regarded as part of the general trauma population. Furthermore, those who were not transferred directly from the injury scene by an ambulance with paramedics (such as those transferred by a helicopter or an ambulance staffed with doctors, and referrals from other hospitals) were also excluded because they might have received some medical interventions before hospital arrival; we aimed to target patients who were explicitly general trauma patients managed by paramedics'.

3. Did the mortality rate differ from just generally hospitalized patients without trauma?
Authors' Response:
Thank you for this important question. We do not have the mortality data of the hospitalized general patients without trauma. According to the statistics published by the Ministry of Health, Labour, and Welfare of Japan, the morality is as follows: accident, 2.4; malignant neoplasm, 2.0; heart disease, 0.7 /100,000 population in the age 5–9 years in 2009.

Cf. The statistics published by the Ministry of Health, Labour, and Welfare of Japan
https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suii09/deth8.html

4. Was mortality also associated to other, latent variables, that might explain the outcomes (e.g. long time without treatment, that also might lead to hypothermia)?
Authors' Response:
Thank you for this important question. In the supplementary file, we described the association between transit time and mortality. Transit time was not associated with mortality in the multivariable logistic analysis.

5. Has coagulopathy been measured?
Authors' Response:
Thank you for the important question. Unfortunately, we did not obtain any information about coagulopathy from the database. We revised the limitations in the discussion section to reflect this. Please refer to our response to your previous comment (#Specific comment 1)

6. How is the data available for replications studies?
Authors' Response:
Thank you for this question. The anonymized JTDB data is available to the institutional members of the Japan Trauma Care and Research for research purposes.

Reviewer: 4
Reviewer Name: Kristien Verdonck
Institution and Country: Institute of Tropical Medicine Antwerp, Belgium
Please state any competing interests or state 'None declared': None declared

Author's Response>
We appreciate you for taking out time to review our manuscript and giving us favourable comments. We agree with all your comments and have revised the manuscript based on your suggestions. Here are our point-by-point responses to your comments.

Please leave your comments for the authors below
The present peer review focuses on the statistical analysis. The authors describe the statistical methods quite clearly. I recomputed some of the crude statistics in the manuscript and obtained the same results as those presented in the paper. However, I do have concerns about the following issues:

- The fact that there are missing data in this retrospective nationwide study is understandable. The authors recognize this as a limitation which is good. However, in the analysis, they use a complete-case approach while there are better ways to deal with missingness. The following references (among others) describe the issue and propose alternative approaches that deserve to be considered in this study: Richter S et al. Handling of Missing Outcome Data in Traumatic Brain Injury Research: A Systematic Review. J Neurotrauma. 2019;36(19):2743-2752; Pedersen et al. Missing data and multiple imputation in clinical epidemiological research. Clin Epidemiol. 2017;9:157-166; Lee KJ et al. Introduction to multiple imputation for dealing with missing data. Respirology. 2014;19(2):162-167.
Authors' Response:
Thank you for this advice. We have conducted a sensitivity analysis using multivariate imputation by chained equations (MICE) to deal with the missing data. We have revised the manuscript and supplementary file accordingly.

(Methods, page 8, lines 162 – 165, revised manuscript)
'Moreover, we performed a sensitivity analysis to deal with the missing values of the BT and outcome. We performed multiple imputations based on the "missing at random" assumption (the detailed method is described in the supplementary file)'.

(Supplementary file)
Based on the assumption of "missing at random", we performed multivariate imputation by chained equations (MICE) method to generate 10 copies of imputed datasets using predictive mean matching and calculated the coefficient and standard error using logistic model. Then, we generated the pooled crude and adjusted OR with 95%CI of the body temperature (BT) for the mortality based on the Rubins's rule. We used the R studio with "mice" package.

- As this is a multi-centre study, I assume the data may be clustered per centre or per region (i.e. correlated data). Although I do not expect a major impact of clustering in this particular study, it would anyway be appropriate to account for it, for example by using generalized estimating equations.
Authors' Response:

Thank you for this advice. We agree with you. We had planned to use the multi-level logistic model or GEE; however, in the JTDB dataset, utilization of the information about clusters such as regions or detailed information of the hospitals are limited in order to keep the data anonymized. Thus, we could not perform any of these. Thank you for your advice.

