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Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial

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Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial

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ABSTRACT

Objectives: Prehospital hypothermia is defined as a core temperature < 36.0°C and has been shown to be an independent risk factor for early death in trauma patients (1). In a retrospective study   a possible correlation between the body temperature at the time of admission to the emergency room and subsequent in-hospital transfusion requirements and the in-hospital mortality rate was explored.

Setting: This is a retrospective single-center study at a primary-care hospital in Germany.

Participants: 15,895 patients were included in this study. Patients were classified by admission temperature and transfusion rate. Excluded were ambulant patients and patients with missing data.

Primary and secondary outcome measures: The primary outcome values were length of stay in days (LOS), in-hospital mortality, the transferred amount of packed red blood cells (PRBCs), and admission to an intensive care unit (ICU). Secondary influencing variables were the patients´age and the Glasgow Coma Scale (GCS).

Results: In 22.85% of the patients hypothermia was documented. Hypothermic patients died earlier in the course of their hospital stay than non-hypothermic (p<0.001). An administration of 1-3 packed red blood cells (PRBC) increased the length of stay significantly (p<0.001) and transfused patients had an increased risk of death (p<0.001). Prehospital hypothermia could be an independent risk factor for transfusion of PRBC (AOR, 1.765; p=0.46) and mortality (AOR 8.521; p=0.001).

Conclusion: Low body temperature during hospital-admission is associated with a higher risk of transfusion and death. Hence, a greater awareness for a prehospital temperature management should be established.

ARTICLE SUMMARY

Prehospital and perioperative hypothermia influence the patients' outcome negatively. It was shown in various trials that it leads to adverse myocardial outcomes, increases transfusion requirements, infections and mortality. Transfusion of red blood cells has been proven to be a risk factor for allergic or febrile hemolytic reactions, post-operative infections and sepsis, and cancer recurrence.

Though various studies about possible negative consequences of hypothermia have been conducted the incidence of prehospital hypothermia is still very high.

Strengths and limitations of this study

To this day, there is only one other trial on prehospital hypothermia and transfusion available (1). In our very large study we found evidence that prehospital hypothermia is a risk factor for increased in-hospital mortality. The combination of prehospital hypothermia with administration of packed red blood cells did show an increase of mortality as well.

Due to the retrospective study design there are certain limitations such as the patients' diagnoses that might have influenced the temperature regulation, medications, and the exact hemoglobin level of the transfused patients.

INTRODUCTION

The incidence of prehospital hypothermia, defined as a core temperature below 36.0°C, is frequently observed in patients admitted to the emergency room (2) mainly due to a difficult and prolonged rescue, infusion of cold resuscitation fluids (3), weather, age and a critical health condition. Together with acidosis and coagulopathy hypothermia has been termed *lethal triad of death* (4).

Hypothermia alters enzymatic reactions of the coagulation cascade during the initiation phase and decreases platelet function (4,5), possibly leading to severe bleeding and consecutively required blood transfusion. It has been shown that the amount of applied fluids and transfused PRBC is directly linked to hypothermia, is associated with a worse clinical outcome (6,1), and increases the risk for postoperative mortality (7). Acute complications after PRBC transfusion can comprise of hypothermia, hypocalcaemia, hypomagnesiaemia, citrate toxicity, lactic acidosis and air embolism (8). Additionally non-infectious serious hazards of transfusion (NISHOTs) ranging from common complications, e.g., allergic or febrile hemolytic reactions (9) to rare, life-threatening entities like the transfusion-related lung injury (TRALI) (10) or the transfusion associated Graft versus Host Disease (TA-GVHD) (11) can still pose a serious threat to patients. The patients´ outcome might also be negatively affected by non-antibody-antigene dependent reactions known as transfusion-related immune modulation (TRIM) (9) that are suspected to increase the   rate of infection and tumor-recurrence after transfusion (12). The aim of this study was to evaluate the effects of prehospital hypothermia on transfusion rate and mortality. This retrospective single-center database analysis was executed in the framework of a Germany-wide multi-center initiative for patient blood management, which aims at reducing the amount of blood transfusion whenever feasible and beneficial for the patient.

Approval for the patient blood management study was given by the ethics committee of the medical faculty of the University of Bonn chaired by Professor K. Racké (number 082/13 from the 7th of May 2013). The present study was purely retrospective and

approval by the ethic committee was not necessary as the General Medical Council explicitly excluded retrospective studies from approval in their code of medical ethics (§15/1) (13).

All collected clinical data evaluated in this study were fully anonymized before analysis. Therefore, according to prior agreement with the local ethics committee and the data protection officer appointed by the University Hospital, verbal or written informed consent was not obtained.

MATERIAL AND METHODS

This study reviewed the University Hospital Bonn (UHB) Emergency Department database from January 1, 2012 until December 31, 2013 that contained anonymized data of 54,732 patients. Included in this study were patients with recorded admission temperature, documented admission and discharge date, age, Glasgow Coma Scale (GCS), intensive care unit (ICU) admission, mode of transportation and information about the in-hospital mortality.

As a standard operating procedure each patient's clinical health status is evaluated by a nurse in the framework of an emergency triage system when admitted to the ED. The triage includes the tympanal measurement of the patient´s temperature. This method is easy and fast, shows accurate results and can be recommended for this purpose (14). The LOS was calculated electronically. The GCS was evaluated by the emergency physician arriving at the scene.

The amount of transfused red blood cells was evaluated by matching our database with the University Hospital Bonn Institute of Transfusion Medicine's database and is presented as raw number of received packages (PRBC). The transfusion-criteria are given in the German guideline: Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten (2014) (15).

According to the German guideline: S3 Vermeidung perioperativer Hypothermie 2014, a patient was defined hypothermic when presented with a temperature below 36.0°C, , normothermic with a temperature from 36.1°C to 38.0°C and hyperthermic when the temperature was >38.1°C on arrival at the ED.

The primary outcome values were length of stay in days (LOS), in-hospital mortality, the transferred amount of PRBCs, and ICU admission.

Secondary influencing variables such as age and GCS were considered further grouping variables to compare the hypothermic with the normothermic and hyperthermic patients.

For quantitative data evaluation the median test and Mann-Whitney-U-Test were used. To objectify if transfusion and mortality was independent of the patient's temperature, age and GCS contingency tables were created and analyzed with a chi² test. To compare means Student's t-test was used. Kaplan Meier analysis was applied to identify whether hypothermic and transfused patients had a higher risk of mortality than the other patients in the study. Binary logistic regression was used to determine risk factors for mortality. The results are given in adjusted odd ratio (AOR) and reached statistical significance with p<0.05. Other results are presented as mean (standard deviation, SD) for ordinal data, median for data which had expected peaks and descriptive data as raw percentages. Statistical analysis was performed using SPSS Statistics Amos 22.0 (IBM Corporation, Armonk, USA).

RESULTS

During the two-year study period 15,895 patients out of 54,732 patients that arrived at the emergency department (ED) were included in the study. 36,418 ambulant patients (admitted and discharged within 24 hours) and patients lacking the required data were excluded. Also excluded were 1,675 patients who required interdisciplinary consultation or were admitted as case conferences from other hospitals.

Of the included patients 22.85% were hypothermic according to the German guideline, 71.78 % normothermic and 5.36% hyperthermic.

The mean LOS for all study-patients was 8.60 days (median 4.90d, SD 12.30). After arrival at the emergency department 13.99% of the patients were transferred to the ICU. In this group 15.56% were hyperthermic, 14.33% normothermic and 12.71% hypothermic (p=0.292)(demographic data see table 1).

Table 1: Demographic data of the study population

Variable	Total (n=15895)	Hypothermic patients (n=3348)	Normothermic patients (n=10517)	Hyperthermic patients (n=786)	p
Age, mean (SD); [median]	57.8 (21.1); [61]	60.3 (20.5);[64]	57.2 (21.1);[60]	56.3 (20.3);[60]	p<0.001
Sex, male (%)	57.3	59.9	55.5	62.1	p<0.001
Temperature, mean (SD); [median]	36.5 (0.8);[36.5]	35.6 (0.5);[35.8]	36.7 (0.4);[36.6]	38.8 (0.6);[38.6]	p<0.001
Transfused (%)	8.2	9.7	7.2	9.4	p<0.001
PRBC total, mean amount	0.6	0.7 (4.3)	0.5 (3.0)	0.6 (4.1)	p<0.001
PRBC during the first 24h,mean(SD)	0.8 (2.8)	1.1 (3.2)	0.5 (1.8)	0.2 (0.9)	p=0.001
PRBC day 2, mean(SD)	1.5 (3.6)	1.8 (4.1)	1.1 (2.6)	0.8 (1.6)	p=0.042
PRBC day 3, mean(SD)	2.2 (4.3)	2.5 (4.8)	1.7 (3.3)	1.2 (1.8)	p=0.05
Systolic BP (mmHg)	140	139	141	135	p<0.001
GCS, mean(SD); [median]	12.8 (4.3);[15]	12.3 (4.5);[15]	13.2 (3.9);[15]	12.7 (4.1);[15]	p=0.001
ICU Admission (%)	14	12.7	14.3	15.6	p=0.292
LOS(d), mean(SD); [median]	8.6 (12.3);[4.9]	8.7 (12.4);[4.7]	8.4 (11.7);[4.8]	10.1 (13.3);[6.2]	p<0.001
Mortality (%)	5.1	7.4	3.4	4.1	p<0.001

Table 1: Demographic data of the study population (SD- Standard deviation, PRBC- packed red blood cells, BP- blood pressure, GCS- Glasgow coma scale, ICU- Intensive care unit, LOS- Length of stay)

Effects of hypothermia

Hypothermic patients died earlier than normothermic and hyperthermic patients (p<0.001) as depict in the Kaplan Meier analysis (figure 1).

Additionally the analysis revealed that patients who died during the study period had an already decreased core temperature when admitted to the ED. Those patients had a significantly lower mean body temperature of 36.27°C (SD 1.12) than patients that were discharged alive (36.57°C SD 0.81)(p<0.001).

Hypothermic patients had a mean LOS of 8.74d (median 4.71d SD 12.42), normothermic a mean LOS of 8.36d (median 4.82d SD 11.65) and hyperthermic patients a mean LOS of 10.07d (median 6.20d SD 13.31). The LOS of the patient groups differed significantly (p<0.001), (figure 2).

Effects of blood transfusion

Of the study patients 1295 patients (8.1%) received PRBC during their stay with a median of 4 PRBC. 1-3 PRBC were transfused to 54.2% of the patients, 4-6 PRBC to 26.6%, 7-11 PRBC to 13.5 % and 14.7% received a massive transfusion, defined as 12 PRBC or more. The more PRBC a patient received the longer was the LOS at the hospital (p<0.001), (figure 3).

The in-hospital mortality rate of 5.1% for all study- included patients increased with the number of administered PRBC. It reached 9.9% for patients with 1-3 PRBC; 14.0% for 4-6 PRBC, 16.9% for 7-11 PRBC and 37.8% for patients with >12 PRBC (p<0.001). Patients who died during their clinical stay received a mean amount of 13.3 (SD 16.4) PRBC.

Patients who were admitted to the ICU had a fivefold increased risk of death (AOR 5.565; 95% Cl 1.957-15.822; p=0.001).

Referring to Kaplan Meier function transfused patients died at a significantly higher rate and earlier than patients without transfusion (p<0.001),(figure 4).

Influence of hypothermia on transfusion

Hypothermic patients received significantly more PRBC (9.7%) during their hospital stay than normothermic (7.2%) and hyperthermic patients (9.4%), (p<0.001). Binary logistic regression model revealed that both body temperature and transfusion rate are risk factors for mortality. Prehospital hypothermia increased the risk of death up to almost 50% (AOR, 1.471; 95%Cl 0.715-3.027; p<0.001) in contrast to normothermia. Transfusion of 1-3 PRBC increased the risk of death by 17% (AOR 0.174; 95%Cl 0.112-0.272; p<0.001), similar to receiving 4-6 PRBC (AOR 0.253; 95% Cl 0.157-0.407), and 7-11 PRBC (AOR 0.296; 95% Cl 0.169-0.521). The risk of death increased by factor 5 for patients with >12 PRBC compared to patients with only 1-3 PRBC (AOR 5.74; 95% Cl 1.301-2.193), (p<0.001).

In a logistic regression model an admission temperature ≤34°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).

Contingency table displayed that 25% of the patients with a GCS≤8 received blood products whereas only 7% patients with a GCS >9 received PCRB during their stay (p<0.001). It also occurred that the mean GCS in transfused patients was significantly lower (GCS 10) than that in non-transfused patients (GCS 13), (p<0.001). A GCS ≤8 (AOR 12.236; 95%Cl 7.803-19.188; p=0.001) and transfusion of PRBC were connected with an increased risk of death (AOR 3.810; 95%Cl 2.048-7.088; p=0.001). The Student´s t-test revealed that hypothermic patients had a significantly lower GCS (median 12.3 SD 4.5) than normothermic patients (median 13.2 SD 3.9), (p<0.001), but there was no significant difference in the GCS of hypothermic to hyperthermic patients (median 12.7 SD 4.1) (p=0.47).

To investigate the influence of the patient´s age on LOS and received PRBCs three different groups were created (i. <45 years, ii. 46-60 years, iii. >61 years). Most patients were older than 61 years (50.6%). There were 28.1% of patients <45 years old and 21.4% between 46-60 years old. Considering the median LOS it appeared that patients belonging to iii. stayed significantly longer at the hospital (median LOS 6.1 days) than younger patients (p < 0.001).Patients belonging to group ii. stayed 4.8 days and patients that were 45 years and younger had a median LOS of 3.3 days.

Considering the transfused blood products patients in group ii. received the largest amount of PRBC (mean value 10.0 PRBC, median 4 PRBC, SD 15.0), whereas patients in group iii. received a mean amount of 6.6 PRBC (median 4 SD 8.8). The patients in group i. received 5.9 PRBC (median 3 SD 9.7).

DISCUSSION

The overall aim of this study was to investigate the impact of hypothermia on transfusion rates and mortality at the UHB. Our findings indicate that patients presenting with hypothermia on admission to the ED have adverse outcomes compared to normothemic and hyperthermic patients. The same is applicable to hypothermic patients that received transfusions of PRBC during their hospital stay. Though it seems to be obvious that hypothermia might be a negative outcome factor during the rescue and recovery process, the incidence of hypothermia in EDs remains a commonly observed phenomenon. Heat loss that may be caused by prolonged rescue time and severe injuries is prolonged throughout the transportation to the next ER due to a non-existing standardized prehospital warming management.

The study-results show that almost one third of the patients arrived hypothermic at the ED. We orientated ourselves on the current German guideline defining hypothermia as a core body temperature < 36.0°C (16). Other studies on this subject defined hypothermia as a core body temperature < 36.5°C; < 35.0°C and < 34.5°C (1,17,18). Setting our temperature-limit at 36.0°C led to the fact that our hypothermic patients group is not as large as in e.g the study by M. Bukur at al.(1).

