PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Klauke, Nora; Graeff, Ingo; Fleischer, Andreas; Boehm, Olaf; Guttenthaler, Vera; Baumgarten, Georg; Meybohm, Patrick; Wittmann, Maria</td>
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VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Eric Ley</th>
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<td>Cedars-Sinai</td>
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<td>USA</td>
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<td>REVIEW RETURNED</td>
<td>28-Sep-2015</td>
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<table>
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<tr>
<th>GENERAL COMMENTS</th>
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<tr>
<td>This paper is about an important topic, namely how admission hypothermia impacts trauma patients' blood transfusion rate and mortality. Unfortunately, at times, the paper loses focus. For example, Figure 3 and Figure 4 do not support the aim of the paper and are rather obvious, as patients who receive more blood transfusion are expected to require a longer length of stay and have a higher mortality. The paper requires major revisions prior to publication.</td>
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<tr>
<td>Some suggestions:</td>
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<tr>
<td>The abstract conclusion notes that low body temperature during hospital admission is associated with a higher risk of transfusion and death. I imagine that the temperature used was the ED temperature which would be a single temperature at admission and not during admission.</td>
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<tr>
<td>The article summary is poorly written</td>
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<tr>
<td>The use of decimals should stop at perhaps one number after the decimal, for example the AOR for mortality of 8.521 would be better written as 8.5.</td>
</tr>
<tr>
<td>Please translate German words for example in the methods translate &quot;Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten.&quot;</td>
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<tr>
<td>The methodology is flawed in that hypothermia is defined as 36C degrees yet 34C is used in the regression model. Why this change? What occurs between 34C and 36C? What were the univariate predictors and the other adjusted predictors of mortality and transfusion requirements? What predictors were used in the regression model? Please expand upon these questions in the methodology and the results sections.</td>
</tr>
</tbody>
</table>
Importantly, the following sentence was provided and it seems to suggest, based on a p value of 0.46, that hypothermia is not a predictor of transfusion requirement. "In a logistic regression model an admission temperature ≤ 34°C was associated with an 8-fold risk of death (AOR, 8.521; 95% CI 2.546-28.520; p=0.001) and an approximately two fold risk for transfusion (AOR, 1.765; 95% CI 1.011-3.082; p=0.46)." This p value indicates that the discussion and conclusion should be modified.

Remove figures that do not support the central aim of this study.

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>PD Dr.med. Oliver M. Theusinger</th>
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<tr>
<td></td>
<td>Universitätsspital Zürich, Switzerland</td>
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<td>REVIEW RETURNED</td>
<td>10-Oct-2015</td>
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</table>

**GENERAL COMMENTS**

The authors present a retrospective data analysis on prehospital hypothermia and transfusion requirements of red blood cells and outcome.

**Majors comments:**

1) FFP and platelet transfusions should be mentioned as well
2) Prehospitals vs in hospital data should be compared and provided
3) How many patients were administered by the EMS? Only those should be included.
4) Was a transfusion algorithm used? Were coagulation factors administered?
5) The authors should make different groups by temperature (e.g 36-33, 33-30 and below 30)
6) Multiple comparisons – p value of 0.001 should be considered significant.
7) Definition of massive transfusion is not the one generally used – why not? Definition of more than 10 RBCs should be considered.
8) The ISS – mentioned in the limitation, should be the criteria to make groups and to compare them. The GCS is not really the best way – e.g. patient is intoxicated with ethanol, low GCS but also maybe low ISS ....
9) Hemoglobin evolution should be mentioned and discussed (at admission and regarding outcome)
10) There are more data that should be integrated and discussed (lab values regarding coagulation etc.)

**Minor comments:**

Abstract – remove the reference in the abstract. How long was the follow up regarding mortality in hospital? 30 days? Hypothermia on admission – what point of time was it measured? Define died earlier.

Introduction: Reference 1 is missing. The two last paragraphs are part of material and methods – please move them.

Material and Methods: Prehospital GCS is it available as well as temperature – if yes please add them this would improve the manuscript. How many days follow up? P values of 0.001 should be considered significant in this setting.