- There are several quantitative variables in this study (e.g. body temperature and age). These are categorised for the analysis (data reduction, see also item 11 of the STROBE checklist). The reason for this choice is not entirely clear. Why were quantitative variables categorised even if this leads to a loss of information (e.g. possible “dose effect” of (low) temperature cannot be evaluated anymore)?

Authors’ Response:
Thank you for this question. We categorized continuous variables to avoid the assumption of a linear relationship between variables and outcome as often done in the research of emergency medicine. However, we agree with the idea that categorization of the continuous variables might lead to the loss of information, and dose-response relationship cannot be evaluated. Thus, in the method section, we explained the reason for the categorization and added restricted cubic spline to show the dose-response relationship between BT and the estimated odds ratio of in-hospital mortality.

(Methods, page 6, lines 124 – 127, revised manuscript)
‘To avoid the assumption of a linear relationship between variables and outcome15, patients were further categorised based on their vital signs…as follows:’

(Methods, page 8, lines 153 – 156, revised manuscript)
‘Furthermore, we used the restricted cubic spline to assess the possible nonlinear or dose-response relationship between BT and the estimated adjusted odds ratio of in-hospital mortality (the detailed method is described in the supplementary file)’.
(Supplementary)
The restricted cubic spline was made using 5 knots at prespecified locations according to the distribution of BT (the 5, 27.5, 50, 72.5, and 95% percentiles) and with multivariable logistic regression model adjusted by confounders as same as the primary analysis in the complete case dataset. The reference was set on 36.5℃. We used the R studio with “rms” package.

Were the definitions of the subgroups defined before the start of the analysis? Different cut-offs could lead to different findings.
Authors’ Response:
Thank you for this question. The definition of the subgroups such as AIS ≥3 and ISS ≥16 are widely accepted cut-offs in trauma research, as mentioned in the manuscript. However, our main and subgroup analyses were not prospectively planned, nor is the analysis protocol registered anywhere; thus, we cannot prove that the definition or cut-offs were pre-defined before the commencement of the analysis. For clarity, we revised the manuscript as follows:

(Methods, page 8, lines 156 – 157, revised manuscript)
‘Additionally, we performed a subgroup analysis to identify whether the association between temperature and in-hospital mortality differed with respect to the following subgroups:’

- In the presentation and the discussion of the study strengths, the authors imply that thanks to the large sample size, it was possible to adjust for confounding. I would like to highlight that large sample sizes are no guarantee against confounding. If relevant information on possible confounders is not collected accurately or goes missing, the risk of confounding and other types of bias remains high.
Authors’ Response:

Thank you for this important criticism. We agree that a large sample size does not equate to the absence of unmeasured confounding. For clarity, we revised the manuscript as follows:

(Discussion, page 11, lines 224 – 230, revised manuscript)
'These previous results are consistent with our results; however, those studies have limitations in terms of generalisability due to their single-centre design. Further, in these studies, the sample sizes and number of outcomes were relatively small; thus, the covariates adjusted by the logistic model were limited. On the other hand, we could adjust for potential confounding using a nationwide multi-institutional database with larger sample size. Although there is some risk of residual unmeasured confounding, we believe that our study results may be more generalizable than those of previous studies.'

- In this study, there is considerable confounding with regard to the main outcome: the crude odds ratio for the association between low body temperature and dying is 7.8 and after adjustment, this goes down to a 2.8. Which variables were included in the regression models that produced the adjusted odds ratios? Which of those variables are the most important confounders? Overall, the fact that the confounding is so pronounced and that the strength of association differs across subgroups (according to type of trauma) complicates the interpretation and particularly the generalisation of the findings.
Authors' Response:
Thank you for this important criticism. We agree that considerable confounding to the outcome exists. Of the confounders, we believe that the most important one is the severity of the trauma, especially head trauma. We agree that we should adjust for confounding in the sub-group analysis, similar to the main analysis. In the sub-group analysis for severe head injury and multiple trauma, we found an association between hypothermia and mortality, even when we adjusted for trauma severity such as injury severity score and Glasgow Coma Scale, which are considered as the most important confounders.

In addition, I have a few minor comments:
- Limitations: "uncoordinated confounding". What does this mean, or is it a typo? This term appears twice in the manuscript.
Authors' Response:
Thank you. We meant 'unmeasured confounding' and have corrected accordingly.