In our study hypothermic patients did not have an increased LOS. Similar results are shown by H. Trentzsch et al. (6), whereas another paper found that patients with a body temperature <35.0°C and major trauma stayed longer at the hospital (19). Accordant results in a retrospective paper by R. Martin et al. showed a significantly increased LOS and ICU admission rate for hypothermic major trauma patients (< 35.0°C) compared to normothermic patients (p<0.001) (17). The differences in our findings compared to the studies by S. Ireland et al. and R. Martin et al. may be either caused by their collective of patients or by the fact that the Kaplan Meier analysis in our study revealed that hypothermic patients had an increased mortality rate and died earlier than patients with normal or febrile temperatures. Martin et al. and Ireland et al. mainly

used results of major trauma patients in their studies whereas we included every patient admitted to the emergency department despite the injury severity score. Our results revealed that hyperthermic patients had the longest LOS and were more often admitted to the ICU. We suggest that those patients were septic or in another febrile critical health condition that needed intensive treatment.

Hypothermic patients showed an increased consumption of PRBC and an increased risk of death. Responsible for these findings might be the partial impairment of the coagulation by hypothermia already outlined in the introduction (4,5,20). Other factors that additionally affected the coagulation of the patients included in this study cannot be retraced due to the retrospective study design.

The in-hospital death rate for patients with >12 PRBC-units of red blood cells rose up to 37.8% whereas patients with 1-3 PRBC units had a death rate of 9.9%.The multi-centered patient blood management initiative, in which this study is integrated in, aims at an increase in patient safety and reduction of liberal admission of 1-3 PRBC because it was shown that already a small amount of allogenic blood transfusion is associated with septic, pulmonary and embolic complications (21). Other possible reasons for increased mortality rate are predisposition to nosocomial and postoperative infections, cancer recurrence and microchimerism through the infusion of PRBC (22). Our results prove that patients with 1-3 PRBC had a significantly increased LOS compared to patients that received no transfusion (p<0.001). They additionally had an enhanced risk of death (AOR 0.174; p<0.001).

Our analysis demonstrated that patients with massive transfusion died earlier than other patients. One-third of the total amount of PRBC for each massive transfused patient in the ED was administered within the first 72 hours. Among this group are most likely patients with severe injuries and major trauma that are in the urgent need of resuscitation fluids e.g. red blood cells as subsidized by a large retrospective study by R.R Barbosa et al. (23).

There was also a significant association between the GCS and PRBC. One fourth of the patients with a GCS of ≤8 were in need of PRBC which seems reasonable since the GCS classifies the consciousness in patients with severe injuries.

Patients of 61 years and older had the longest LOS. Despite of this result, patients in the middle-aged group (46-60 years) received the most PRBC during their stay at the hospital. The study by R.R. Barbosa displayed that age was independently associated with a higher risk of mortality in an observed 30-day period among transfused patients after trauma (23). According to this our study showed that patients who died during the stay at the hospital had a mean age of 71.34 (SD 14.34) whereas patients that were discharged alive had a mean age of 57.12 (SD 21.16), (p<0.001).

Limitations

Due to the retrospective study design it was not possible to create a causal connection between the admission temperature and the distribution of PRBC as it would be in a prospective clinical trial. This study did not include the patients' diagnoses that might have influenced the temperature regulation. Additionally, medications such as anticoagulants could not have been retraced. We were not able to retrace the exact hemoglobin level of the transfused patients and to differentiate between patients with accidental and induced hypothermia retrospectively. It has to be taken into account that ambulances are able to cool patients, and that this is a standard procedure in patients with heart attacks, cardiac arrest and patients with possible brain damage as these patients benefit from a lower core body temperature (24–25).

It has to be taken into consideration that our review did not analyze the connection of the injury severity score (ISS) of each patient with the body temperature and the transfusion requirement. This is due to the fact that it was not possible to reproduce the ISS in retrospect. A prospective controlled clinical trial on a connection between temperature, transfusion requirement and ISS could prove the importance of this subject.

CONCLUSION

Despite the mentioned limitations this large retrospective study was able to show that prehospital hypothermia is associated with an increased transfusion requirement and a worse outcome compared to normothermic and not transfused patients.

This study should create further awareness for the importance of the patient's body temperature and a more restrictive transfusion regime for patients that are not in life-threatening need of resuscitation fluids. Patients with low prehospital body core temperatures, due to the injury severity or a prolonged rescue should be protected from further heat loss with trauma warming blankets. An effective warming management installed on all ambulances and in the EDs could help preventing hypothermic patients from a worse outcome as induced through the primary injury. It is to emphasize that this is a hypothesis suggested by the findings of this study, a prospective randomized controlled trial should be conducted to investigate, if a prehospital worming is beneficial for the patients.

Extra data, which is not included in this paper is available by emailing the corresponding author Mrs. Maria Wittmann.

Contributorship statement:

NK: data alalysis, literature research, writing of the manuscript

IG: planning of the trial

AF: data analysis

OB: writing of the manuscript

GB: planning the trial, writing the manuscript

VG: writing the manuscript

MW: planning of the trial, data alalysis, literature research, writing of the manuscript

We declare no funding and no competing interests.

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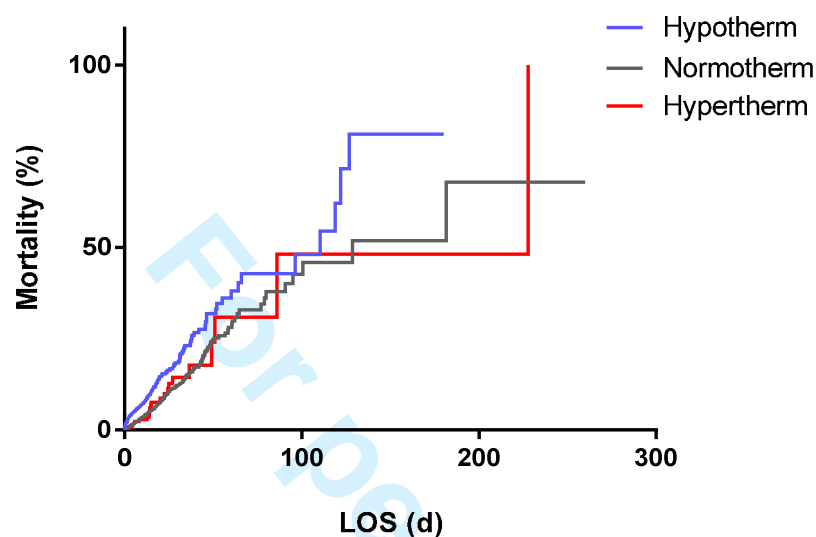Figure 1: Mortality curve for each temperature group

Figure 1: Kaplan Meier analysis: Hypothermic patients had the highest mortality rate (LOS (d): length of stay in days)

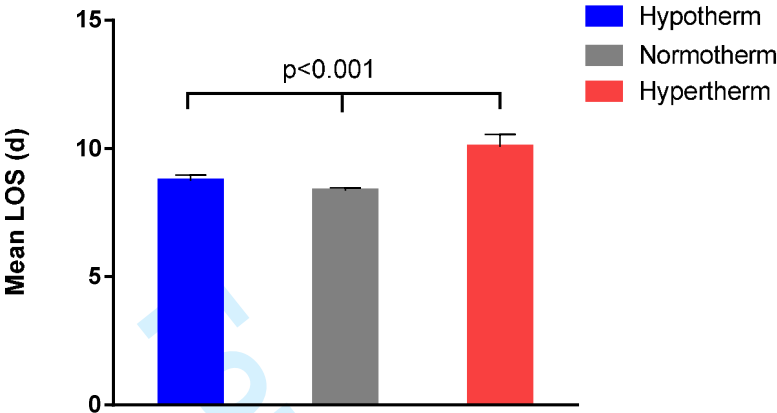Figure 2: Length of stay for each temperature group

Figure 2: LOS in days ± SEM for each temperature category

(LOS (d): length of stay in days, SEM: standard error of the mean)

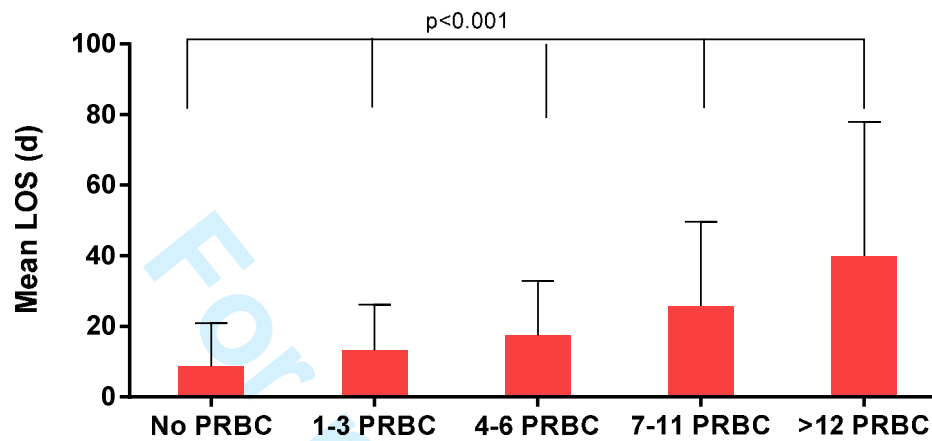Figure 3: Effects of blood transfusion on the length of stay

Figure 3: mean LOS (d) in relation to amount of PRBC

(LOS (d): length of stay in days; PRBC: packed red blood cells)

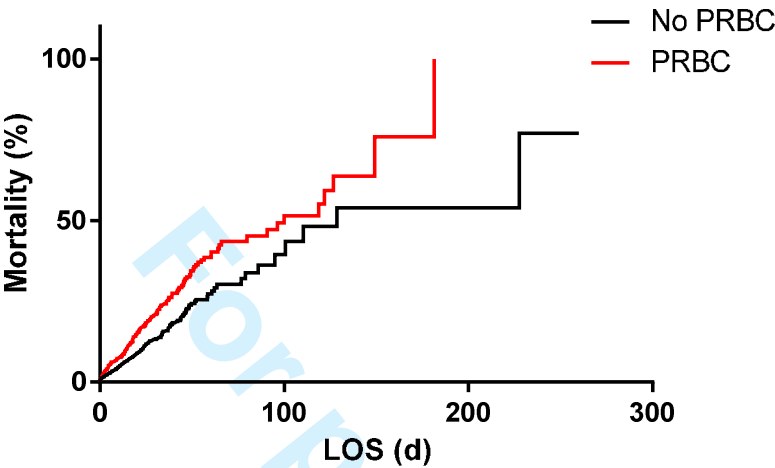Figure 4: Mortality rate for transfused patients

Figure 4: Kaplan Meier Analysis: Mortality of transfused patients compared to not transfused patients

(LOS (d): length of stay in days; PRBC: packed red blood cells)

STROBE Statement by Nora Klauke

	Item No	Recommendation
Title and abstract	1	*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		See page: 1
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		See page: 4
Objectives	3	State specific objectives, including any prespecified hypotheses
		See page: 4
Methods		
Study design	4	Present key elements of study design early in the paper
		See page: 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		See page: 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		See page: 6-7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		See page: 6
Bias	9	Describe any efforts to address potential sources of bias
		See page: 14
Study size	10	Explain how the study size was arrived at
		See page: 8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **See page: 7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **See page: 7**

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram **See page: 8**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **See page: 8 and Table 1**
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **See pages: 9-10**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **See pages: 9-10**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **See page: 11**

Discussion		
Key results	18	Summarise key results with reference to study objectives
		See page: 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
		Discuss both direction and magnitude of any potential bias
		See page: 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,
		multiplicity of analyses, results from similar studies, and other relevant evidence
		See pages: 12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results
		See page: 13
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,
		for the original study on which the present article is based
		See page: Cover letter/Title page - no funding declared
Ethics	23	**See pages: 4-5**

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Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial

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Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial

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1 **ABSTRACT**

2 *Objectives:* Prehospital hypothermia is defined as a core temperature < 36.0°C and has

3 been shown to be an independent risk factor for early death in trauma patients. In a

4 retrospective study a possible correlation between the body temperature at the time of

5 admission to the emergency room and subsequent in-hospital transfusion requirements

6 and the in-hospital mortality rate was explored.

7 *Setting:* This is a retrospective single-center study at a primary-care hospital in

8 Germany.

9 *Participants:* 15,895 patients were included in this study. Patients were classified by

10 admission temperature and transfusion rate. Excluded were ambulant patients and

11 patients with missing data.

12 *Primary and secondary outcome measures:* The primary outcome values were length of

13 stay in days (LOS), in-hospital mortality, the transferred amount of packed red blood

14 cells (PRBCs), and admission to an intensive care unit (ICU). Secondary influencing

15 variables were the patients´age and the Glasgow Coma Scale (GCS).

16 *Results:* In 22.85% of the patients hypothermia was documented. Hypothermic patients

17 died earlier in the course of their hospital stay than non-hypothermic ($p < 0.001$). An

18 administration of 1-3 packed red blood cells (PRBC) increased the length of stay

19 significantly ($p < 0.001$) and transfused patients had an increased risk of death ($p < 0.001$).

20 Prehospital hypothermia could be an independent risk factor for transfusion of PRBC

21 (AOR, 1.765; $p = 0.46$) and mortality (AOR 8.521; $p = 0.001$).

22 *Conclusion:* Low body temperature at hospital-admission is associated with a higher

23 risk of transfusion and death. Hence, a greater awareness for a prehospital temperature

24 management should be established.

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1   **ARTICLE SUMMARY**

2   *Strengths and limitations of this study*

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4   - Using a retrospective design we investigated the effects of pre-hospital
5   hypothermia on patient in-hospital mortality, length of hospital stay, ICU
6   admission and transfusion requirements in the university hospital setting

7   - The hospital database captured a total of 54,732 subjects admitted to the
8   emergency department of the University Hospital of Bonn between 1 January
9   2012 and 31 December 2013

10   - 15,895 subjects with inpatient-status recorded admission temperature, hospital
11   admission and discharge dates, demographics, Glasgow Coma Scale (GCS),
12   intensive care unit (ICU) admission, mode of transportation and information
13   about the in-hospital mortality were eligible for full set data analyses

14   - The retrospective approach does not allow for causal relationships between pre-
15   hospital hypothermia and any of the designated outcome measures

16   - The potential influence of patients diagnoses on temperature regulation,
17   medication regimes and hemoglobin levels of transfused patients was not
18   accounted for and may therefore confound observed effects

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1 **INTRODUCTION**

2 The incidence of prehospital hypothermia, defined as a core temperature below 36.0°C,

3 is frequently observed in patients admitted to the emergency room (1) mainly due to a

4 difficult and prolonged rescue, infusion of cold resuscitation fluids (2), weather, age and

5 a critical health condition. Together with acidosis and coagulopathy hypothermia has

6 been termed *lethal triad of death* (3).

7 Hypothermia alters enzymatic reactions of the coagulation cascade during the initiation

8 phase and decreases platelet function (3,4), possibly leading to severe bleeding and

9 consecutively required blood transfusion. It has been shown that the amount of applied

10 fluids and transfused PRBC is directly linked to hypothermia, is associated with a worse

11 clinical outcome (5,6), and increases the risk for postoperative mortality (7). Acute

12 complications after PRBC transfusion can comprise of hypothermia, hypocalcaemia,

13 hypomagnesiaemia, citrate toxicity, lactic acidosis and air embolism (8). Additionally

14 non-infectious serious hazards of transfusion (NISHOTs) ranging from common

15 complications, e.g., allergic or febrile hemolytic reactions (9) to rare, life-threatening

16 entities like the transfusion-related lung injury (TRALI) (10) or the transfusion

17 associated Graft versus Host Disease (TA-GVHD) (11) can still pose a serious threat to

18 patients. The patients´ outcome might also be negatively affected by non-antibody-

19 antigene dependent reactions known as transfusion-related immune modulation (TRIM)

20 (9) that are suspected to increase the rate of infection and tumor-recurrence after

21 transfusion (12). The aim of this study was to evaluate the effects of prehospital

22 hypothermia on transfusion rate and mortality. This retrospective single-center database

23 analysis was executed in the framework of a Germany-wide multi-center initiative for

24 patient blood management, which aims at reducing the amount of blood transfusion

25 whenever feasible and beneficial for the patient.

