Original Articles

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Change in Body Temperature Is Useful for Prognostic Prediction of Severe Trauma

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Objective: Hypothermia, metabolic acidosis, and coagulopathy are the components of the "lethal triad," which contributes to high mortality of severe trauma. However, the important factors remain unclear. This study was performed to clarify whether these factors are correlated with the mortality of severe trauma at 24 h after the therapeutic intervention.
Materials: The retrospective study was performed from January 2012 to December 2012 in 15 Japanese hospitals.
Methods: 687 trauma patients, aged ≥18 years with an Injury Severity Score (ISS) of ≥16 were involved. Changes in the body temperature (BT), fibrinogen, prothrombin time-international normalized ratio, fibrin/fibrinogen degradation products, pH, base excess, lactate, and platelet count during 24 h after admission were analyzed, while providing adequate medical care including various therapeutic interventions such as fluid therapy, blood transfusion, and surgery. Extraneous factors such as age, sex, ISS, Revised Trauma Score, and probability of survival were also evaluated. The endpoint was 28-day survival, and all parameters were compared between the survivor (n=646) and non-survivor (n=41) groups.
Results: Age and ISS were significantly higher in the non-survivor group. The univariate analysis showed a BT increase of 1.0℃ in the survivor group relative to an increase of only 0.4℃ in the non-survivor group, indicating that BT variation contributes to survival after trauma (odds ratio, 4.07). Additionally, the increase in fibrinogen was significantly higher in the survivor than non-survivor group (54 vs. 17 mg/d*l*, respectively; odds ratio, 4.68). The multivariate logistic regression analysis revealed that increases in BT and fibrinogen were independent variables for 28-day survival.
Conclusion: BT and fibrinogen were independent variables for 28-day survival. In the study, these results may have suggested the importance of therapeutic interventions for the BT and coagulation in trauma patients.

Key words: body temperature variation, prognostic prediction, severe trauma

Introduction

Massive hemorrhage is often the cause of death in patients with severe trauma. Patients' outcomes following major trauma have improved as our understanding of the homeostatic system has progressed. A damage control protocol can provide good survival rates in patients with severe trauma.[1)-3)]

The human body maintains homeostasis through three phases: the vascular phase (vascular spasm), platelet phase (platelet plug formation, and coagulation phase (clotting factor production). However, this process can be disrupted by the "lethal triad," which comprises coagulopathy, acidosis, and hypothermia.

Hypothermia is usually considered to be present in trauma patients with a core body temperature (BT) of <35℃.[4)] Some retrospective studies of trauma patients have shown an independent association between mortality and an admission BT

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of <35℃.[5] In addition, one study showed that a BT of <32℃ on admission was associated with a patient survival rate of 0%.[6]

The present study was performed to clarify whether changes in coagulation disorders, acidosis, and BT at 24 h after therapeutic interventions determine the prognosis in patients with trauma.

Material & Methods

This study was conducted at 15 tertiary emergency and critical care centers participating in the Japanese Observational Study for Coagulation and Thrombolysis in Early Trauma (J-OCTET) under the approval of the Japanese Association for the Surgery of Trauma and the ethics committees in all participating centers (Appendix 1). This retrospective case control study was designed to investigate coagulation and thrombolysis disorders in patients with severe trauma. All patients were aged ≥18 years and presented with severe trauma with an Injury Severity Score (ISS)[7] of ≥16[8,9] from January 2012 to December 2012. The patients were registered retrospectively based on the medical records in the respective centers. The following patient information was registered in the databank: age, sex, mechanisms of injury, ISS, Revised Trauma Score (RTS), and probability of survival; *i.e.*, the patient's estimated survival rate as determined by the Trauma and Injury Severity Score (TRISS).[10] The BT and laboratory test data on arrival, amount of blood transfusion (PRBCs, fresh frozen plasma [FFP], platelet concentrate [PC]), the execution of transcatheter arterial embolization (TAE) and surgical treatment within 24hour after arrival, and 24hour, 28-day mortality were obtained.

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the Juntendo University Urayasu hospital and it conforms to the provisions of the Declaration of Helsinki.