Results: Table 1 – p values are related to what? overall versus the different groups?
Reviewer 1:
1) This paper is about an important topic, namely how admission hypothermia impacts trauma patients' blood transfusion rate and mortality. Unfortunately, at times, the paper loses focus. For example, Figure 3 and Figure 4 do not support the aim of the paper and are rather obvious, as patients who receive more blood transfusion are expected to require a longer length of stay and have a higher mortality. The paper requires major revisions prior to publication.

Thank you for your insight. This work is a substudy of the German patient blood management (PBM) project. PBM is an evidence-based, multidisciplinary approach to optimizing the care of patients who might require transfusion. We agree, that it seems logical, that patients who receive more blood transfusion are expected to require a longer length of stay (LOS) and have a higher mortality. Nevertheless, we think that it is important to depict the almost linear correlation between transfusion and LOS and the effects on mortality.

2) The abstract conclusion notes that low body temperature during hospital admission is associated with a higher risk of transfusion and death. I imagine that the temperature used was the ED temperature which would be a single temperature at admission and not during admission.

Thank you for this comment. We changed the wording in: “Low body temperature at hospital admission is associated with a higher risk of transfusion and death. (see p.2, l. 22)

3) The article summary is poorly written

We apologize for the inconvenience and thoroughly revised the language and changed the content of the article summary according to the author’s instructions (see p.3, l. 1-18).

4) The use of decimals should stop at perhaps one number after the decimal, for example the AOR for mortality of 8.521 would be better written as 8.5.

The decimals have been changed accordingly throughout the manuscript.

5) Please translate German words for example in the methods translate "Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten."

We followed your proposal and translated the respective German terms into English (see p.5, l. 17-19).

6) The methodology is flawed in that hypothermia is defined as 36°C degrees yet 34°C is used in the regression model. Why this change? What occurs between 34°C and 36°C?

Due to previous reviewer comments and due to the word limitations we removed sections that would have explained this change. We apologize if this point was not clearly described in the manuscript. We now added the following section and hope that we were able to clarify this point:

“To evaluate the influence of prehospital hypothermia on the transfusion rate further subgroups were created (a.≤34.5°C; b.34.6-34.9°C; c. 35.0-35.4°C; d.35.5-36.0°C). This subgroup-analysis showed...”
that a further decreased body core temperature was associated with a rising amount of PRBCs. The analysis revealed that the amount of administered PRBCs rose from group d. (9.0%) to group a. (16.1%). In comparison with the hypothermic patients only 7.2% in the normothermic group (36.1-38.0°C) and 9.4% in the hyperthermic group (>38.1) received a transfusion (p<0.001)." (see p. 9, l. 14-20)

7) What were the univariate predictors and the other adjusted predictors of mortality and transfusion requirements? What predictors were used in the regression model? Please expand upon these questions in the methodology and the results sections.

Thank you for this important comment. The univariate predictors in the binary logistic regression model were temperature and transfusion. This information was included into the methods section (see p.6, l. 7).

8) Importantly, the following sentence was provided and it seems to suggest, based on a p value of 0.46, that hypothermia is not a predictor of transfusion requirement, "In a logistic regression model an admission temperature ≤ 34.5°C was associated with an 8-fold risk of death (AOR, 8.521; 95% Cl 2.546-28.520; p=0.001) and an approximately two fold risk for transfusion (AOR, 1.765; 95% Cl 1.011-3.082; p=0.46)." This p value indicates that the discussion and conclusion should be modified.