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1 **MATERIAL AND METHODS**

2 This study reviewed the University Hospital Bonn (UHB) Emergency Department

3 database from January 1, 2012 until December 31, 2013 that contained anonymized data

4 of 54,732 patients. Included in this study were patients with recorded admission

5 temperature, documented admission and discharge date, age, Glasgow Coma Scale

6 (GCS), intensive care unit (ICU) admission, mode of transportation and information

7 about the in-hospital mortality.

8 As a standard operating procedure each patient's clinical health status is evaluated by a

9 nurse in the framework of an emergency triage system when admitted to the ED. The

10 triage includes the tympanal measurement of the patient´s temperature. This method is

11 easy and fast, shows accurate results and can be recommended for this purpose (13).

12 The LOS was calculated electronically. The GCS was evaluated by the emergency

13 physician arriving at the scene.

14 The amount of transfused red blood cells was evaluated by matching our database with

15 the University Hospital Bonn Institute of Transfusion Medicine's database and is

16 presented as raw number of received packages (PRBC). The transfusion-criteria are

17 given in the German guideline: Cross-Sectional guidelines for therapy with blood

18 components and plasma derivates (2014) (14).

19 According to the German guideline: S3 prevention of perioperative hypothermia (2014),

20 a patient was defined hypothermic when presented with a temperature below 36.0°C, ,

21 normothermic with a temperature from 36.1°C to 38.0°C and hyperthermic when the

22 temperature was >38.1°C on arrival at the ED.

23 The primary outcome values were length of stay in days (LOS), in-hospital mortality,

24 the transferred amount of PRBCs, and ICU admission.

25 Secondary influencing variables such as age and GCS were considered further grouping

26 variables to compare the hypothermic with the normothermic and hyperthermic patients.

1 For quantitative data evaluation the median test and Mann-Whitney-U-Test were used.

2 To objectify if transfusion and mortality was independent of the patient's temperature,

3 age and GCS contingency tables were created and analyzed with a chi² test. To compare

4 means Student's t-test was used. Kaplan Meier analysis was applied to identify whether

5 hypothermic and transfused patients had a higher risk of mortality than the other

6 patients in the study. Binary logistic regression was used to determine risk factors for

7 mortality. The univariate predictors were the body temperature and transfusion. The

8 results are given in adjusted odd ratio (AOR) and reached statistical significance with

9 $p < 0.001$. Other results are presented as mean (standard deviation, SD) for ordinal data,

10 median for data which had expected peaks and descriptive data as raw percentages.

11 Statistical analysis was performed using SPSS Statistics Amos 22.0 (IBM Corporation,

12 Armonk, USA).

13 Approval for the patient blood management study was given by the ethics committee of

14 the medical faculty of the University of Bonn chaired by Professor K. Racké (number

15 082/13 from the 7th of May 2013). The present study was purely retrospective and

16 approval by the ethic committee was not necessary as the General Medical Council

17 explicitly excluded retrospective studies from approval in their code of medical ethics

18 (§15/1) (15).

19 All collected clinical data evaluated in this study were fully anonymized before

20 analysis. Therefore, according to prior agreement with the local ethics committee and

21 the data protection officer appointed by the University Hospital, verbal or written

22 informed consent was not obtained.

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1   **RESULTS**

2   During the two-year study period 15,895 patients out of 54,732 patients that arrived at

3   the emergency department (ED) were included in the study. 36,418 ambulant patients

4   (admitted and discharged within 24 hours) and patients lacking the required data were

5   excluded. Also excluded were 1,675 patients who required interdisciplinary consultation

6   or were admitted as case conferences from other hospitals.

7   Of the included patients 22.6% were hypothermic according to the German guideline,

8   71.8 % normothermic and 5.4% hyperthermic.

9   The mean LOS for all study-patients was 8.6 days (median 4.9d, SD 12.3). After arrival

10   at the emergency department 14.0% of the patients were transferred to the ICU. In this

11   group 15.6% were hyperthermic, 14.3% normothermic and 12.7% hypothermic

12   (p=0.3)(demographic data see table 1).

Table 1: Demographic data of the study population

Variable	Total (n=15895)	Hypothermic patients (n=3348)	Normothermic patients (n=10517)	Hyperthermic patients (n=786)	p
Age, mean (SD); [median]	57.8 (21.1); [61]	60.3 (20.5);[64]	57.2 (21.1);[60]	56.3 (20.3);[60]	p<0.001
Sex, male (%)	57.3	59.9	55.5	62.1	p<0.001
Temperature, mean (SD); [median]	36.5 (0.8);[36.5]	35.6 (0.5);[35.8]	36.7 (0.4);[36.6]	38.8 (0.6);[38.6]	p<0.001
Transfused (%)	8.2	9.7	7.2	9.4	p<0.001
PRBC total, mean amount	0.6	0.7 (4.3)	0.5 (3.0)	0.6 (4.1)	p<0.001
PRBC during the first 24h,mean(SD)	0.8 (2.8)	1.1 (3.2)	0.5 (1.8)	0.2 (0.9)	p=0.001
PRBC day 2, mean(SD)	1.5 (3.6)	1.8 (4.1)	1.1 (2.6)	0.8 (1.6)	p=0.042
PRBC day 3, mean(SD)	2.2 (4.3)	2.5 (4.8)	1.7 (3.3)	1.2 (1.8)	p=0.05
Systolic BP (mmHg)	140	139	141	135	p<0.001
GCS, mean(SD); [median]	12.8 (4.3);[15]	12.3 (4.5);[15]	13.2 (3.9);[15]	12.7 (4.1);[15]	p=0.001
ICU Admission (%)	14	12.7	14.3	15.6	p=0.292
LOS(d), mean(SD); [median]	8.6 (12.3);[4.9]	8.7 (12.4);[4.7]	8.4 (11.7);[4.8]	10.1 (13.3);[6.2]	p<0.001
Mortality (%)	5.1	7.4	3.4	4.1	p<0.001

Table 1: Demographic data of the study population (SD-Standard deviation, PRBC-packed red blood cells, BP- blood pressure, GCS- Glasgow coma scale, ICU- Intensive care unit, LOS- Length of stay)

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1 *Effects of hypothermia*

2 Hypothermic patients died earlier than normothermic and hyperthermic patients

3 (p<0.001) as depict in the Kaplan Meier analysis (figure 1).

4 Additionally the analysis revealed that patients who died during the study period had an

5 already decreased core temperature when admitted to the ED. Those patients had a

6 significantly lower mean body temperature of 36.3°C (SD 1.1) than patients that were

7 discharged alive (36.6°C SD 0.8)(p<0.001).

8 Hypothermic patients had a mean LOS of 8.7d (median 4.7d SD 12.4), normothermic a

9 mean LOS of 8.4d (median 4.8d SD 11.6) and hyperthermic patients a mean LOS of

10 10.1d (median 6.2d SD 13.3). The LOS of the patient groups differed significantly

11 (p<0.001), (figure 2).

12 *Effects of blood transfusion*

13 Of the study patients 1295 patients (8.1%) received PRBC during their stay with a

14 median of 4 PRBC. 1-3 PRBC were transfused to 45.2% of the patients, 4-6 PRBC to

15 26.6%, 7-9 PRBC to 9.9 % and 18.3% received a massive transfusion, defined as 10

16 PRBC or more. The more PRBC a patient received the longer was the LOS at the

17 hospital (p<0.001), (figure 3).

18 The in-hospital mortality rate of 5.1% for all study- included patients increased with the

19 number of administered PRBC. It reached 9.9% for patients with 1-3 PRBC; 14.0% for

20 4-6 PRBC, 19.0% for 7-9 PRBC and 32.5% for patients with >=10 PRBC (p<0.001).

21 Patients who died during their clinical stay received a mean amount of 13.3 (SD 16.4)

22 PRBC.

23 Patients who were admitted to the ICU had a fivefold increased risk of death (AOR 5.6;

24 95% Cl 2.0-15.8; p=0.001).

1 Referring to Kaplan Meier function transfused patients died at a significantly higher rate

2 and earlier than patients without transfusion (p<0.001),(figure 4).

3 *Influence of hypothermia on transfusion*

4 Hypothermic patients received significantly more PRBC (9.7%) during their hospital

5 stay than normothermic (7.2%) and hyperthermic patients (9.4%), (p<0.001). Binary

6 logistic regression model revealed that both body temperature and transfusion rate are

7 risk factors for mortality. Prehospital hypothermia ($\leq 36°C$) increased the risk of death

8 up to almost 50% (AOR, 1.5; 95%Cl 0.7-3.; p<0.001) in contrast to normothermia.

9 Transfusion of 1-3 PRBC increased the risk of death by 20% (AOR 0.2; 95%Cl 0.1-

10 0.3), similar to receiving 4-6 PRBC (AOR 0.3; 95% Cl 0.2-0.4), and 7-9 PRBC (AOR

11 0.5; 95% Cl 0.3-0.8) (p<0.001). The administration of ≥ 10 PRBC increased the risk of

12 death by factor 5 compared to patients with only 1-3 PRBC (AOR 5.7; 95% Cl 1.3-2.2),

13 (p<0.001).

14 To evaluate the influence of prehospital hypothermia on the transfusion rate further

15 subgroups were created (a.$\leq 34.5°C$; b.34.6-34.9°C;c. 35.0-35.4°C; d.35.5-36.0°C). This

16 subgroup-analysis showed that a further decreased body core temperature was

17 associated with a rising amount of PRBCs. The analysis revealed that the amount of

18 administered PRBCs rose from group d. (9.0%) to group a. (16.1%). In comparison with

19 the hypothermic patients only 7.2% in the normothermic group (36.1-38.0°C) and 9.4%

20 in the hyperthermic group (>38.1) received a transfusion (p<0.001).

21 In a logistic regression model an admission temperature $\leq 34.5°C$ was associated with

22 an 8-fold risk of death (AOR, 8.5; 95% Cl 2.5-28.5; p=0.001) and an approximately two

23 fold risk for transfusion (AOR, 1.8; 95% Cl 1.0-3.1; p=0.46).

24 Contingency table displayed that 25% of the patients with a GCS≤ 8 received blood

25 products whereas only 7% patients with a GCS >9 received PCRB during their stay

26 (p<0.001). It also occurred that the mean GCS in transfused patients was significantly

1 lower (GCS 10) than that in non-transfused patients (GCS 13), (p<0.001). A GCS ≤8

2 (AOR 12.2; 95%Cl 7.8-19.2; p=0.001) and transfusion of PRBC were connected with

3 an increased risk of death (AOR 3.8; 95%Cl 2.1-7.1; p=0.001). The Student´s t-test

4 revealed that hypothermic patients had a significantly lower GCS (median 12.3 SD 4.5)

5 than normothermic patients (median 13.2 SD 3.9), (p<0.001), but there was no

6 significant difference in the GCS of hypothermic to hyperthermic patients (median 12.7

7 SD 4.1) (p=0.47).

8 In our analysis we found that 26.8% of patients accompanied by an emergency

9 physician were hypothermic and only 19.2% of patients accompanied by paramedics

10 were hypothermic (p<0.001).

11 To investigate the influence of the patient´s age on LOS and received PRBCs three

12 different groups were created (i. <45 years, ii. 46-60 years, iii. >61 years). Most patients

13 were older than 61 years (50.6%). There were 28.1% of patients <45 years old and

14 21.4% between 46-60 years old. Considering the median LOS it appeared that patients

15 belonging to iii. stayed significantly longer at the hospital (median LOS 6.1 days) than

16 younger patients (p < 0.001).Patients belonging to group ii. stayed 4.8 days and patients

17 that were 45 years and younger had a median LOS of 3.3 days.

18 Considering the transfused blood products patients in group ii. received the largest

19 amount of PRBC (mean value 10.0 PRBC, median 4 PRBC, SD 15.0), whereas patients

20 in group iii. received a mean amount of 6.6 PRBC (median 4 SD 8.8). The patients in

21 group i. received 5.9 PRBC (median 3 SD 9.7).

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1   **DISCUSSION**

2   The overall aim of this study was to investigate the impact of hypothermia on

3   transfusion rates and mortality at the UHB. Our findings indicate that patients

4   presenting with hypothermia on admission to the ED have adverse outcomes compared

5   to normothemic and hyperthermic patients. The same is applicable to hypothermic

6   patients that received transfusions of PRBC during their hospital stay. Though it seems

7   to be obvious that hypothermia might be a negative outcome factor during the rescue

8   and recovery process, the incidence of hypothermia in EDs remains a commonly

9   observed phenomenon. Heat loss that may be caused by prolonged rescue time and

10   severe injuries is prolonged throughout the transportation to the next ER due to a non-

11   existing standardized prehospital warming management.

12   The study-results show that almost one third of the patients arrived hypothermic at the

13   ED. We orientated ourselves on the current German guideline defining hypothermia as a

14   core body temperature < 36.0°C (16). Other studies on this subject defined hypothermia

15   as a core body temperature < 36.5°C; < 35.0°C and < 34.5°C (6,17,18). Setting our

16   temperature-limit at 36.0°C led to the fact that our hypothermic patients group is not as

17   large as in e.g the study by M. Bukur at al.(6).

18   In our study hypothermic patients did not have an increased LOS. Similar results are

19   shown by H. Trentzsch et al. (5), whereas another paper found that patients with a

20   body temperature <35.0°C and major trauma stayed longer at the hospital (19).

21   Accordant results in a retrospective paper by R. Martin et al. showed a significantly

22   increased LOS and ICU admission rate for hypothermic major trauma patients (<

23   35.0°C) compared to normothermic patients (p<0.001) (17). The differences in our

24   findings compared to the studies by S. Ireland et al. and R. Martin et al. may be either

25   caused by their collective of patients or by the fact that the Kaplan Meier analysis in our

26   study revealed that hypothermic patients had an increased mortality rate and died earlier

27   than patients with normal or febrile temperatures. Martin et al. and Ireland et al. mainly

1 used results of major trauma patients in their studies whereas we included every patient

2 admitted to the emergency department despite the injury severity score. Our results

3 revealed that hyperthermic patients had the longest LOS and were more often admitted

4 to the ICU. We suggest that those patients were septic or in another febrile critical

5 health condition that needed intensive treatment.

6 Hypothermic patients showed an increased consumption of PRBC and an increased risk

7 of death. Responsible for these findings might be the partial impairment of the

8 coagulation by hypothermia already outlined in the introduction (3,4,20). Other factors

9 that additionally affected the coagulation of the patients included in this study cannot be

10 retraced due to the retrospective study design.