- Statistical methods: "and each outcome as an objective variable". What is meant with this expression?
Authors' Response:
We are sorry for the typographical error. We have corrected it as appropriate.

- Outcome. "The overall in-hospital mortality value was 2.5%". The word "value" does not seem appropriate in this context.
Authors' Response:
Thank you for this suggestion. We deleted the word 'value'.

- Previous literature and strength. The use of words such as "while" and "however" suggests that the findings from this study go against those of previously published studies. But that does not seem to be the case here, because if I understood it correctly, all cited literature suggests that low body temperature is associated with a higher risk of dying? I found this somewhat confusing.
Authors' Response:
Thank you for this suggestion. We have corrected these.

VERSION 2 – REVIEW

REVIEWER	Andrew Kiragu Children's of Minnesota and Hennepin Healthcare
REVIEW RETURNED	30-Apr-2020

GENERAL COMMENTS	While the study offers potential insights into the association of body temperature in this cohort of Japanese children it is unclear how the authors can make the broad conclusions they do based on the data they present. While they have made an effort to provide clarification to the questions raised by the reviewers previously, I do not feel they have done so adequately. For instance, what degree of hypothermia seemed to correlate with higher mortality? There is a difference between the patient arriving with a temperature of 31 degrees Celsius and 36 degrees Celsius. In addition, the authors fail to address the severity of injury and its possible implications for mortality. The ISS scores appear higher for the <36 degree Celsius group than the other groups. The authors do not discuss this or the implications of the higher AIS scores in these patients. Clearly, a patient who is less severely injured would be expected to have a better outcome. In addition, the authors hypothesize that the increased mortality in the <36 degree group is due to coagulopathy. They, however, do not present any hematologic data. They also fail to account for the potential for severe brain injuries to result in a consumptive coagulopathy regardless of body temperature. They provide little data to support their conclusion that a body temperature >= 37 is not associated with worse outcomes and their recommendation for aggressive rewarming.

REVIEWER	Alexander B. Leichtle Insel Data Science Center Inselspital - Bern University Hospital Murtenstrasse 42 3008 Bern Switzerland
REVIEW RETURNED	01-May-2020

GENERAL COMMENTS	All of my suggestions and concerns have been adequately addressed.

REVIEWER	Kristien Verdonck Institute of Tropical Medicine Antwerp, Belgium
REVIEW RETURNED	30-Apr-2020

GENERAL COMMENTS	The authors have provided an adequate rebuttal to the concerns I had raised in the previous review round. At this stage, I have a few minor suggestions regarding formulation: - In the abstract (results), I read " (226/9,012)]" which I do not understand. Typo? - In the section describing strengths and limitations (and elsewhere), there is a phrase "create unmeasured confounding". This sounds strange: I guess the study did not "create" confounding. You rather admit that confounding may be present and that you could not measure it. Please consider reformulating.

	- In the presentation of the sensitivity analysis, I read "to deal with" missing values. The purpose of the sensitivity analysis is to assess the impact of the choices that were made. The sensitivity analysis tries to answer the question: do different approaches to deal with missing data lead to different conclusions? Please consider reformulating. Finally, I keep on noticing that the main OR (for association between hypothermia and death) varies considerably (bivariate: 7.5; multivariable: 2.8; with impulation: 1.2). This makes, in my opinion, the causal inference not very solid. But I imagine that apart from being transparent, there is not much you can do about it at this stage.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4
Reviewer Name: Kristien Verdonck
Institution and Country: Institute of Tropical Medicine Antwerp, Belgium
Please state any competing interests or state 'None declared': None declared
Authors' Response:
We appreciate you for taking out time to review our manuscript and giving these favorable comments. We agree with all your comments and revised the manuscript based on your suggestions. Here are our point-by-point responses to your comments.