We have to apologize for the misunderstanding and thank you for your thoroughly review. In our manuscript it says: "Prehospital hypothermia (≤ 36.0°C) increased the risk of death up to almost 50% (AOR, 1.5; 95%CI 0.7-3.; p<0.001) in contrast to normothermia." (see p.9, l.7-9). With "In a logistic regression model an admission temperature ≤ 34.5°C was associated with an 8-fold risk of death (AOR, 8.521; 95% CI 2.546-28.520; p=0.001) and an approximately two fold risk for transfusion (AOR, 1.765; 95% CI 1.011-3.082; p=0.46)." we wanted to emphasize that a further decreased body temperature might be a risk factor for transfusion. We agree with the reviewer that a p value of 0.46 is not significant enough to say that a body temperature of ≤34.5°C is a risk factor for transfusion. What we are able to say is that hypothermic patients received significantly more PRBC (9.7%) during their hospital stay than normothermic (7.2%) and hyperthermic patients (9.4%), (p<0.001).

9) Remove figures that do not support the central aim of this study.

Thank you again for your comment and we would like to refer to our answer on your first comment.

Reviewer: 2
The authors present a retrospective data analysis on prehospital hypothermia and transfusion requirements of red blood cells and outcome.
Major comments:
1) FFP and platelet transfusions should be mentioned as well.

We agree with the reviewer, that the amount of FFP and platelet transfusions would be an interesting analysis, but this study was performed in the context of the German Patient Blood Management Project. Here, the focus is the transfusion of packed red blood cells (PRBCs).

2) Prehospital vs in hospital data should be compared and provided.

Thank you very much for this advice. A temperature measurement in the prehospital setting was not performed. We analysed the temperature at admission depending on the mode of transportation. Here, we found that patients accompanied by an emergency physician were more often hypothermic than patients accompanied by a paramedic. We included this information in the manuscript (see p.10,
3) How many patients were administered by the EMS? Only those should be included.

We did only include the patients, who were admitted to the hospital (15,895) not depending on the mode of transportation among these are also 6040 patients who came in private cars. Ambulatory patients (36,418) were excluded from the trial.

4) Was a transfusion algorithm used? Were coagulation factors administered?

Thank you for this question. The transfusion algorithm was used according to the Cross-Sectional guidelines for therapy with blood components and plasma derivates. The coagulation factors were not documented.

5) The authors should make different groups by temperature (e.g. 36-33, 33-30 and below 30)

Thank you very much for this comment. A subgroup analysis was performed, but not mentioned in the manuscript due to the word-count limitations. Because this subgroup analysis seems to be of interest, we followed your advice and re-inserted the following section:
To evaluate the influence of prehospital hypothermia on the transfusion rate further subgroups were created (a.≤34.5°C; b.34.6-34.9°C; c. 35.0-35.4°C; d.35.5-36.0°C). This subgroup-analysis showed that a further decreased body core temperature was associated with a rising amount of PRBCs. The analysis revealed that the amount of administered PRBCs rose from group d. (9.0%) to group a. (16.1%). In comparison with the hypothermic patients only 7.2% in the normothermic group (36.1-38.0°C) and 9.4% in the hyperthermic group (>38.1) received a transfusion (p<0.001).” (see p. 9, l. 14-20)

6) Multiple comparisons – p value of 0.001 should be considered significant.

Thank you for your comment, we now consider a p value of 0.001 as statistically significant. We changed this in the methods section. The results remain unchanged because the p-values were below 0.001 already (see p.6, l. 9).

7) Definition of massive transfusion is not the one generally used – why not? Definition of more than 10 RBCs should be considered.

We apologize, that we did not follow the common definition and agree, that the definition of massive transfusion is more than 10 RBCs (see p.8, l.15-16). We changed the results according to the definition and added these to the manuscript.

8) The ISS – mentioned in the limitation, should be the criteria to make groups and to compare them. The GCS is not really the best way – e.g. patient is intoxicated with ethanol, low GCS but also maybe low ISS …. 

We agree with this reviewer’s comment, that the ISS would be a good parameter to classify the patients, but this score is not routinely documented at the Emergency Department, so we could not use this score.

9) Hemoglobin evolution should be mentioned and discussed (at admission and regarding outcome)

To follow the hemoglobin evolution in each patient was not possible due to the high number of patients included into the study. We think, that in this retrospective study a high number of patients is
more important, than a distinctive analysis of some cases.

10) There are more data that should be integrated and discussed (lab values regarding coagulation etc.)