11 The in-hospital death rate for patients with >10 PRBC-units of red blood cells rose up to

12 37.8% whereas patients with 1-3 PRBC units had a death rate of 9.9%.The multi-

13 centered patient blood management initiative, in which this study is integrated in, aims

14 at an increase in patient safety and reduction of liberal admission of 1-3 PRBC because

15 it was shown that already a small amount of allogenic blood transfusion is associated

16 with septic, pulmonary and embolic complications (21). Other possible reasons for

17 increased mortality rate are predisposition to nosocomial and postoperative infections,

18 cancer recurrence and microchimerism through the infusion of PRBC (22). Our results

19 prove that patients with 1-3 PRBC had a significantly increased LOS compared to

20 patients that received no transfusion (p<0.001). They additionally had an enhanced risk

21 of death (AOR 0.174; p<0.001).

22 Our analysis demonstrated that patients with massive transfusion died earlier than other

23 patients. One-third of the total amount of PRBC for each massive transfused patient in

24 the ED was administered within the first 72 hours. Among this group are most likely

25 patients with severe injuries and major trauma that are in the urgent need of

26 resuscitation fluids e.g. red blood cells as subsidized by a large retrospective study by

27 R.R Barbosa et al. (23).

1 There was also a significant association between the GCS and PRBC. One fourth of the

2 patients with a GCS of ≤8 were in need of PRBC which seems reasonable since the

3 GCS classifies the consciousness in patients with severe injuries.

4 In addition there was a difference in the occurrence of hypothermia depending on the

5 mode of transportation. The incidence of hypothermia was significantly higher on an

6 ambulance with an emergency physician present compared to ambulances operated by

7 paramedics. These results indicate that patients accompanied by an emergency

8 physician were either hypothermic due to their injuries and cold resuscitation fluids or

9 their body temperature was lowered protectively.

10 Patients of 61 years and older had the longest LOS. Despite of this result, patients in the

11 middle-aged group (46-60 years) received the most PRBC during their stay at the

12 hospital. The study by R.R. Barbosa displayed that age was independently associated

13 with a higher risk of mortality in an observed 30-day period among transfused patients

14 after trauma (23). According to this our study showed that patients who died during the

15 stay at the hospital had a mean age of 71.34 (SD 14.34) whereas patients that were

16 discharged alive had a mean age of 57.12 (SD 21.16), (p<0.001).

17 *Limitations*

18 Due to the retrospective study design it was not possible to create a causal connection

19 between the admission temperature and the distribution of PRBC as it would be in a

20 prospective clinical trial. This study did not include the patients' diagnoses that might

21 have influenced the temperature regulation. Additionally, medications such as

22 anticoagulants could not have been retraced. We were not able to retrace the exact

23 hemoglobin level of the transfused patients and to differentiate between patients with

24 accidental and induced hypothermia retrospectively. It has to be taken into account that

25 ambulances are able to cool patients, and that this is a standard procedure in patients

26 with heart attacks, cardiac arrest and patients with possible brain damage as these

27 patients benefit from a lower core body temperature (24–25).

1 It has to be taken into consideration that our review did not analyze the connection of

2 the injury severity score (ISS) of each patient with the body temperature and the

3 transfusion requirement. This is due to the fact that it was not possible to reproduce the

4 ISS in retrospect. A prospective controlled clinical trial on a connection between

5 temperature, transfusion requirement and ISS could prove the importance of this

6 subject.

7 **CONCLUSION**

8 Despite the mentioned limitations this large retrospective study was able to show that

9 prehospital hypothermia is associated with an increased transfusion requirement and a

10 worse outcome compared to normothermic and not transfused patients.

11 This study should create further awareness for the importance of the patient's body

12 temperature and a more restrictive transfusion regime for patients that are not in life-

13 threatening need of resuscitation fluids. Patients with low prehospital body core

14 temperatures, due to the injury severity or a prolonged rescue should be protected from

15 further heat loss with trauma warming blankets. An effective warming management

16 installed on all ambulances and in the EDs could help preventing hypothermic patients

17 from a worse outcome as induced through the primary injury. It is to emphasize that this

18 is a hypothesis suggested by the findings of this study, a prospective randomized

19 controlled trial should be conducted to investigate, if a prehospital worming is

20 beneficial for the patients.

21

22 Extra data, which is not included in this paper is available by emailing the

23 corresponding author Mrs. Maria Wittmann.

24

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1   Contributorship statement:

2   NK: data analysis, literature research, writing the manuscript

3   IG: planning of the trial

4   AF: data analysis

5   OB: writing the manuscript

6   GB: planning the trial, writing the manuscript

7   VG: writing the manuscript

8   MW: planning of the trial, data analysis, literature research, writing the manuscript

9   Competing interests:

10   We declare no funding and no competing interests.

11   Data sharing:

12   No additional data available.

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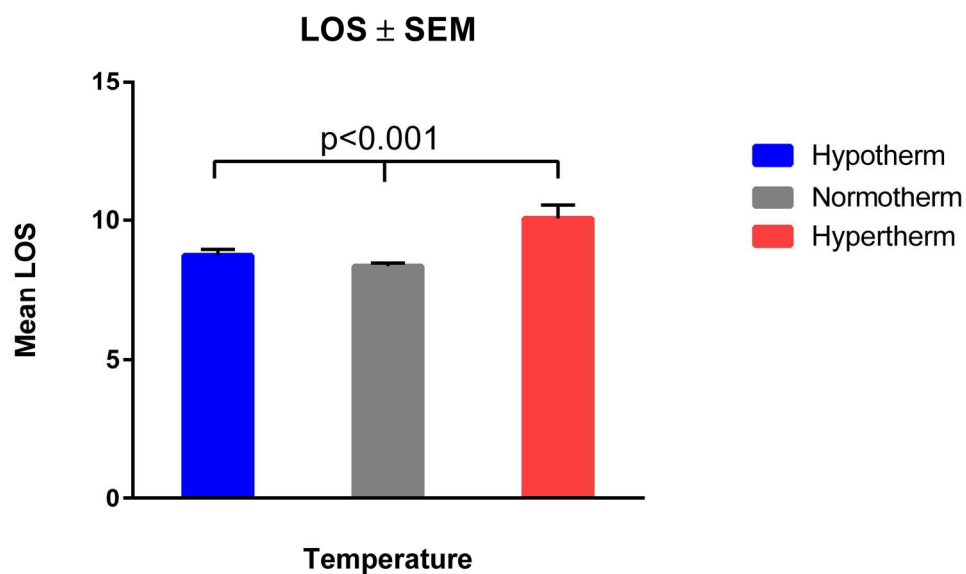
Figure 2: Length of stay for each temperature group
Legend: Figure 2: LOS in days ± SEM for each temperature category
(LOS (d): length of stay in days, SEM: standard error of the mean)
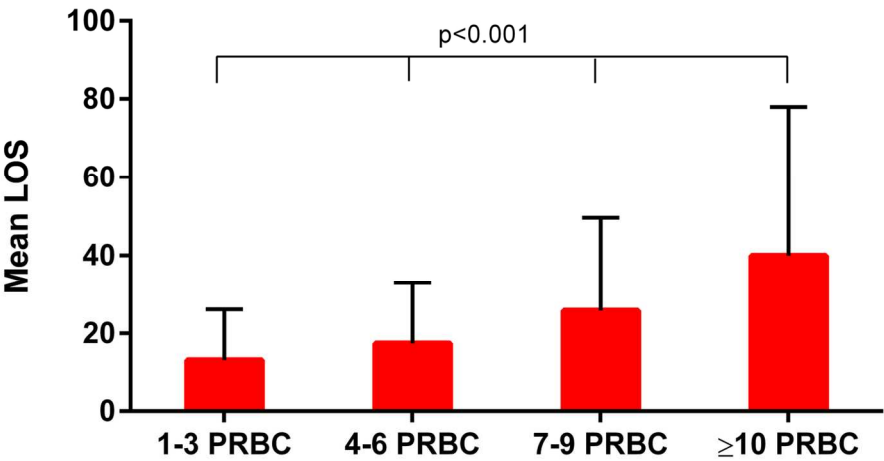
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Figure 3: Effects of blood transfusion on the length of stay
Legend: Figure 3: mean LOS (d) in relation to amount of PRBC
(LOS (d): length of stay in days; PRBC: packed red blood cells)
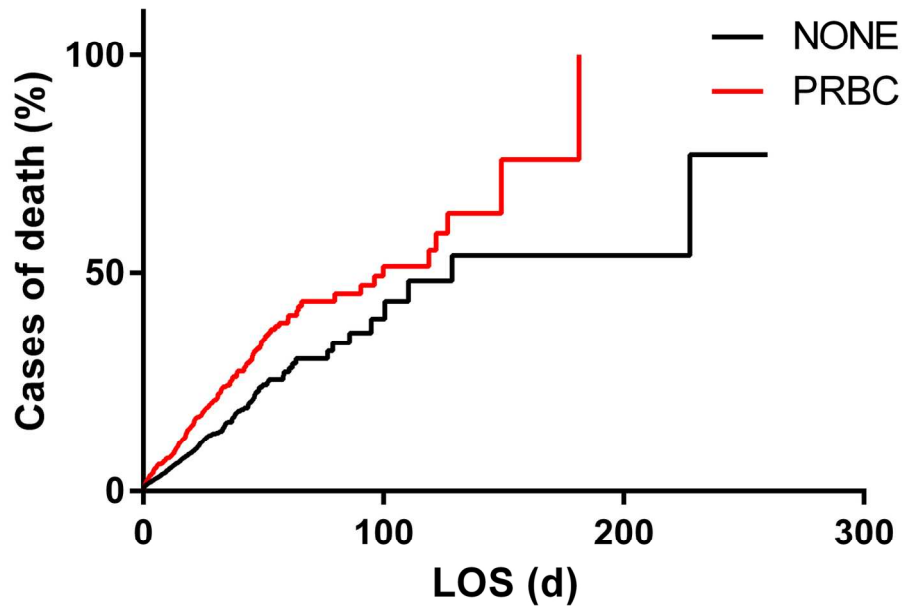
68x35mm (600 x 600 DPI)

Figure 4: Mortality rate for transfused patients
Legend: Figure 4: Kaplan Meier Analysis: Mortality of transfused patients compared to not transfused patients
(LOS (d): length of stay in days; PRBC: packed red blood cells)
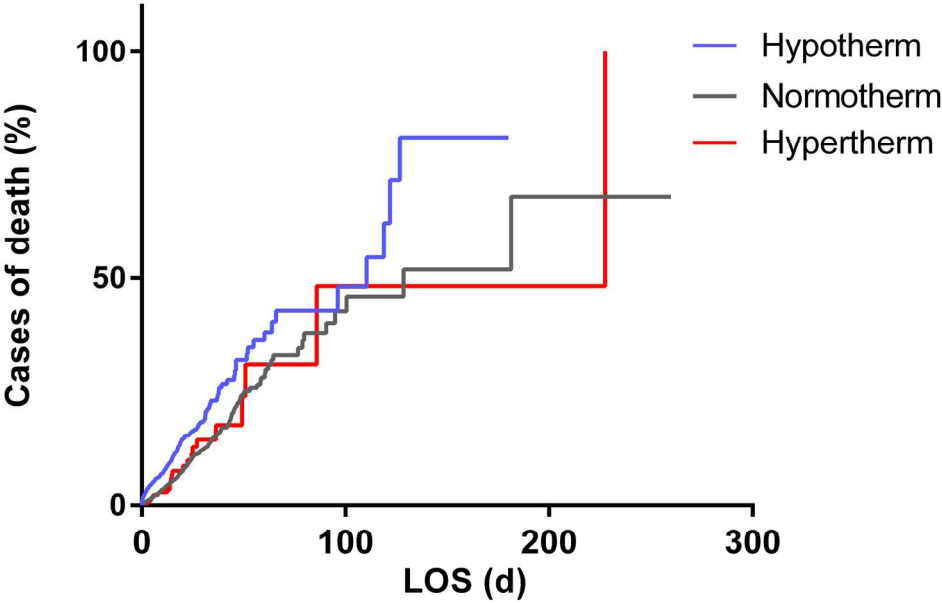
73x51mm (600 x 600 DPI)

Figure 1: Mortality curve for each temperature group
Legend: Figure 1: Kaplan Meier analysis: Hypothermic patients had the highest mortality rate (LOS (d): length of stay in days)
85x57mm (600 x 600 DPI)

STROBE Statement by Nora Klauke

	Item No	Recommendation
Title and abstract	1	*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		See page: 1
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		See page: 4
Objectives	3	State specific objectives, including any prespecified hypotheses
		See page: 4
Methods		
Study design	4	Present key elements of study design early in the paper
		See page: 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		See page: 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		See page: 6-7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		See page: 6
Bias	9	Describe any efforts to address potential sources of bias
		See page: 14
Study size	10	Explain how the study size was arrived at
		See page: 8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		See page: 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
		See page: 7

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		See page: 8
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
		See page: 8 and Table 1
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
		See pages: 9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
		See pages: 9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		See page: 11

Discussion		
Key results	18	Summarise key results with reference to study objectives **See page: 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **See page: 14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **See pages: 12-15**
Generalisability	21	Discuss the generalisability (external validity) of the study results See page: 13
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **See page: Cover letter/Title page - no funding declared**
Ethics	23	**See pages: 4-5**

BMJ Open

Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial

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Manuscripts

1 **Effects of prehospital hypothermia**

2 **on transfusion requirements and outcomes – a retrospective**

3 **observatory trial**

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15 *Keywords*: patient blood management, prehospital hypothermia, transfusion

16 *Word count:* 3737 words

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1 **ABSTRACT**

2 *Objectives:* Prehospital hypothermia is defined as a core temperature < 36.0°C and has

3 been shown to be an independent risk factor for early death in trauma patients. In a

4 retrospective study a possible correlation between the body temperature at the time of

5 admission to the emergency room and subsequent in-hospital transfusion requirements

6 and the in-hospital mortality rate was explored.

7 *Setting:* This is a retrospective single-center study at a primary-care hospital in

8 Germany.

9 *Participants:* 15,895 patients were included in this study. Patients were classified by

10 admission temperature and transfusion rate. Excluded were ambulant patients and

11 patients with missing data.

12 *Primary and secondary outcome measures:* The primary outcome values were length of

13 stay in days (LOS), in-hospital mortality, the transferred amount of packed red blood

14 cells (PRBCs), and admission to an intensive care unit (ICU). Secondary influencing

15 variables were the patients´age and the Glasgow Coma Scale (GCS).

16 *Results:* In 22.85% of the patients hypothermia was documented. Hypothermic patients

17 died earlier in the course of their hospital stay than non-hypothermic ($p<0.001$). An

18 administration of 1-3 packed red blood cells (PRBC) increased the length of stay

19 significantly ($p<0.001$) and transfused patients had an increased risk of death ($p<0.001$).

20 Prehospital hypothermia could be an independent risk factor for mortality (AOR 8.521;

21 $p=0.001$) and increases the relative risk for transfusion by factor 2.0 (OR 2.007;

22 $p=0.002$).

23 *Conclusion:* Low body temperature at hospital-admission is associated with a higher

24 risk of transfusion and death. Hence, a greater awareness for a prehospital temperature

25 management should be established.