1. Exclusion criteria

Patients who were referred by another hospital, were pregnant, had cirrhosis, had cardiopulmonary arrest prior to or upon arrival, had an ISS of ≥16 and only spinal cord injury not caused by a high-energy external force, and/or had burn injuries were excluded from registration.[8] Patients who died within 24 h of arrival were excluded from this study. Additionally, we calculated the nonparametric 95% confidence interval (CI) of the BT on arrival and patients with a BT outside the CI (<33.9℃ and >37.7℃) were excluded.

2. Data extraction and assessment

In this study, we examined eight clinical parameters associated with the three factors of interest (coagulation disorder, acidosis, and BT): prothrombin time-international normalized ratio (PT-INR), fibrinogen level, fibrin/fibrinogen degradation product (FDP) level, platelet count (Plt), pH, base excess (BE), lactate level, and BT. In addition, age, sex, ISS, RTS, and TRISS-associated probability of survival were collected as patient background factors.

Changes in all parameters from arrival to 24 h thereafter were calculated. Briefly, as shown by the following equations, the difference between the value of each parameter on arrival and the value 24 h after arrival was defined as the change represented by Δ.

$$\Delta t = t_{24h} - t_{initial}$$
$$\Delta X = X_{24h} - X_{initial}$$

Here, t_{24h} and $t_{initial}$ refer to the BT 24 h after arrival and on arrival, respectively. The change (Δ) between arrival and 24 h thereafter was similarly calculated for the other parameters; *i.e.*, fibrinogen level, FDP level, pH, BE, lactate level, and Plt.

The difference in PT-INR from 1 [the normal value (absolute deviation)] was examined. Briefly, ΔPT-INR was calculated using the following equations:

$$dPT-INR_{initial} = |PT-INR_{initial} - 1|$$
$$dPT-INR_{24h} = |PT-INR_{24h} - 1|$$
$$\Delta PT-INR = dPT-INR_{initial} - dPT-INR_{24h}$$

3. Outcome Measures

The study outcome was set as 28-day survival. Based on this outcome, the patients were divided into the 28-day survival group and the non-survival group and subjected to analyses.

4. Statistical analysis

Odds ratios were calculated using logistic regression analysis which included TRISS Ps as a covariate and a contingency table. The odds ratios and their CIs in the contingency table were calculated using Fisher's exact test. The Mann-Whitney U test was used to determine differences.

Missing data were complemented by generating 500 data sets by means of multiple imputations using the algorithm of multiple imputations by chained equations (MICE)[11) 12)] and integrating them according to Rubin's rule.[13)] The logistic regression analysis was repeated 10,000 times to find the odds ratio and its 95% CI of each dataset according to Rubin's rule. Statistical significance was determined by combining the 95% CI and p-value. The analysis was performed using R for Windows 3.3.1 and R version 3.2.2 for Linux. We adopted a significance level of 5%.

Results

Difference in clinical characteristics between survival and non-survival groups. Among 796 patients, 73 who died within 24 h after arrival and 36 already showing an abnormal BT on arrival were excluded. Consequently, 687 patients were subjected to analyses in this study (Figure-1). At 28 days after injury, 646 patients were alive and 41 patients had died (28-day survival rate of 94.0%). Table-1 showed the patient characteristics in the survival and non-survival groups. Age (64 vs. 56