We have to apologize but we included all data that was available for us.

Minor comments:
Abstract – remove the reference in the abstract. How long was the follow up regarding mortality in hospital? 30 days? Hypothermia on admission – what point of time was it measured? Define died earlier.

Thank you for your comments. We removed the reference from the abstract. The follow up regarding the in hospital mortality was in fact 30 days. The temperature in our emergency room is measured at the first contact of a nurse with the patient based on the Manchester Triage System, here the nurse is responsible for taking the patient’s vital signs (RR, pulse, temperature) right after the patient is admitted to the ER.

Introduction: Reference 1 is missing. The two last paragraphs are part of material and methods – please move them
Thank you, according to your advice we moved the last two paragraphs of the introduction to the material and methods part (see p.6, l.13-22). Reference 1 is located in the article summary section (see p. 3, l. 4). If this is not appropriate please let us know and we will make the required changes.
Material and Methods: Prehospital GCS is it available as well as temperature – if yes please add them this would improve the manuscript. How many days follow up? P values of 0.001 should be considered significant in this setting.
We apologize but the prehospital GCS is not available in retrospect. Please find our answers to the other comments in previous answers.

Results: Table 1 – p values are related to what? Overall versus the different groups?
We apologize if the results of the table are not pointed out well enough. The p values at the end of each line show that the results in this line/row are significantly different e.g the PRBC total mean amount of the hypothermic patients compared to the normothermic and hyperthermic patients are significantly different as well as the normothermic compared to the hyperthermic and hypothermic patients. Each line is an overall comparison in this particular group.

**VERSION 2 – REVIEW**

| REVIEWER | Eric Ley  
| Cedars-Sinai  
| USA |
| REVIEW RETURNED | 17-Nov-2015 |

**GENERAL COMMENTS**
The abstract still states, "prehospital hypothermia could be an independent risk factor for transfusion of PRBC (AOR, 1.765; p=0.46)" and "Low body temperature at hospital-admission is associated with a higher risk of transfusion and death." Based on the p value of .46 the data indicates the prehospital hypothermia is not an independent risk factor for transfusion of prbc. Conclusions about the crude rate of transfusion for subsets of hypothermia should not apply as patients with lower body temperatures had worse injury and therefore the regression model must be used to adjust the data.
The data regarding which univariate predictors were used in your regression model remains unknown. On univariate analysis what were the OR for age>65 years, SBP<90, ISS>16, head AIS>3, blunt v penetrating?

REVIEWER
PD Dr Oliver M. Theusinger
Universität Zürich und Universitätsklinik Zürich
Institut für Anästhesiologie, Zürich, Switzerland

REVIEW RETURNED
07-Dec-2015

GENERAL COMMENTS
The authors made an effort to improve the manuscript. All questions were addressed. Unfortunately a lot of data is not available which could be useful and helpful to the reader.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:
1) The abstract still states, "prehospital hypothermia could be an independent risk factor for transfusion of PRBC (AOR, 1.765; p=0.46)" and "Low body temperature at hospital-admission is associated with a higher risk of transfusion and death." Based on the p value of .46 the data indicates the prehospital hypothermia is not an independent risk factor for transfusion of PRBC. Conclusions about the crude rate of transfusion for subsets of hypothermia should not apply as patients with lower body temperatures had worse injury and therefore the regression model must be used to adjust the data.

Thank you for your comment and we apologize for creating a misunderstanding. We rewrote this section (see p. 2; l.20-21, p.10;l.2-5).

However, we calculated the relative risk for receiving PRBC in the group of hypothermic patients. The analysis shows that hypothermic patients have a double relative risk (2.0; CI 95% 1.3-3.1) for transfusion compared to normothermic patients (p=0.002). This fact allows the conclusion that hypothermia seems to be associated with a higher risk of transfusion.

2) The data regarding which univariate predictors were used in your regression model remains unknown. On univariate analysis what were the OR for age>65 years, SBP<90, ISS>16, head AIS>3, blunt v penetrating?