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3   1   **ARTICLE SUMMARY**
4
5   2   *Strengths and limitations of this study*
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9   4   • Using a retrospective design we investigated the effects of pre-hospital
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11   5   hypothermia on patient in-hospital mortality, length of hospital stay, ICU
12
13   6   admission and transfusion requirements in the university hospital setting
14
15   7   • The hospital database captured a total of 54,732 subjects admitted to the
16
17   8   emergency department of the University Hospital of Bonn between 1 January
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19   9   2012 and 31 December 2013
20
21   10   • 15,895 subjects with inpatient-status recorded admission temperature, hospital
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23   11   admission and discharge dates, demographics, Glasgow Coma Scale (GCS),
24
25   12   intensive care unit (ICU) admission, mode of transportation and information
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27   13   about the in-hospital mortality were eligible for full set data analyses
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29   14   • The retrospective approach does not allow for causal relationships between pre-
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31   15   hospital hypothermia and any of the designated outcome measures
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33   16   • The potential influence of patients diagnoses on temperature regulation,
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35   17   medication regimes and hemoglobin levels of transfused patients was not
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37   18   accounted for and may therefore confound observed effects
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1   **INTRODUCTION**

2   The incidence of prehospital hypothermia, defined as a core temperature below 36.0°C,

3   is frequently observed in patients admitted to the emergency room (1) mainly due to a

4   difficult and prolonged rescue, infusion of cold resuscitation fluids (2), weather, age and

5   a critical health condition. Together with acidosis and coagulopathy hypothermia has

6   been termed *lethal triad of death* (3).

7   Hypothermia alters enzymatic reactions of the coagulation cascade during the initiation

8   phase and decreases platelet function (3,4), possibly leading to severe bleeding and

9   consecutively required blood transfusion. It has been shown that the amount of applied

10   fluids and transfused PRBC is directly linked to hypothermia, is associated with a worse

11   clinical outcome (5,6), and increases the risk for postoperative mortality (7). Acute

12   complications after PRBC transfusion can comprise of hypothermia, hypocalcaemia,

13   hypomagnesiaemia, citrate toxicity, lactic acidosis and air embolism (8). Additionally

14   non-infectious serious hazards of transfusion (NISHOTs) ranging from common

15   complications, e.g., allergic or febrile hemolytic reactions (9) to rare, life-threatening

16   entities like the transfusion-related lung injury (TRALI) (10) or the transfusion

17   associated Graft versus Host Disease (TA-GVHD) (11) can still pose a serious threat to

18   patients. The patients´ outcome might also be negatively affected by non-antibody-

19   antigene dependent reactions known as transfusion-related immune modulation (TRIM)

20   (9) that are suspected to increase the rate of infection and tumor-recurrence after

21   transfusion (12). The aim of this study was to evaluate the effects of prehospital

22   hypothermia on transfusion rate and mortality. This retrospective single-center database

23   analysis was executed in the framework of a Germany-wide multi-center initiative for

24   patient blood management, which aims at reducing the amount of blood transfusion

25   whenever feasible and beneficial for the patient.

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1   **MATERIAL AND METHODS**

2   This study reviewed the University Hospital Bonn (UHB) Emergency Department

3   database from January 1, 2012 until December 31, 2013 that contained anonymized data

4   of 54,732 patients. Included in this study were patients with recorded admission

5   temperature, documented admission and discharge date, age, Glasgow Coma Scale

6   (GCS), intensive care unit (ICU) admission, mode of transportation and information

7   about the in-hospital mortality.

8   As a standard operating procedure each patient's clinical health status is evaluated by a

9   nurse in the framework of an emergency triage system when admitted to the ED. The

10   triage includes the tympanal measurement of the patient´s temperature. This method is

11   easy and fast, shows accurate results and can be recommended for this purpose (13).

12   The LOS was calculated electronically. The GCS was evaluated by the emergency

13   physician arriving at the scene.

14   The amount of transfused red blood cells was evaluated by matching our database with

15   the University Hospital Bonn Institute of Transfusion Medicine's database and is

16   presented as raw number of received packages (PRBC). The transfusion-criteria are

17   given in the German guideline: Cross-Sectional guidelines for therapy with blood

18   components and plasma derivates (2014) (14).

19   According to the German guideline: S3 prevention of perioperative hypothermia (2014),

20   a patient was defined hypothermic when presented with a temperature below 36.0°C, ,

21   normothermic with a temperature from 36.1°C to 38.0°C and hyperthermic when the

22   temperature was >38.1°C on arrival at the ED.

23   The primary outcome values were length of stay in days (LOS), in-hospital mortality,

24   the transferred amount of PRBCs, and ICU admission.

25   Secondary influencing variables such as age and GCS were considered further grouping

26   variables to compare the hypothermic with the normothermic and hyperthermic patients.

1   For quantitative data evaluation the median test and Mann-Whitney-U-Test were used.

2   To objectify if transfusion and mortality was independent of the patient's temperature,

3   age and GCS contingency tables were created and analyzed with a chi² test. To compare

4   means Student's t-test was used. Kaplan Meier analysis was applied to identify whether

5   hypothermic and transfused patients had a higher risk of mortality than the other

6   patients in the study. Binary logistic regression was used to determine risk factors for

7   mortality. The univariate predictors were the body temperature and transfusion. The

8   results are given in adjusted odd ratio (AOR) and reached statistical significance with

9    $p < 0.001$. Other results are presented as mean (standard deviation, SD) for ordinal data,

10   median for data which had expected peaks and descriptive data as raw percentages.

11   Statistical analysis was performed using SPSS Statistics Amos 22.0 (IBM Corporation,

12   Armonk, USA).

13   Approval for the patient blood management study was given by the ethics committee of

14   the medical faculty of the University of Bonn chaired by Professor K. Racké (number

15   082/13 from the 7th of May 2013). The present study was purely retrospective and

16   approval by the ethic committee was not necessary as the General Medical Council

17   explicitly excluded retrospective studies from approval in their code of medical ethics

18   (§15/1) (15).

19   All collected clinical data evaluated in this study were fully anonymized before

20   analysis. Therefore, according to prior agreement with the local ethics committee and

21   the data protection officer appointed by the University Hospital, verbal or written

22   informed consent was not obtained.

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1   **RESULTS**

2   During the two-year study period 15,895 patients out of 54,732 patients that arrived at

3   the emergency department (ED) were included in the study. 36,418 ambulant patients

4   (admitted and discharged within 24 hours) and patients lacking the required data were

5   excluded. Also excluded were 1,675 patients who required interdisciplinary consultation

6   or were admitted as case conferences from other hospitals.

7   Of the included patients 22.6% were hypothermic according to the German guideline,

8   71.8 % normothermic and 5.4% hyperthermic.

9   The mean LOS for all study-patients was 8.6 days (median 4.9d, SD 12.3). After arrival

10   at the emergency department 14.0% of the patients were transferred to the ICU. In this

11   group 15.6% were hyperthermic, 14.3% normothermic and 12.7% hypothermic

12   (p=0.3)(demographic data see table 1).

Table 1: Demographic data of the study population

Variable	Total (n=15895)	Hypothermic patients (n=3348)	Normothermic patients (n=10517)	Hyperthermic patients (n=786)	p
Age, mean (SD); [median]	57.8 (21.1); [61]	60.3 (20.5);[64]	57.2 (21.1);[60]	56.3 (20.3);[60]	p<0.001
Sex, male (%)	57.3	59.9	55.5	62.1	p<0.001
Temperature, mean (SD); [median]	36.5 (0.8);[36.5]	35.6 (0.5);[35.8]	36.7 (0.4);[36.6]	38.8 (0.6);[38.6]	p<0.001
Transfused (%)	8.2	9.7	7.2	9.4	p<0.001
PRBC total, mean amount	0.6	0.7 (4.3)	0.5 (3.0)	0.6 (4.1)	p<0.001
PRBC during the first 24h,mean(SD)	0.8 (2.8)	1.1 (3.2)	0.5 (1.8)	0.2 (0.9)	p=0.001
PRBC day 2, mean(SD)	1.5 (3.6)	1.8 (4.1)	1.1 (2.6)	0.8 (1.6)	p=0.042
PRBC day 3, mean(SD)	2.2 (4.3)	2.5 (4.8)	1.7 (3.3)	1.2 (1.8)	p=0.05
Systolic BP (mmHg)	140	139	141	135	p<0.001
GCS, mean(SD); [median]	12.8 (4.3);[15]	12.3 (4.5);[15]	13.2 (3.9);[15]	12.7 (4.1);[15]	p=0.001
ICU Admission (%)	14	12.7	14.3	15.6	p=0.292
LOS(d), mean(SD); [median]	8.6 (12.3);[4.9]	8.7 (12.4);[4.7]	8.4 (11.7);[4.8]	10.1 (13.3);[6.2]	p<0.001
Mortality (%)	5.1	7.4	3.4	4.1	p<0.001

Table 1: Demographic data of the study population (SD- Standard deviation, PRBC- packed red blood cells, BP- blood pressure, GCS- Glasgow coma scale, ICU- Intensive care unit, LOS- Length of stay)

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1 *Effects of hypothermia*

2 Hypothermic patients died earlier than normothermic and hyperthermic patients

3 (p<0.001) as depict in the Kaplan Meier analysis (figure 1).

4 Additionally the analysis revealed that patients who died during the study period had an

5 already decreased core temperature when admitted to the ED. Those patients had a

6 significantly lower mean body temperature of 36.3°C (SD 1.1) than patients that were

7 discharged alive (36.6°C SD 0.8)(p<0.001).

8 Hypothermic patients had a mean LOS of 8.7d (median 4.7d SD 12.4), normothermic a

9 mean LOS of 8.4d (median 4.8d SD 11.6) and hyperthermic patients a mean LOS of

10 10.1d (median 6.2d SD 13.3). The LOS of the patient groups differed significantly

11 (p<0.001), (figure 2).

12 *Effects of blood transfusion*

13 Of the study patients 1295 patients (8.1%) received PRBC during their stay with a

14 median of 4 PRBC. 1-3 PRBC were transfused to 45.2% of the patients, 4-6 PRBC to

15 26.6%, 7-9 PRBC to 9.9 % and 18.3% received a massive transfusion, defined as 10

16 PRBC or more. The more PRBC a patient received the longer was the LOS at the

17 hospital (p<0.001), (figure 3).

18 The in-hospital mortality rate of 5.1% for all study- included patients increased with the

19 number of administered PRBC. It reached 9.9% for patients with 1-3 PRBC; 14.0% for

20 4-6 PRBC, 19.0% for 7-9 PRBC and 32.5% for patients with >=10 PRBC (p<0.001).

21 Patients who died during their clinical stay received a mean amount of 13.3 (SD 16.4)

22 PRBC.

23 Patients who were admitted to the ICU had a fivefold increased risk of death (AOR 5.6;

24 95% Cl 2.0-15.8; p=0.001).

1 Referring to Kaplan Meier function transfused patients died at a significantly higher rate

2 and earlier than patients without transfusion (p<0.001),(figure 4).

3 Referring to the used regression model an univariate analysis for SPB ≤90/>90 and age

4 ≥65/<65 years showed that patients with SBP>90 had an increased risk of death by

5 factor 0.1 (OR 0.109; Cl 95% 0.087-0.138) (p<0.001) and that patients ≥65 had a

6 threefold risk of death compared to patients <65 (OR 3.140; 2.688-3.669) (p< 0.001).

7 *Influence of hypothermia on transfusion*

8 Hypothermic patients received significantly more PRBC (9.7%) during their hospital

9 stay than normothermic (7.2%) and hyperthermic patients (9.4%), (p<0.001). Binary

10 logistic regression model revealed that both body temperature and transfusion rate are

11 risk factors for mortality. Prehospital hypothermia (≤ 36°C) increased the risk of death

12 up to almost 50% (AOR, 1.5; 95%Cl 0.7-3.; p<0.001) in contrast to normothermia.

13 Transfusion of 1-3 PRBC increased the risk of death by 20% (AOR 0.2; 95%Cl 0.1-

14 0.3), similar to receiving 4-6 PRBC (AOR 0.3; 95% Cl 0.2-0.4), and 7-9 PRBC (AOR

15 0.5; 95% Cl 0.3-0.8) (p<0.001). The administration of ≥10 PRBC increased the risk of

16 death by factor 5 compared to patients with only 1-3 PRBC (AOR 5.7; 95% Cl 1.3-2.2),

17 (p<0.001).

18 To evaluate the influence of prehospital hypothermia on the transfusion rate further

19 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

20 subgroup-analysis showed that a further decreased body core temperature was

21 associated with a rising amount of PRBCs. The analysis revealed that the amount of

22 administered PRBCs rose from group d. (9.0%) to group a. (16.1%). In comparison with

23 the hypothermic patients only 7.2% in the normothermic group (36.1-38.0°C) and 9.4%

24 in the hyperthermic group (>38.1) received a transfusion (p<0.001).

25 In a logistic regression model an admission temperature ≤34.5°C was associated with

26 an 8-fold risk of death (AOR, 8.5; 95% Cl 2.5-28.5; p=0.001) and it increased and an

1   approximately two fold risk for transfusion (AOR, 1.8; 95% Cl 1.0-3.1; p=0.46).

2   However, we calculated the relative risk for receiving PRBC in the group of patients

3   admitted with a body temperature ≤34.5°C. The analysis showed that these patients had

4   a doubled relative risk (OR 2.0; Cl 95% 1.3-3.1) for transfusion compared to

5   normothermic patients (p=0.002).

6   Referring to the regression model other univariate predictors were again SPB ≤90/>90

7   and age ≥65/<65 years. This analysis showed that that patients with a SBP>90 had an

8   increased risk for transfusion by factor 0.4 (OR 0.389; 0.301-0.503) (p<0.001) and that

9   patients of ≥65 years showed a doubled risk for receiving transfusion compared to

10 younger patients (OR 1.935; 1.722-2.175) (p<0.001).

11 Contingency table displayed that 25% of the patients with a GCS≤8 received blood

12 products whereas only 7% patients with a GCS >9 received PCRB during their stay

13 (p<0.001). It also occurred that the mean GCS in transfused patients was significantly

14 lower (GCS 10) than that in non-transfused patients (GCS 13), (p<0.001). A GCS ≤8

15 (AOR 12.2; 95%Cl 7.8-19.2; p=0.001) and transfusion of PRBC were connected with

16 an increased risk of death (AOR 3.8; 95%Cl 2.1-7.1; p=0.001). The Student´s t-test

17 revealed that hypothermic patients had a significantly lower GCS (median 12.3 SD 4.5)

18 than normothermic patients (median 13.2 SD 3.9), (p<0.001), but there was no

19 significant difference in the GCS of hypothermic to hyperthermic patients (median 12.7

20 SD 4.1) (p=0.47).

21 In our analysis we found that 26.8% of patients accompanied by an emergency

22 physician were hypothermic and only 19.2% of patients accompanied by paramedics

23 were hypothermic (p<0.001).

24 To investigate the influence of the patient´s age on LOS and received PRBCs three

25 different groups were created (i. <45 years, ii. 46-60 years, iii. >61 years). Most patients

26 were older than 61 years (50.6%). There were 28.1% of patients <45 years old and

1   21.4% between 46-60 years old. Considering the median LOS it appeared that patients

2   belonging to iii. stayed significantly longer at the hospital (median LOS 6.1 days) than

3   younger patients (p < 0.001).Patients belonging to group ii. stayed 4.8 days and patients

4   that were 45 years and younger had a median LOS of 3.3 days.

5   Considering the transfused blood products patients in group ii. received the largest

6   amount of PRBC (mean value 10.0 PRBC, median 4 PRBC, SD 15.0), whereas patients

7   in group iii. received a mean amount of 6.6 PRBC (median 4 SD 8.8). The patients in

8   group i. received 5.9 PRBC (median 3 SD 9.7).