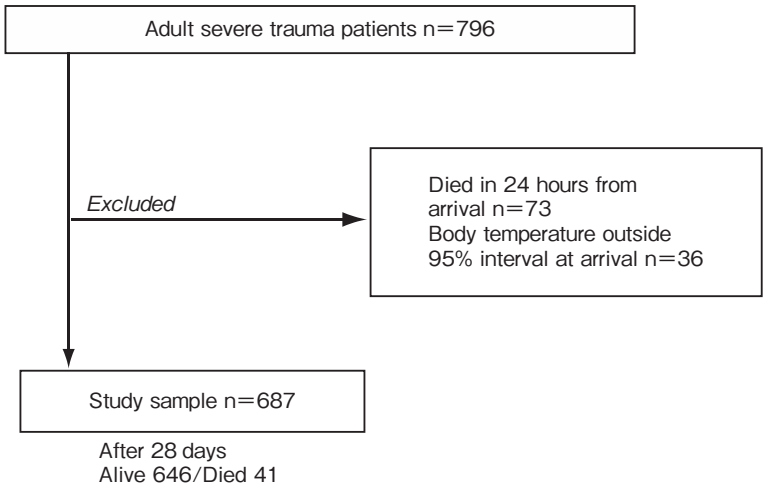

Figure-1
Study flow chart

Table-1 Baseline characteristics of included patients

Parameter	Survival group n=646	Non-survival group n=41	p-value	NA
Age (years)	56 (37, 71)	64 (45, 74)	0.04	0
Sex, men (%)	472 (73.1)	31 (75.6)	0.9	0
ISS	21 (17, 26)	25 (25, 30)	<0.001	0
RTS	7.84 (6.90, 7.84)	5.03 (4.09, 5.97)	<0.001	0
TRISS Ps on arrival (%)	93.9 (86.1, 97.4)	58.8 (27.5, 77.1)	<0.001	0
Body temperature (℃)	36.3 (35.8, 36.7)	36.2 (35.6, 36.5)	0.3	18
PT-INR	1.04 (0.98, 1.11)	1.10 (1.04, 1.28)	<0.001	79
Fibrinogen (mg/d*l*)	241 (202, 281)	221 (199, 288)	0.4	128
FDP (μg/m*l*)	40.5 (19.1, 83.7)	135 (65.7, 230.1)	<0.001	281
pH	7.39 (7.35, 7.42)	7.37 (7.34, 7.40)	0.09	94
BE (mmol/*l*)	-1.0 (-3.1, 0.2)	-3.0 (-4.9, -0.7)	0.002	96
Lactate (mmol/*l*)	2.3 (1.7, 3.3)	2.7 (2.1, 4.1)	0.049	107
Plt ($\times 10^4$/μ*l*)	20.6 (16.7, 25.5)	17.9 (13.5, 22.6)	0.005	3

NA, number of unavailable dataset: ISS, Injury Severity Score; RTS, Revised Trauma Score; TRISS, Trauma and Injury Severity Score; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin/fibrinogen degradation product; BE, base excess; Plt, platelet count

years, p = 0.04) and the ISS (25 vs. 21, p < 0.001) were significantly higher whereas the RTS (5.0 vs. 7.8) and probability of survival (58.8% vs. 93.9%) were significantly lower in the non-survival than survival group.

1. Intergroup comparisons of BT and coagulability on arrival

On arrival, no significant difference was detected in the BT, fibrinogen level, or pH. Meanwhile, the PT-INR (1.10 vs. 1.04, p < 0.001) and FDP level (135 vs. 40.5 μg/m*l*, p < 0.001) were significantly higher in the non-survival group (Table-1). Moreover, the BE was significantly lower (-3.0 vs. -1.0 mmol/*l*, p = 0.002) whereas the lactate level was significantly higher (2.7 vs. 2.3 mmol/*l*, p = 0.049) in the non-survival group. In addition, Plt on arrival was significantly lower in the non-survival group (17.9 vs. 20.6 × 10^4/μ*l*, p = 0.005).

2. Changes in BT in the two groups

Figure-2 showed the changes in the BT between arrival and 24 h thereafter in the two groups. The BT (37.3℃ vs. 36.4℃, p < 0.001) and BT elevation (ΔT) (1.00℃ vs. 0.40℃, p = 0.015) were significantly higher 24 h after arrival in the survival than non-survival group. In other words, the BT substantially increased within 24 h after arrival, indicating better thermogenesis in the survival group than non-survival group. Moreover, the contingency table analysis based on ΔT ≥ 0 (increase or no change) or ΔT < 0 (decrease) showed a very highly significant difference (p < 0.001; odds ratio, 4.07; 95% CI, 1.92-8.38).

Changes (ΔX) between arrival and 24 h thereafter were calculated from the blood gas analysis data and blood coagulation test values. No significant difference in pH, BE, lactate level, Plt, or PT-INR was detected at 24 h between the groups. A significant difference was detected in only Δfibrinogen and ΔFDP between the groups.