Please leave your comments for the authors below
The authors have provided an adequate rebuttal to the concerns I had raised in the previous review round. At this stage, I have a few minor suggestions regarding formulation:
- In the abstract (results), I read " (226/9,012)]" which I do not understand. Typo?
Authors' Response:
Thank you for your comment. We apologize for any misleading statements we may have made. '(226/9012)' means 'mortality number (n=226) / total patients (n=9012). Accordingly, we have revised the manuscript to reflect this as follows:
(Abstract, page 2, lines 44, revised manuscript)
'mortality: 2.5% (mortality number was 226 in total 9,012 patients)'

- In the section describing strengths and limitations (and elsewhere), there is a phrase "create unmeasured confounding". This sounds strange: I guess the study did not "create" confounding. You rather admit that confounding may be present and that you could not measure it. Please consider reformulating.
Authors' Response:
Thank you for this important suggestion. We apologize for the misleading statements we may have made. Accordingly, we have revised the manuscript to reflect this as follows:
(Strengths and limitations of this study, page 3, lines 58-59, revised manuscript)
'Regional differences in the environment and prehospital care provided might create might be an unmeasured confounding.'
(Discussion, page 14, lines 291-292, revised manuscript)
'Third, regional differences in the environment and type of prehospital care provided might create might be an unmeasured confounding factor.'

- In the presentation of the sensitivity analysis, I read "to deal with" missing values. The purpose of the sensitivity analysis is to assess the impact of the choices that were made. The sensitivity analysis tries to answer the question: do different approaches to deal with missing data lead to different conclusions? Please consider reformulating.
Authors' Response:

We apologize for any misleading statements we may have made. We agree your opinion.
Accordingly, we have revised the manuscript to reflect this as follows:
(Methods, page 8, lines 163-165, revised manuscript)
Moreover, we performed multiple imputation as a sensitivity analysis to assess the robustness of the primary analysis, based on the “missing at random” assumption (the detailed method is described in the supplementary file).

Finally, I keep on noticing that the main OR (for association between hypothermia and death) varies considerably (bivariate: 7.5; multivariable: 2.8; with impulation: 1.2). This makes, in my opinion, the causal inference not very solid. But I imagine that apart from being transparent, there is not much you can do about it at this stage.
Authors’ Response:
Thank you for this query and the important suggestion. We agree with your suggestion that outcome can vary depending on the treatment of missing data. Our result of the sensitivity analysis might not be robust with the causal inference. Accordingly, we have revised the manuscript to reflect this as follows:

(Discussion, page 14, lines 288-290, revised manuscript)
Although the results of sensitivity analysis also showed that the hypothermia was associated with the mortality as same as primary analysis, the point estimate was slightly different. Thus, there might be a little concern about the robustness of main analysis.

Reviewer: 1
Reviewer Name: Andrew Kiragu
Institution and Country: Children's of Minnesota and Hennepin Healthcare
Please state any competing interests or state ‘None declared’: None
Authors’ Response:
We appreciate you for taking out time to review our manuscript and giving these favorable comments. We agree with all your comments and revised the manuscript based on your suggestions. Here are our point-by-point responses to your comments.

Please leave your comments for the authors below
While the study offers potential insights into the association of body temperature in this cohort of Japanese children it is unclear how the authors can make the broad conclusions they do based on the data they present. While they have made an effort to provide clarification to the questions raised by the reviewers previously, I do not feel they have done so adequately.
For instance, what degree of hypothermia seemed to correlate with higher mortality? There is a difference between the patient arriving with a temperature of 31 degrees Celsius and 36 degrees Celsius.
Authors’ Response:
Thank you for this query and the important suggestion. As same as your question, we were also curious about what degree of lower BT influence the mortality.
We have shown the non-liner association between BT as a continuous variable and in-hospital mortality using restricted cubic spline in the figure2 of revised version. This figure shows that the odds ratio is increasing as BT dropped below 36 degrees in the range of 34 to 36 degrees. Thus, we guessed that the higher mortality is expected in lower BT on arrival.

(In the range of less than 34 degrees, the number of patients were not adequate to accurately estimate the association with in-hospital mortality. Therefore, we did not shown the range.)
Accordingly, we have revised the manuscript to reflect this as follows:
(Results, page 9, lines 192-193, revised manuscript)
'The odds ratio was shown to increase as BT dropped below BT <36.0 ºC.'