9

10

11   **DISCUSSION**

12   The overall aim of this study was to investigate the impact of hypothermia on

13   transfusion rates and mortality at the UHB. Our findings indicate that patients

14   presenting with hypothermia on admission to the ED have adverse outcomes compared

15   to normothemic and hyperthermic patients. The same is applicable to hypothermic

16   patients that received transfusions of PRBC during their hospital stay. Though it seems

17   to be obvious that hypothermia might be a negative outcome factor during the rescue

18   and recovery process, the incidence of hypothermia in EDs remains a commonly

19   observed phenomenon. Heat loss that may be caused by prolonged rescue time and

20   severe injuries is prolonged throughout the transportation to the next ER due to a non-

21   existing standardized prehospital warming management.

22   The study-results show that almost one third of the patients arrived hypothermic at the

23   ED. We orientated ourselves on the current German guideline defining hypothermia as a

24   core body temperature < 36.0°C (16). Other studies on this subject defined hypothermia

25   as a core body temperature < 36.5°C; < 35.0°C and < 34.5°C (6,17,18). Setting our

1   temperature-limit at 36.0°C led to the fact that our hypothermic patients group is not as

2   large as in e.g the study by M. Bukur at al.(6).

3   In our study hypothermic patients did not have an increased LOS. Similar results are

4   shown by H. Trentzsch et al. (5), whereas another paper found that patients with a

5   body temperature <35.0°C and major trauma stayed longer at the hospital (19).

6   Accordant results in a retrospective paper by R. Martin et al. showed a significantly

7   increased LOS and ICU admission rate for hypothermic major trauma patients (<

8   35.0°C) compared to normothermic patients (p<0.001) (17). The differences in our

9   findings compared to the studies by S. Ireland et al. and R. Martin et al. may be either

10   caused by their collective of patients or by the fact that the Kaplan Meier analysis in our

11   study revealed that hypothermic patients had an increased mortality rate and died earlier

12   than patients with normal or febrile temperatures. Martin et al. and Ireland et al. mainly

13   used results of major trauma patients in their studies whereas we included every patient

14   admitted to the emergency department despite the injury severity score. Our results

15   revealed that hyperthermic patients had the longest LOS and were more often admitted

16   to the ICU. We suggest that those patients were septic or in another febrile critical

17   health condition that needed intensive treatment.

18   Hypothermic patients showed an increased consumption of PRBC and an increased risk

19   of death. Responsible for these findings might be the partial impairment of the

20   coagulation by hypothermia already outlined in the introduction (3,4,20). Other factors

21   that additionally affected the coagulation of the patients included in this study cannot be

22   retraced due to the retrospective study design.

23   The in-hospital death rate for patients with >10 PRBC-units of red blood cells rose up to

24   37.8% whereas patients with 1-3 PRBC units had a death rate of 9.9%.The multi-

25   centered patient blood management initiative, in which this study is integrated in, aims

26   at an increase in patient safety and reduction of liberal admission of 1-3 PRBC because

27   it was shown that already a small amount of allogenic blood transfusion is associated

1   with septic, pulmonary and embolic complications (21). Other possible reasons for

2   increased mortality rate are predisposition to nosocomial and postoperative infections,

3   cancer recurrence and microchimerism through the infusion of PRBC (22). Our results

4   prove that patients with 1-3 PRBC had a significantly increased LOS compared to

5   patients that received no transfusion (p<0.001). They additionally had an enhanced risk

6   of death (AOR 0.174; p<0.001).

7   Our analysis demonstrated that patients with massive transfusion died earlier than other

8   patients. One-third of the total amount of PRBC for each massive transfused patient in

9   the ED was administered within the first 72 hours. Among this group are most likely

10   patients with severe injuries and major trauma that are in the urgent need of

11   resuscitation fluids e.g. red blood cells as subsidized by a large retrospective study by

12   R.R Barbosa et al. (23).

13   There was also a significant association between the GCS and PRBC. One fourth of the

14   patients with a GCS of ≤8 were in need of PRBC which seems reasonable since the

15   GCS classifies the consciousness in patients with severe injuries.

16   In addition there was a difference in the occurrence of hypothermia depending on the

17   mode of transportation. The incidence of hypothermia was significantly higher on an

18   ambulance with an emergency physician present compared to ambulances operated by

19   paramedics. These results indicate that patients accompanied by an emergency

20   physician were either hypothermic due to their injuries and cold resuscitation fluids or

21   their body temperature was lowered protectively.

22   Patients of 61 years and older had the longest LOS. Despite of this result, patients in the

23   middle-aged group (46-60 years) received the most PRBC during their stay at the

24   hospital. The study by R.R. Barbosa displayed that age was independently associated

25   with a higher risk of mortality in an observed 30-day period among transfused patients

26   after trauma (23). According to this our study showed that patients who died during the

1 stay at the hospital had a mean age of 71.34 (SD 14.34) whereas patients that were

2 discharged alive had a mean age of 57.12 (SD 21.16), (p<0.001).

3 *Limitations*

4 Due to the retrospective study design it was not possible to create a causal connection

5 between the admission temperature and the distribution of PRBC as it would be in a

6 prospective clinical trial. This study did not include the patients' diagnoses that might

7 have influenced the temperature regulation. Additionally, medications such as

8 anticoagulants could not have been retraced. We were not able to retrace the exact

9 hemoglobin level of the transfused patients and to differentiate between patients with

10 accidental and induced hypothermia retrospectively. It has to be taken into account that

11 ambulances are able to cool patients, and that this is a standard procedure in patients

12 with heart attacks, cardiac arrest and patients with possible brain damage as these

13 patients benefit from a lower core body temperature (24–25).

14 It has to be taken into consideration that our review did not analyze the connection of

15 the injury severity score (ISS) of each patient with the body temperature and the

16 transfusion requirement. This is due to the fact that it was not possible to reproduce the

17 ISS in retrospect. A prospective controlled clinical trial on a connection between

18 temperature, transfusion requirement and ISS could prove the importance of this

19 subject.

20 **CONCLUSION**

21 Despite the mentioned limitations this large retrospective study was able to show that

22 prehospital hypothermia is associated with an increased transfusion requirement and a

23 worse outcome compared to normothermic and not transfused patients.

24 This study should create further awareness for the importance of the patient's body

25 temperature and a more restrictive transfusion regime for patients that are not in life-

26 threatening need of resuscitation fluids. Patients with low prehospital body core

1   temperatures, due to the injury severity or a prolonged rescue should be protected from

2   further heat loss with trauma warming blankets. An effective warming management

3   installed on all ambulances and in the EDs could help preventing hypothermic patients

4   from a worse outcome as induced through the primary injury. It is to emphasize that this

5   is a hypothesis suggested by the findings of this study, a prospective randomized

6   controlled trial should be conducted to investigate, if a prehospital worming is

7   beneficial for the patients.

8

9   Data sharing

10   No additional data available.

11

12   Contributorship statement:

13   NK: data analysis, literature research, writing the manuscript

14   IG: planning of the trial

15   AF: data analysis

16   OB: writing the manuscript

17   GB: planning the trial, writing the manuscript

18   VG: writing the manuscript

19   MW: planning of the trial, data analysis, literature research, writing the manuscript

20

21   Competing interests

22   We declare no funding and no competing interests.

23

24

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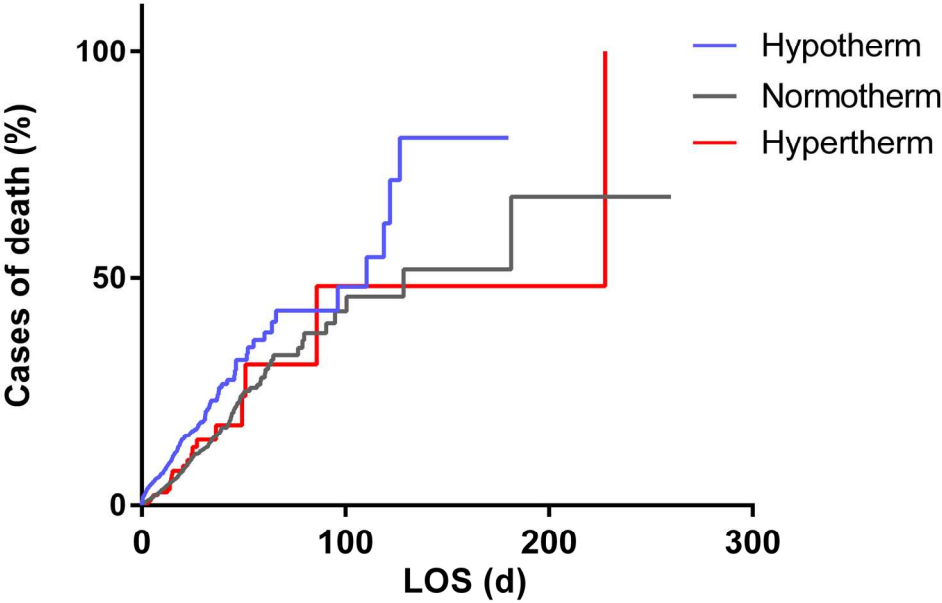13 with severe brain injury. *J Neurotrauma.* 2002 Mar;19(3):293–301.

Figure 1.
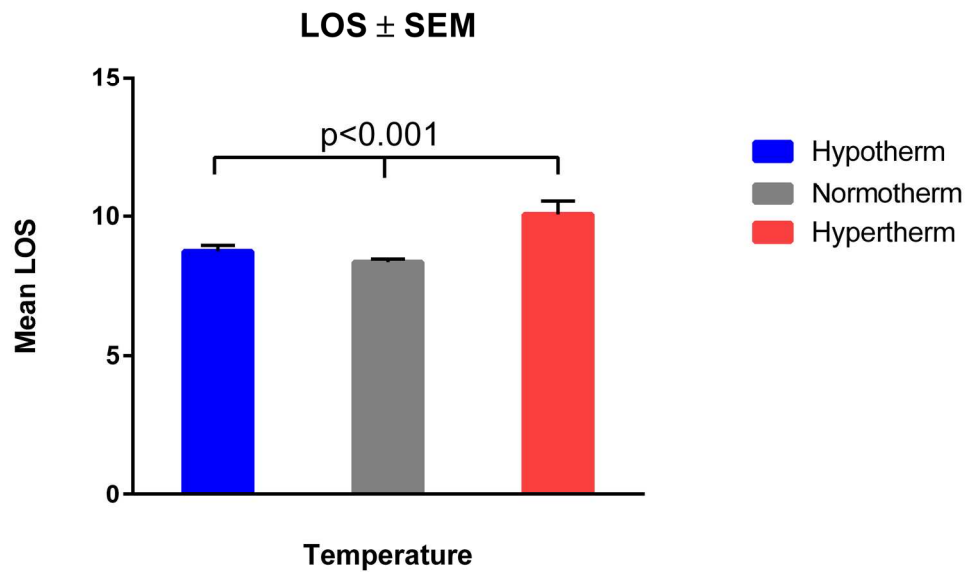Mortality curve for each temperature group
85x57mm (600 x 600 DPI)

Figure 2.
Length of stay for each temperature group
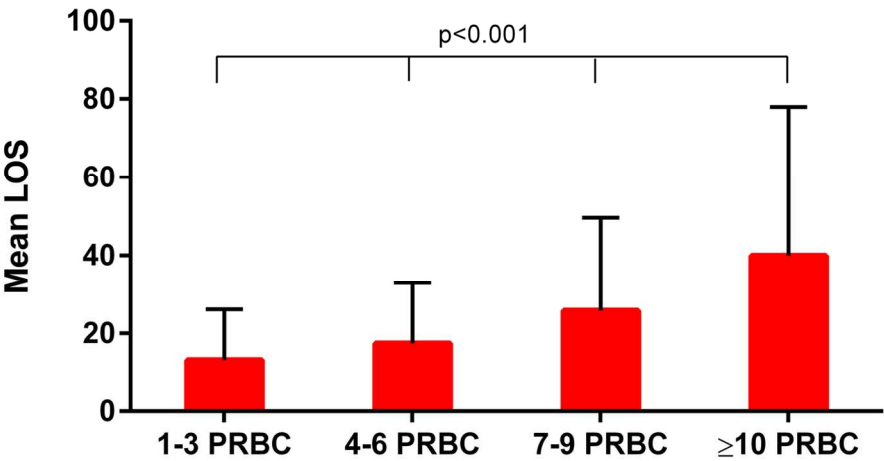91x56mm (600 x 600 DPI)

Figure 3.
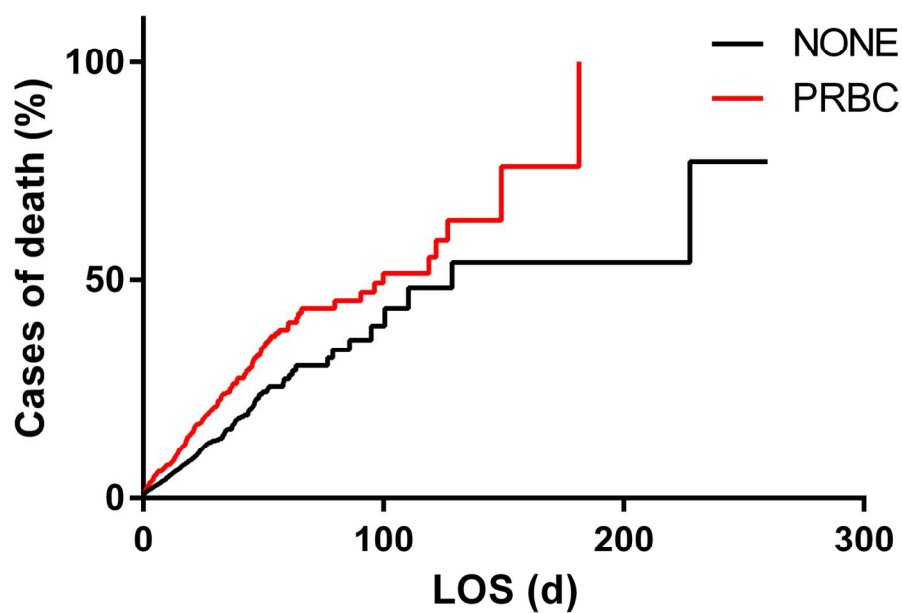Effects of blood transfusion on the length of stay
68x35mm (600 x 600 DPI)

Figure 4.
Mortality rate for transfused patients
73x51mm (600 x 600 DPI)

STROBE Statement by Nora Klauke

	Item No	Recommendation
Title and abstract	1	*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		See page: 1-2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		See page: 4
Objectives	3	State specific objectives, including any prespecified hypotheses
		See page: 4
Methods		
Study design	4	Present key elements of study design early in the paper
		See page: 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		See page: 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		See page: 5-6
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		See page: 5-6
Bias	9	Describe any efforts to address potential sources of bias
		See page: 14-15
Study size	10	Explain how the study size was arrived at
		See page: 7

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		See page: 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
		See page: 5-6

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		See page: 7
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
		See page: 7 and Table 1
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
		See pages: 7-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
		See pages: 7-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		See page: 10-11

Discussion		
Key results	18	Summarise key results with reference to study objectives
		See page: 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
		See page: 3; 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		See pages: 12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results
		See page: **13**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
		See page: Cover letter/Title page - no funding declared
Ethics	23	**See pages: 6**

BMJ Open

Effects of prehospital hypothermia on transfusion requirements and outcomes – a retrospective observatory trial

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Manuscripts

Effects of prehospital hypothermia

on transfusion requirements and outcomes – a retrospective

observatory trial

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1 **ABSTRACT**

2 *Objectives:* Prehospital hypothermia is defined as a core temperature < 36.0°C and has

3 been shown to be an independent risk factor for early death in trauma patients. In a

4 retrospective study a possible correlation between the body temperature at the time of

5 admission to the emergency room and subsequent in-hospital transfusion requirements

6 and the in-hospital mortality rate was explored.