As shown in Figure-3, the increase in the fibrinogen level within 24 h after arrival (Δfibrinogen) was significantly higher in the survival than non-survival group (54 vs. 17 mg/d*l*, p < 0.001). Moreover, the contingency table analysis based on the increase (including no change) or decrease in the fibrinogen level 24 h after arrival showed a highly significant difference (p < 0.001; odds ratio, 4.68; 95% CI, 2.32-9.42).

For ΔT and Δfibrinogen, a logistic regression analysis was conducted using 28-day survival as an explained variable and changes in addition to ΔT and Δfibrinogen (ΔPlt, ΔPT-INR, ΔFDP, ΔpH, ΔBE, and Δlactate) as explanatory variables to determine the log odds ratio adjusted for TRISS and probability

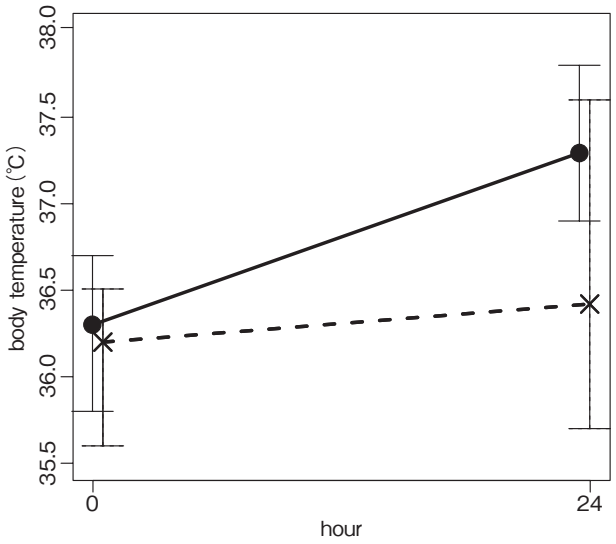

Figure-2 Changes in body temperature between arrival and 24 h thereafter
The solid and broken lines indicate the changes in patients who were alive or had died by 28 days after arrival, respectively, whereas the vertical lines represent the first and third quartiles.

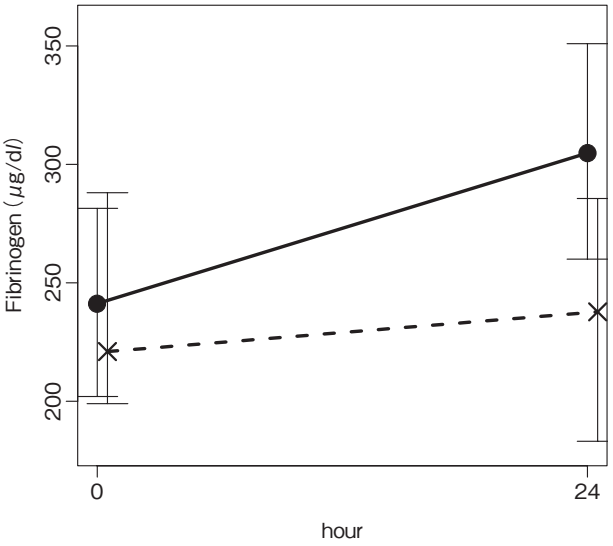

Figure-3 Changes in fibrinogen level between arrival and 24 h thereafter
The solid and broken lines indicate the changes in patients who were alive or had died by 28 days after arrival, respectively, whereas the vertical lines represent the first and third quartiles.

Table-2 Results of the logistic regression analysis using 500 datasets of each factor

Parameter	Log odds ratio	95% CI (lower and upper limits)	p-value
Δfibrinogen (mg/d*l*)	0.004	0.0003, 0.009	<0.001
Δt (℃)	0.36	0.001, 0.69	0.02
ΔLactate (mmol/*l*)	−0.15	−0.53, 0.13	0.08
ΔPlt ($\times 10^4$/μ*l*)	0.02	−0.048, 0.10	0.3
ΔFDP (μg/m*l*)	0.0006	−0.002, 0.004	0.5
ΔpH	0.96	−5.2, 7.1	0.7
ΔBE (mmol/*l*)	−0.01	−0.20, 0.16	0.7
ΔPT-INR	0.48	−2.12, 2.42	0.8

CI, confidence interval; Plt, platelet count; FDP, fibrin/fibrinogen degradation product; BE, base excess; PT-INR, prothrombin time-international normalized ratio

of survival (Table-2). Only ΔT and Δfibrinogen were significant explanatory variables.