In addition, the authors fail to address the severity of injury and its possible implications for mortality. The ISS scores appear higher for the <36 degree Celsius group than the other groups. The authors do not discuss this or the implications of the higher AIS scores in these patients. Clearly, a patient who is less severely injured would be expected to have a better outcome.
Authors' Response:
We apologize for any misleading statements we may have made. We agree with your opinion that the injury of the disease affects mortality. However, we performed logistic regression analysis, adjusting for the severity of injury such as ISS as a covariate (Factors adjusted as covariates: sex, categorized age, type of injury, categorized RR and HR, GCS, transit time, and ISS). We chose ISS as the covariate to represent the anatomical severity of the injury. In the result, even after adjusting for the severity of the injury, hypothermia was associated with in-hospital mortality. We have highlighted covariates in the methods because our description may be misleading to the reader.
We think your input has made the description more accessible to readers. We appreciate your point of view.
(Methods, page 8, lines 153-154, revised manuscript)
'We chose ISS as the covariate to represent the severity of injury.

In addition, the authors hypothesize that the increased mortality in the <36 degree group is due to coagulopathy. They, however, do not present any hematologic data. They also fail to account for the potential for severe brain injuries to result in a consumptive coagulopathy regardless of body temperature. They provide little data to support their conclusion that a body temperature >= 37 is not associated with worse outcomes and their recommendation for aggressive rewarming.
Authors' Response:
We apologize for any misleading statements we may have made. We agree that our database did not include blood data, such as clotting factors, and the association between the coagulopathy and BT was not investigate. We should comment about the coagulopathy only in the discussion part as one of the hypothesis to interpret the results. We revised the statement to avoid misleading to the reader. Moreover, we removed "coagulopathy" from the keyword. Accordingly, we have revised the manuscript to reflect this as follows:
(Discussion, page 12, lines 254-256, revised manuscript)
In our hypothesis, the potential mechanism behind our primary finding is that hypothermia may worsen the degree of coagulopathy in paediatrics with a severe head injury, which may, in turn, lead to fatal secondary brain injuries and poor outcomes.
(Discussion, page 13, lines 267-268, revised manuscript)
Thus, we believe that the mechanism we have suggested is reasonable.→ our hypothesis may be reasonable.

(Discussion, page 13, lines 277-279, revised manuscript)
'Furthermore, according to the results on higher BT values (≥37.0), aggressive warming among paediatric trauma patients in pre-hospital settings may be justified allowed and preferable to hypothermia, even if the presence of severe head trauma is still an assumption.'

Reviewer: 3

Reviewer Name: Alexander B. Leichtle
Institution and Country:
Insel Data Science Center
Inselspital - Bern University Hospital
Murtenstrasse 42
3008 Bern
Switzerland
Please state any competing interests or state ‘None declared’: None declared

All of my suggestions and concerns have been adequately addressed.
Authors’ Response:
Thank you for this query and the important suggestion. We think your input has made the description more accessible to readers. We appreciate your point of view.

VERSION 3 – REVIEW

REVIEWER	Andrew Kiragu Children's of Minnesota and Hennepin Healthcare
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	I appreciate the authors' responses to the questions raised in the previous review. Some questions and additional requests for clarification: 1. Are the differences between patients in each temperature group statistically significant? I am especially interested in the GCS, ISS, and AIS scores. The reason this needs clarification is that the hypothermia group seems to have higher injury severity scores and could that be an explanation for the differences in mortality? 2. With regard to their statistical analysis, they used multivariate logistic regression? What was the research question that was answered by this statistical method? 3. How did they come up with these conclusions based on Multivariate logistic regression? What was the Wald's test statistic for each of the parameters that they used in their multivariate logistic regression? 4. While increased coagulopathy may hypothetically be responsible for the increased mortality, it seems less plausible particularly in the absence of any hematologic data and the difference in injury severity. Hypothermia has also been associated with fluid and electrolyte shifts, impacts on metabolism, changes in hemodynamics and dysrhythmias, and coagulopathy among others. I think the authors should amend this statement and offer other potential reasons for the mortality difference 5. Given the increased mortality associated with hyperthermia, the recommendation by the authors to vigorously warm patients who are normothermic seems unwarranted and should be removed or clarified.

REVIEWER	Kristien Verdonck Institute of Tropical Medicine Antwerp, Belgium
REVIEW RETURNED	07-Aug-2020

GENERAL COMMENTS	My suggestions and concerns have been adequately addressed.