7 *Setting:* This is a retrospective single-center study at a primary-care hospital in

8 Germany.

9 *Participants:* 15,895 patients were included in this study. Patients were classified by

10 admission temperature and transfusion rate. Excluded were ambulant patients and

11 patients with missing data.

12 *Primary and secondary outcome measures:* The primary outcome values were length of

13 stay in days (LOS), in-hospital mortality, the transferred amount of packed red blood

14 cells (PRBCs), and admission to an intensive care unit (ICU). Secondary influencing

15 variables were the patients´age and the Glasgow Coma Scale (GCS).

16 *Results:* In 22.85% of the patients hypothermia was documented. Hypothermic patients

17 died earlier in the course of their hospital stay than non-hypothermic (p<0.001). An

18 administration of 1-3 packed red blood cells (PRBC) increased the length of stay

19 significantly (p<0.001) and transfused patients had an increased risk of death (p<0.001).

20 Prehospital hypothermia could be an independent risk factor for mortality (AOR 8.521;

21 p=0.001) and increases the relative risk for transfusion by factor 2.0 (OR 2.007;

22 p=0.002).

23 *Conclusion:* Low body temperature at hospital-admission is associated with a higher

24 risk of transfusion and death. Hence, a greater awareness for a prehospital temperature

25 management should be established.

26

1 **ARTICLE SUMMARY**

2 *Strengths and limitations of this study*

3

4 • Using a retrospective design we investigated the effects of pre-hospital

5 hypothermia on patient in-hospital mortality, length of hospital stay, ICU

6 admission and transfusion requirements in the university hospital setting

7 • The hospital database captured a total of 54,732 subjects admitted to the

8 emergency department of the University Hospital of Bonn between 1 January

9 2012 and 31 December 2013

10 • 15,895 subjects with inpatient-status recorded admission temperature, hospital

11 admission and discharge dates, demographics, Glasgow Coma Scale (GCS),

12 intensive care unit (ICU) admission, mode of transportation and information

13 about the in-hospital mortality were eligible for full set data analyses

14 • The retrospective approach does not allow for causal relationships between pre-

15 hospital hypothermia and any of the designated outcome measures

16 • The potential influence of patients diagnoses on temperature regulation,

17 medication regimes and hemoglobin levels of transfused patients was not

18 accounted for and may therefore confound observed effects

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1 **INTRODUCTION**

2 The incidence of prehospital hypothermia, defined as a core temperature below 36.0°C,

3 is frequently observed in patients admitted to the emergency room (1) mainly due to a

4 difficult and prolonged rescue, infusion of cold resuscitation fluids (2), weather, age and

5 a critical health condition. Together with acidosis and coagulopathy hypothermia has

6 been termed *lethal triad of death* (3).

7 Hypothermia alters enzymatic reactions of the coagulation cascade during the initiation

8 phase and decreases platelet function (3,4), possibly leading to severe bleeding and

9 consecutively required blood transfusion. It has been shown that the amount of applied

10 fluids and transfused PRBC is directly linked to hypothermia, is associated with a worse

11 clinical outcome (5,6), and increases the risk for postoperative mortality (7). Acute

12 complications after PRBC transfusion can comprise of hypothermia, hypocalcaemia,

13 hypomagnesiaemia, citrate toxicity, lactic acidosis and air embolism (8). Additionally

14 non-infectious serious hazards of transfusion (NISHOTs) ranging from common

15 complications, e.g., allergic or febrile hemolytic reactions (9) to rare, life-threatening

16 entities like the transfusion-related lung injury (TRALI) (10) or the transfusion

17 associated Graft versus Host Disease (TA-GVHD) (11) can still pose a serious threat to

18 patients. The patients´ outcome might also be negatively affected by non-antibody-

19 antigene dependent reactions known as transfusion-related immune modulation (TRIM)

20 (9) that are suspected to increase the rate of infection and tumor-recurrence after

21 transfusion (12). The aim of this study was to evaluate the effects of prehospital

22 hypothermia on transfusion rate and mortality. This retrospective single-center database

23 analysis was executed in the framework of a Germany-wide multi-center initiative for

24 patient blood management, which aims at reducing the amount of blood transfusion

25 whenever feasible and beneficial for the patient.

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1   **MATERIAL AND METHODS**

2   This study reviewed the University Hospital Bonn (UHB) Emergency Department

3   database from January 1, 2012 until December 31, 2013 that contained anonymized data

4   of 54,732 patients. Included in this study were patients with recorded admission

5   temperature, documented admission and discharge date, age, Glasgow Coma Scale

6   (GCS), intensive care unit (ICU) admission, mode of transportation and information

7   about the in-hospital mortality.

8   As a standard operating procedure each patient's clinical health status is evaluated by a

9   nurse in the framework of an emergency triage system when admitted to the ED. The

10   triage includes the tympanal measurement of the patient´s temperature. This method is

11   easy and fast, shows accurate results and can be recommended for this purpose (13).

12   The LOS was calculated electronically. The GCS was evaluated by the emergency

13   physician arriving at the scene.

14   The amount of transfused red blood cells was evaluated by matching our database with

15   the University Hospital Bonn Institute of Transfusion Medicine's database and is

16   presented as raw number of received packages (PRBC). The transfusion-criteria are

17   given in the German guideline: Cross-Sectional guidelines for therapy with blood

18   components and plasma derivates (2014) (14).

19   According to the German guideline: S3 prevention of perioperative hypothermia (2014),

20   a patient was defined hypothermic when presented with a temperature below 36.0°C, ,

21   normothermic with a temperature from 36.1°C to 38.0°C and hyperthermic when the

22   temperature was >38.1°C on arrival at the ED.

23   The primary outcome values were length of stay in days (LOS), in-hospital mortality,

24   the transferred amount of PRBCs, and ICU admission.

25   Secondary influencing variables such as age and GCS were considered further grouping

26   variables to compare the hypothermic with the normothermic and hyperthermic patients.

1 For quantitative data evaluation the median test and Mann-Whitney-U-Test were used.

2 To objectify if transfusion and mortality was independent of the patient's temperature,

3 age and GCS contingency tables were created and analyzed with a chi² test. To compare

4 means Student's t-test was used. Kaplan Meier analysis was applied to identify whether

5 hypothermic and transfused patients had a higher risk of mortality than the other

6 patients in the study. Binary logistic regression was used to determine risk factors for

7 mortality. The univariate predictors were the body temperature and transfusion. The

8 results are given in adjusted odd ratio (AOR) and reached statistical significance with

9 $p<0.001$. Other results are presented as mean (standard deviation, SD) for ordinal data,

10 median for data which had expected peaks and descriptive data as raw percentages.

11 Statistical analysis was performed using SPSS Statistics Amos 22.0 (IBM Corporation,

12 Armonk, USA).

13 Approval for the patient blood management study was given by the ethics committee of

14 the medical faculty of the University of Bonn chaired by Professor K. Racké (number

15 082/13 from the 7th of May 2013). The present study was purely retrospective and

16 approval by the ethic committee was not necessary as the General Medical Council

17 explicitly excluded retrospective studies from approval in their code of medical ethics

18 (§15/1) (15).

19 All collected clinical data evaluated in this study were fully anonymized before

20 analysis. Therefore, according to prior agreement with the local ethics committee and

21 the data protection officer appointed by the University Hospital, verbal or written

22 informed consent was not obtained.

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1 **RESULTS**

2 During the two-year study period 15,895 patients out of 54,732 patients that arrived at

3 the emergency department (ED) were included in the study. 36,418 ambulant patients

4 (admitted and discharged within 24 hours) and patients lacking the required data were

5 excluded. Also excluded were 1,675 patients who required interdisciplinary consultation

6 or were admitted as case conferences from other hospitals.

7 Of the included patients 22.6% were hypothermic according to the German guideline,

8 71.8 % normothermic and 5.4% hyperthermic.

9 The mean LOS for all study-patients was 8.6 days (median 4.9d, SD 12.3). After arrival

10 at the emergency department 14.0% of the patients were transferred to the ICU. In this

11 group 15.6% were hyperthermic, 14.3% normothermic and 12.7% hypothermic

12 (p=0.3)(demographic data see table 1).

Table 1: Demographic data of the study population

Variable	Total (n=15895)	Hypothermic patients (n=3348)	Normothermic patients (n=10517)	Hyperthermic patients (n=786)	p
Age, mean (SD); [median]	57.8 (21.1); [61]	60.3 (20.5);[64]	57.2 (21.1);[60]	56.3 (20.3);[60]	p<0.001
Sex, male (%)	57.3	59.9	55.5	62.1	p<0.001
Temperature, mean (SD); [median]	36.5 (0.8);[36.5]	35.6 (0.5);[35.8]	36.7 (0.4);[36.6]	38.8 (0.6);[38.6]	p<0.001
Transfused (%)	8.2	9.7	7.2	9.4	p<0.001
PRBC total, mean amount	0.6	0.7 (4.3)	0.5 (3.0)	0.6 (4.1)	p<0.001
PRBC during the first 24h,mean(SD)	0.8 (2.8)	1.1 (3.2)	0.5 (1.8)	0.2 (0.9)	p=0.001
PRBC day 2, mean(SD)	1.5 (3.6)	1.8 (4.1)	1.1 (2.6)	0.8 (1.6)	p=0.042
PRBC day 3, mean(SD)	2.2 (4.3)	2.5 (4.8)	1.7 (3.3)	1.2 (1.8)	p=0.05
Systolic BP (mmHg)	140	139	141	135	p<0.001
GCS, mean(SD); [median]	12.8 (4.3);[15]	12.3 (4.5);[15]	13.2 (3.9);[15]	12.7 (4.1);[15]	p=0.001
ICU Admission (%)	14	12.7	14.3	15.6	p=0.292
LOS(d), mean(SD); [median]	8.6 (12.3);[4.9]	8.7 (12.4);[4.7]	8.4 (11.7);[4.8]	10.1 (13.3);[6.2]	p<0.001
Mortality (%)	5.1	7.4	3.4	4.1	p<0.001

Table 1: Demographic data of the study population (SD- Standard deviation, PRBC- packed red blood cells, BP- blood pressure, GCS- Glasgow coma scale, ICU- Intensive care unit, LOS- Length of stay)

13

1   *Effects of hypothermia*

2   Hypothermic patients died earlier than normothermic and hyperthermic patients

3   (p<0.001) as depict in the Kaplan Meier analysis (figure 1).

4   Additionally the analysis revealed that patients who died during the study period had an

5   already decreased core temperature when admitted to the ED. Those patients had a

6   significantly lower mean body temperature of 36.3°C (SD 1.1) than patients that were

7   discharged alive (36.6°C SD 0.8)(p<0.001).

8   Hypothermic patients had a mean LOS of 8.7d (median 4.7d SD 12.4), normothermic a

9   mean LOS of 8.4d (median 4.8d SD 11.6) and hyperthermic patients a mean LOS of

10   10.1d (median 6.2d SD 13.3). The LOS of the patient groups differed significantly

11   (p<0.001), (figure 2).

12   *Effects of blood transfusion*

13   Of the study patients 1295 patients (8.1%) received PRBC during their stay with a

14   median of 4 PRBC. 1-3 PRBC were transfused to 45.2% of the patients, 4-6 PRBC to

15   26.6%, 7-9 PRBC to 9.9 % and 18.3% received a massive transfusion, defined as 10

16   PRBC or more. The more PRBC a patient received the longer was the LOS at the

17   hospital (p<0.001).

18   The in-hospital mortality rate of 5.1% for all study- included patients increased with the

19   number of administered PRBC. It reached 9.9% for patients with 1-3 PRBC; 14.0% for

20   4-6 PRBC, 19.0% for 7-9 PRBC and 32.5% for patients with >=10 PRBC (p<0.001).

21   Patients who died during their clinical stay received a mean amount of 13.3 (SD 16.4)

22   PRBC.

23   Patients who were admitted to the ICU had a fivefold increased risk of death (AOR 5.6;

24   95% Cl 2.0-15.8; p=0.001).

1 Referring to Kaplan Meier function transfused patients died at a significantly higher rate

2 and earlier than patients without transfusion (p<0.001),(figure 3).

3 Referring to the used regression model an univariate analysis for SPB ≤90/>90 and age

4 ≥65/<65 years showed that patients with SBP>90 had an increased risk of death by

5 factor 0.1 (OR 0.109; Cl 95% 0.087-0.138) (p<0.001) and that patients ≥65 had a

6 threefold risk of death compared to patients <65 (OR 3.140; 2.688-3.669) (p< 0.001).

7 *Influence of hypothermia on transfusion*

8 Hypothermic patients received significantly more PRBC (9.7%) during their hospital

9 stay than normothermic (7.2%) and hyperthermic patients (9.4%), (p<0.001). Binary

10 logistic regression model revealed that both body temperature and transfusion rate are

11 risk factors for mortality. Prehospital hypothermia (≤ 36.0°C) increased the risk of

12 death up to almost 50% (AOR, 1.5; 95%Cl 0.7-3.; p<0.001) in contrast to

13 normothermia. Transfusion of 1-3 PRBC increased the risk of death by 20% (AOR 0.2;

14 95%Cl 0.1-0.3), similar to receiving 4-6 PRBC (AOR 0.3; 95% Cl 0.2-0.4), and 7-9

15 PRBC (AOR 0.5; 95% Cl 0.3-0.8) (p<0.001). The administration of ≥10 PRBC

16 increased the risk of death by factor 5 compared to patients with only 1-3 PRBC (AOR

17 5.7; 95% Cl 1.3-2.2), (p<0.001).

18 To evaluate the influence of prehospital hypothermia on the transfusion rate further

19 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

20 subgroup-analysis showed that a further decreased body core temperature was

21 associated with a rising amount of PRBCs. The analysis revealed that the amount of

22 administered PRBCs rose from group d. (9.0%) to group a. (16.1%). In comparison with

23 the hypothermic patients only 7.2% in the normothermic group (36.1-38.0°C) and 9.4%

24 in the hyperthermic group (>38.1) received a transfusion (p<0.001).

25 In a logistic regression model an admission temperature ≤34.5°C was associated with

26 an 8-fold risk of death (AOR, 8.5; 95% Cl 2.5-28.5; p=0.001) and with an

1 approximately two fold risk for transfusion (AOR, 1.8; 95% Cl 1.0-3.1; p=0.46).

2 However, we calculated the relative risk for receiving PRBC in the group of patients

3 admitted with a body temperature ≤34.5°C and the analysis showed that these patients

4 had a doubled relative risk (OR 2.0; Cl 95% 1.3-3.1) for transfusion compared to

5 normothermic patients (p=0.002).

6 Referring to the regression model other univariate predictors were again SPB ≤90/>90

7 and age ≥65/<65 years. This analysis showed that that patients with a SBP>90 had an

8 increased risk for transfusion by factor 0.4 (OR 0.389; 0.301-0.503) (p<0.001) and that

9 patients of ≥65 years showed a doubled risk for receiving transfusion compared to

10 younger patients (OR 1.935; 1.722-2.175) (p<0.001).