Thank you for this insight. We made a univariate analysis of age ≥< 65 years and SBP >/≤ 90. We are now able to give you the following results:
Odds Ratio: SPB ≤90/>90 for mortality: OR 0.109 (0.087-0.138) p<0.001; that means that patients with SBP>90 have an increased risk of death by factor 0.1.

Odds Ratio: SPB ≤90/>90 for transfusion: OR 0.389 (0.301-0.503) p<0.001; that means that patients with a SBP>90 have an increased risk for transfusion by factor 0.4.

Odds Ratio: age ≥65/<65 years for mortality: OR 3.140 (2.688-3.669) p 0.001; the analysis shows that patients ≥65 had threefold risk of death compared to patients <65.
Odds Ratio: age ≥65/<65 years for transfusion: OR 1.935 (1.722-2.175) p<0.001; Patients of 65 or older showed a double risk for receiving transfusion compared to younger patients.

We could not do an analysis of the ORs to the ISS/head AIS because we do not have access to these data of the analyzed patients in retrospect.

We gladly inserted these additional data into the manuscript (see p. 9; l.3-6 and p.10; l.6-10).

### VERSION 3 - REVIEW

<table>
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<th>REVIEWER</th>
<th>Eric Ley</th>
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<td>Cedars-Sinai Medical Center</td>
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<td></td>
<td>USA</td>
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<td>REVIEW RETURNED</td>
<td>11-Jan-2016</td>
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| GENERAL COMMENTS  | While the paper has made improvements there is confusion over what defines hypothermia. The methods state <36°C is hypothermia. Yet the the regression model uses <34.5°C. Please update the regression model for patients with <36°C. Also, Figure 1 and 2 do not include temperatures. Figure 3 should be removed. |

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<th>REVIEWER</th>
<th>Theusinger Oliver M.</th>
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<td>University Hospital Zurich and University Zurich, Switzerland</td>
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<td>REVIEW RETURNED</td>
<td>26-Jan-2016</td>
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| GENERAL COMMENTS  | The reviewer completed the checklist but made no further comments. |

### VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

1. While the paper has made improvements there is confusion over what defines hypothermia. The methods state <36°C is hypothermia. Yet the the regression model uses <34.5°C. Please update the regression model for patients with <36°C.

   Thank you for this input. Our definition of hypothermia is temperatures below 36.0°C. We apologize for the confusion. In the text it says:” Prehospital hypothermia (≤ 36.0°C) increased the risk of death up to almost 50% (AOR, 1.5; 95% CI 0.7-3.; p<0.001) in contrast to normothermia.” (see p. 9; l 11-13). And it also says in the text: "In a logistic regression model an admission temperature ≤34.5°C was associated with an 8-fold risk of death (AOR, 8.5; 95% CI 2.5-28.5; p=0.001).” (see p.9; l 25-26). Based on the first results of the regression model we wanted to analyze further hypothermia subgroups. So we expanded the regression model by <34.5°C. We wanted to show that the lower the body core temperature decreases the more dangerous for the patient and their outcome.

2. Also, Figure 1 and 2 do not include temperatures. Figure 3 should be removed.

   We gladly changed the figures according to your advice and we removed figure 3. Figure 4 is now figure 3 (see p. 9; l.2) and figure 1/2 now include the temperatures.
| REVIEWER | Eric Ley  
|          | USA          |
| REVIEW RETURNED | 17-Feb-2016 |

| GENERAL COMMENTS | The reviewer completed the checklist but made no further comments. |

| REVIEWER | PD Dr O.M. Theusinger  
|          | University Hospital Zurich, University Zurich, Switzerland |
| REVIEW RETURNED | 03-Mar-2016 |

| GENERAL COMMENTS | The reviewer completed the checklist but made no further comments. |
Effects of prehospital hypothermia on transfusion requirements and outcomes: a retrospective observatory trial

Nora Klauke, Ingo Gräff, Andreas Fleischer, Olaf Boehm, Vera Gutenthaler, Georg Baumgarten, Patrick Meybohm and Maria Wittmann

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