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 4
Reviewer Name: Kristien Verdonck
Institution and Country: Institute of Tropical Medicine Antwerp, Belgium
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
My suggestions and concerns have been adequately addressed.
(Respond)
We really appreciate the reviewer#4 for the valuable comments.

Reviewer: 1
Reviewer Name: Andrew Kiragu
Institution and Country: Children's of Minnesota and Hennepin Healthcare
Please state any competing interests or state 'None declared': No competing interests

Please leave your comments for the authors below
I appreciate the authors' responses to the questions raised in the previous review. Some questions and additional requests for clarification:
(Respond)
We really appreciate the reviewer#1 for the valuable comments and constructive criticism. We, authors have discussed the comment from the reviewer, and sincerely respond to them. We believe that these reviewing process should have improved the quality of our manuscript. We expect that reviewer#1 also assessed the manuscript as suitable for publication similar to other reviewers. Thank you again for taking the time to review our manuscript.

1. Are the differences between patients in each temperature group statistically significant? I am especially interested in the GCS, ISS, and AIS scores. The reason this needs clarification is that the hypothermia group seems to have higher injury severity scores and could that be an explanation for the differences in mortality?
(Respond)
Thank you for the important question. The main results in this study suggested that the patients with hypothermia (BT <36.0 degree) on hospital arrival was associated with the in-hospital mortality using multivariable logistic regression analysis. We agree with the potential reason the reviewer suggested that the hypothermia group seems to have higher injury severity scores; however, in this analysis, the confounders such as age, type of injury, respiratory rate, heart rate, transit time, GCS, and ISS (including AIS) were adjusted by logistic regression model. Thus, we believe that the calculated adjusted odds ratio indicated the independent association between the body temperature and mortality regardless of these factors.

2. With regard to their statistical analysis, they used multivariate logistic regression? What was the research question that was answered by this statistical method?
3. How did they come up with these conclusions based on Multivariate logistic regression? What was the Wald's test statistic for each of the parameters that they used in their multivariate logistic regression?

(Respond for comment 2 and 3)

As mentioned in method part, we performed multivariable logistic regression analysis to estimate the adjusted odds ratio of Hypothermia or hyperthermia group compared to normothermia group for in-hospital mortality. This adjusted odds ratio means the association between exposure and outcome. With regard to the statistical analysis, we were advised by coauthor who was specialized epidemiology and medical statistics (author T.K.) as described in the section of authors' contribution. We believe that this statistical analysis was standard method for estimating independent association between exposure and outcome, and the reviewer #4 specialized in statistical analysis also checked it and approved it as suitable in review process.
Generally, the adjusted odds ratio and confidence interval are representative statistical value to assess the association between exposure and outcome. We agree that the p-value in Wald's test have been used in the medical research; however, some authority stated that it is not necessary in the presence of 95% confidence intervals. (American Statistical Association, American Journal of Public Health, American Journal of Epidemiology, etc..) Further, we were advised not to use the P-value by other reviewer in the process of reviewing other manuscript in BMJ open. Therefore, we did not indicate p-value; however, if the editor think it should be required, we are willing to add it.

4. While increased coagulopathy may hypothetically be responsible for the increased mortality, it seems less plausible particularly in the absence of any hematologic data and the difference in injury severity. Hypothermia has also been associated with fluid and electrolyte shifts, impacts on metabolism, changes in hemodynamics and dysrhythmias, and coagulopathy among others. I think the authors should amend this statement and offer other potential reasons for the mortality difference

(Respond)
Thank you for important suggestion. We agree with the opinion and mentioned these potential mechanisms in the discussion part as below.

(Interpretation in Discussion part)
On the other hand, hypothermia might cause the fluid and electrolyte shifts, impact on metabolism, changes in hemodynamics and dysrhythmias other than coagulopathy. Therefore, there are some other potential mechanism to explain this result. Further research should be warranted to understand the mechanism completely.

5. Given the increased mortality associated with hyperthermia, the recommendation by the authors to vigorously warm patients who are normothermic seems unwarranted and should be removed or clarified.
(Respond)
We kindly would like to correct the reviewer's misunderstanding. This study did NOT indicate apparent association between the hyperthermia and mortality using multivariable logistic regression analysis (Please see Figure 2 and Table 3). Therefore, we believe that it is not necessary to remove the statement. However, if the editor judge that these statements should be removed, we are willing to do it.