11 Contingency table displayed that 25% of the patients with a GCS≤8 received blood

12 products whereas only 7% patients with a GCS >9 received PCRB during their stay

13 (p<0.001). It also occurred that the mean GCS in transfused patients was significantly

14 lower (GCS 10) than that in non-transfused patients (GCS 13), (p<0.001). A GCS ≤8

15 (AOR 12.2; 95%Cl 7.8-19.2; p=0.001) and transfusion of PRBC were connected with

16 an increased risk of death (AOR 3.8; 95%Cl 2.1-7.1; p=0.001). The Student´s t-test

17 revealed that hypothermic patients had a significantly lower GCS (median 12.3 SD 4.5)

18 than normothermic patients (median 13.2 SD 3.9), (p<0.001), but there was no

19 significant difference in the GCS of hypothermic to hyperthermic patients (median 12.7

20 SD 4.1) (p=0.47).

21 In our analysis we found that 26.8% of patients accompanied by an emergency

22 physician were hypothermic and only 19.2% of patients accompanied by paramedics

23 were hypothermic (p<0.001).

24 To investigate the influence of the patient´s age on LOS and received PRBCs three

25 different groups were created (i. <45 years, ii. 46-60 years, iii. >61 years). Most patients

26 were older than 61 years (50.6%). There were 28.1% of patients <45 years old and

1 21.4% between 46-60 years old. Considering the median LOS it appeared that patients

2 belonging to iii. stayed significantly longer at the hospital (median LOS 6.1 days) than

3 younger patients (p < 0.001).Patients belonging to group ii. stayed 4.8 days and patients

4 that were 45 years and younger had a median LOS of 3.3 days.

5 Considering the transfused blood products patients in group ii. received the largest

6 amount of PRBC (mean value 10.0 PRBC, median 4 PRBC, SD 15.0), whereas patients

7 in group iii. received a mean amount of 6.6 PRBC (median 4 SD 8.8). The patients in

8 group i. received 5.9 PRBC (median 3 SD 9.7).

9

10

11 **DISCUSSION**

12 The overall aim of this study was to investigate the impact of hypothermia on

13 transfusion rates and mortality at the UHB. Our findings indicate that patients

14 presenting with hypothermia on admission to the ED have adverse outcomes compared

15 to normothemic and hyperthermic patients. The same is applicable to hypothermic

16 patients that received transfusions of PRBC during their hospital stay. Though it seems

17 to be obvious that hypothermia might be a negative outcome factor during the rescue

18 and recovery process, the incidence of hypothermia in EDs remains a commonly

19 observed phenomenon. Heat loss that may be caused by prolonged rescue time and

20 severe injuries is prolonged throughout the transportation to the next ER due to a non-

21 existing standardized prehospital warming management.

22 The study-results show that almost one third of the patients arrived hypothermic at the

23 ED. We orientated ourselves on the current German guideline defining hypothermia as a

24 core body temperature < 36.0°C (16). Other studies on this subject defined hypothermia

25 as a core body temperature < 36.5°C; < 35.0°C and < 34.5°C (6,17,18). Setting our

1 temperature-limit at 36.0°C led to the fact that our hypothermic patients group is not as

2 large as in e.g the study by M. Bukur at al.(6).

3 In our study hypothermic patients did not have an increased LOS. Similar results are

4 shown by H. Trentzsch et al. (5), whereas another paper found that patients with a

5 body temperature <35.0°C and major trauma stayed longer at the hospital (19).

6 Accordant results in a retrospective paper by R. Martin et al. showed a significantly

7 increased LOS and ICU admission rate for hypothermic major trauma patients (<

8 35.0°C) compared to normothermic patients (p<0.001) (17). The differences in our

9 findings compared to the studies by S. Ireland et al. and R. Martin et al. may be either

10 caused by their collective of patients or by the fact that the Kaplan Meier analysis in our

11 study revealed that hypothermic patients had an increased mortality rate and died earlier

12 than patients with normal or febrile temperatures. Martin et al. and Ireland et al. mainly

13 used results of major trauma patients in their studies whereas we included every patient

14 admitted to the emergency department despite the injury severity score. Our results

15 revealed that hyperthermic patients had the longest LOS and were more often admitted

16 to the ICU. We suggest that those patients were septic or in another febrile critical

17 health condition that needed intensive treatment.

18 Hypothermic patients showed an increased consumption of PRBC and an increased risk

19 of death. Responsible for these findings might be the partial impairment of the

20 coagulation by hypothermia already outlined in the introduction (3,4,20). Other factors

21 that additionally affected the coagulation of the patients included in this study cannot be

22 retraced due to the retrospective study design.

23 The in-hospital death rate for patients with >10 PRBC-units of red blood cells rose up to

24 37.8% whereas patients with 1-3 PRBC units had a death rate of 9.9%.The multi-

25 centered patient blood management initiative, in which this study is integrated in, aims

26 at an increase in patient safety and reduction of liberal admission of 1-3 PRBC because

27 it was shown that already a small amount of allogenic blood transfusion is associated

1 with septic, pulmonary and embolic complications (21). Other possible reasons for

2 increased mortality rate are predisposition to nosocomial and postoperative infections,

3 cancer recurrence and microchimerism through the infusion of PRBC (22). Our results

4 prove that patients with 1-3 PRBC had a significantly increased LOS compared to

5 patients that received no transfusion (p<0.001). They additionally had an enhanced risk

6 of death (AOR 0.174; p<0.001).

7 Our analysis demonstrated that patients with massive transfusion died earlier than other

8 patients. One-third of the total amount of PRBC for each massive transfused patient in

9 the ED was administered within the first 72 hours. Among this group are most likely

10 patients with severe injuries and major trauma that are in the urgent need of

11 resuscitation fluids e.g. red blood cells as subsidized by a large retrospective study by

12 R.R Barbosa et al. (23).

13 There was also a significant association between the GCS and PRBC. One fourth of the

14 patients with a GCS of ≤8 were in need of PRBC which seems reasonable since the

15 GCS classifies the consciousness in patients with severe injuries.

16 In addition there was a difference in the occurrence of hypothermia depending on the

17 mode of transportation. The incidence of hypothermia was significantly higher on an

18 ambulance with an emergency physician present compared to ambulances operated by

19 paramedics. These results indicate that patients accompanied by an emergency

20 physician were either hypothermic due to their injuries and cold resuscitation fluids or

21 their body temperature was lowered protectively.

22 Patients of 61 years and older had the longest LOS. Despite of this result, patients in the

23 middle-aged group (46-60 years) received the most PRBC during their stay at the

24 hospital. The study by R.R. Barbosa displayed that age was independently associated

25 with a higher risk of mortality in an observed 30-day period among transfused patients

26 after trauma (23). According to this our study showed that patients who died during the

1   stay at the hospital had a mean age of 71.34 (SD 14.34) whereas patients that were

2   discharged alive had a mean age of 57.12 (SD 21.16), (p<0.001).

3   *Limitations*

4   Due to the retrospective study design it was not possible to create a causal connection

5   between the admission temperature and the distribution of PRBC as it would be in a

6   prospective clinical trial. This study did not include the patients' diagnoses that might

7   have influenced the temperature regulation. Additionally, medications such as

8   anticoagulants could not have been retraced. We were not able to retrace the exact

9   hemoglobin level of the transfused patients and to differentiate between patients with

10   accidental and induced hypothermia retrospectively. It has to be taken into account that

11   ambulances are able to cool patients, and that this is a standard procedure in patients

12   with heart attacks, cardiac arrest and patients with possible brain damage as these

13   patients benefit from a lower core body temperature (24–25).

14   It has to be taken into consideration that our review did not analyze the connection of

15   the injury severity score (ISS) of each patient with the body temperature and the

16   transfusion requirement. This is due to the fact that it was not possible to reproduce the

17   ISS in retrospect. A prospective controlled clinical trial on a connection between

18   temperature, transfusion requirement and ISS could prove the importance of this

19   subject.

20   **CONCLUSION**

21   Despite the mentioned limitations this large retrospective study was able to show that

22   prehospital hypothermia is associated with an increased transfusion requirement and a

23   worse outcome compared to normothermic and not transfused patients.

24   This study should create further awareness for the importance of the patient's body

25   temperature and a more restrictive transfusion regime for patients that are not in life-

26   threatening need of resuscitation fluids. Patients with low prehospital body core

1 temperatures, due to the injury severity or a prolonged rescue should be protected from

2 further heat loss with trauma warming blankets. An effective warming management

3 installed on all ambulances and in the EDs could help preventing hypothermic patients

4 from a worse outcome as induced through the primary injury. It is to emphasize that this

5 is a hypothesis suggested by the findings of this study, a prospective randomized

6 controlled trial should be conducted to investigate, if a prehospital worming is

7 beneficial for the patients.

8

9 Contributorship statement:

10 NK: data analysis, literature research, writing the manuscript

11 IG: planning of the trial

12 AF: data analysis

13 OB: writing the manuscript

14 GB: planning the trial, writing the manuscript

15 VG: writing the manuscript

16 PM: planning the trial

17 MW: planning of the trial, data analysis, literature research, writing the manuscript

18 Competing interests:

19 We declare no funding and no competing interests.

20 Data sharing:

21 No additional data available.

22

23

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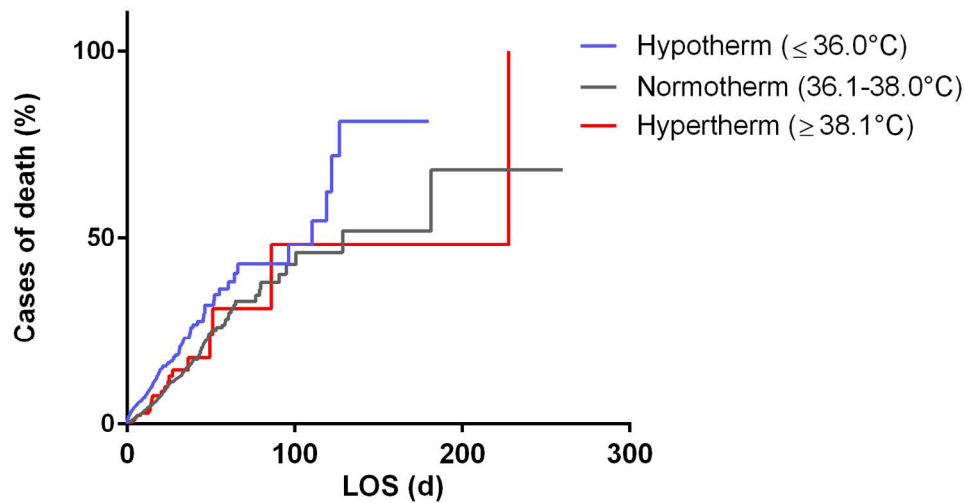
Figure 1
Kaplan Meier analysis: Hypothermic patients had the highest mortality rate (LOS (d): length of stay in days)
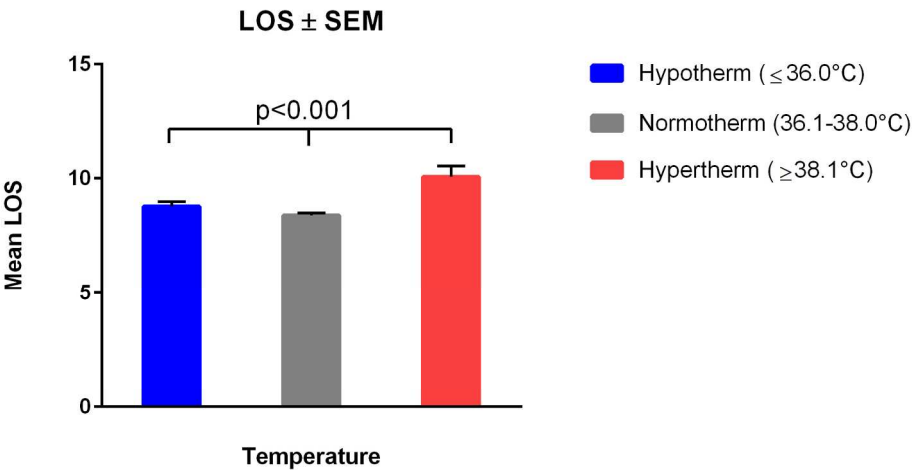151x85mm (300 x 300 DPI)

Figure 2
LOS in days ± SEM for each temperature category
(LOS (d): length of stay in days, SEM: standard error of the mean)
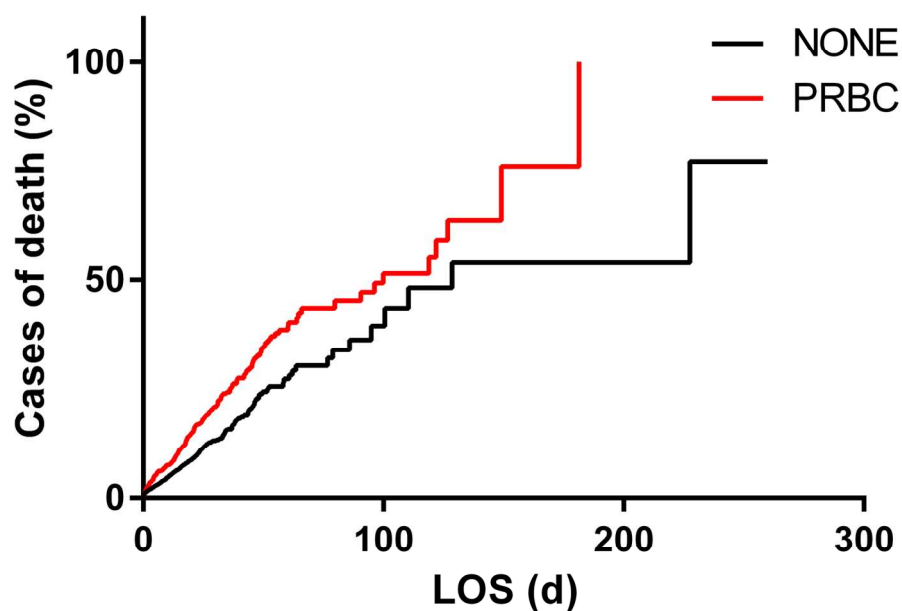
182x91mm (300 x 300 DPI)

Figure 3
Legend: Kaplan Meier Analysis: Mortality of transfused patients compared to not transfused patients (LOS
(d): length of stay in days; PRBC: packed red blood cells)
73x51mm (600 x 600 DPI)

STROBE Statement by Nora Klauke

	Item No	Recommendation
Title and abstract	1	*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		See page: 1-2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		See page: 4
Objectives	3	State specific objectives, including any prespecified hypotheses
		See page: 4
Methods		
Study design	4	Present key elements of study design early in the paper
		See page: 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		See page: 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		See page: 5-6
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		See page: 5-6
Bias	9	Describe any efforts to address potential sources of bias
		See page: 14-15
Study size	10	Explain how the study size was arrived at
		See page: 7

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **See page: 6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **See page: 5-6**

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram **See page: 7**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **See page: 7 and Table 1**
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		*Cross-sectional study—*Report numbers of outcome events or summary measures **See pages: 7-10**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **See pages: 7-10**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **See page: 10-11**

Discussion		
Key results	18	Summarise key results with reference to study objectives
		See page: 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
		See page: 3; 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		See pages: 12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results
		See page: **13**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
		See page: Cover letter/Title page - no funding declared
Ethics	23	**See pages: 6**