Discussion

Various reports have described the lethal triad in surgery for trauma. According to these reports, a radical operation should be avoided and damage control surgery prioritizing only hemostasis and protection against infection should be considered when hypothermia (<35℃), acidosis (pH <7.2), or coagulopathy (PT-INR >1.50)[8] is found. A cross sectional study reported that the point of 24 hour after admission could predict the prognosis in trauma with high accuracy[14]. Thus, The present study was conducted to clarify whether changes in the BT, acid-base equilibrium, or coagulation disorder at 24 h after therapeutic interventions can be used to predict the prognosis of patients with severe trauma. This retrospective analysis was based on a multicenter large-scale database. In this study, we statistically extracted the factors that predicted the vital prognosis on day 28 after injury, for which medical care including various therapeutic interventions such as fluid therapy, blood transfusion, and surgery were performed after arrival. As a result, increases in the BT and fibrinogen level within 24 h after arrival were found to be significant factors for prediction of the 28-day vital prognosis. With respect to the BT, the survival group showed an increase in the median temperature by Δ1℃, whereas the temperature in the non-survival group did not increase by more than Δ0.4℃. This indicates that aggressive warming may be effective during treatment and that BT elevation is an important factor for survival. Additionally, from the viewpoint of prognostic prediction, patients unable to elevate their BT by more than 1℃ had difficulty surviving for 28 days even if they were alive 24 h after arrival.

Several studies on the elevation of BT by thermogenesis after surgical invasion have been reported and a study revealed that the importance of rewarming in trauma[15]. Shiozaki *et al* focused on the time until rewarming to 37℃ postoperatively as the rate of temperature rise and demonstrated that patients with a low rate of temperature rise (*i.e.*, poor rewarming) had a poor prognosis[16]. Likewise, the results of our study showed that patients with poor elevation of their BT during the first 24 h after admission had a poor prognosis.

The present study also revealed that Δfibrinogen influences the prognosis of trauma. In one study, the administration of fibrinogen concentration to trauma patients resulted in an improvement of the predicted mortality rate from 33.7% to 24.4%.[17] Inaba *et al* reported that a fibrinogen level of ≤100 mg/d*l* on arrival was a strong independent risk factor[18]. In the present study, the median fibrinogen level increased to 54 mg/d*l* in the survival group, whereas it did not increase by more than 17 mg/d*l* in the non-survival group. This indicates that supplementation of fibrinogen during treatment is associated with survival. Additionally, from the viewpoint of prognostic prediction, patients who did not show a fibrinogen elevation of more than 54 mg/d*l* had poor 28-day survival even if they were alive 24 h after arrival.

Neither the indexes of acidosis (lactate, pH, and

BE) nor the PT-INR were significant explanatory variables in the present study. The reason for this contradiction with previous reports is that the criteria of the lethal triad indicates the short-term goal for the avoidance of intraoperative death; however, our study focused on risk factors for the 28-day prognosis. In this context, the results of this study indicate the necessity of therapeutic interventions to rewarm the patient by ≥1℃ from admission and recover the fibrinogen level up to 54 mg/d*l* within the initial 24 h rather than determine the indications for resuscitative surgery.

This study has several limitations. It was a multicenter follow-up study using a databank, and it did not evaluate the presence or absence of actual warming methods and/or the administration volume of fresh frozen plasma. Hence, substantial involvement of the extent of the therapeutic interventions is likely. For example, whether the goal setting of rewarming was insufficient or patients did not reach the goal despite aggressive rewarming cannot be distinguished. Randomized comparative studies are necessary to clarify causal relationships with therapeutic interventions. Another limitation is that statistical multicollinearity of the indexes for acidosis (pH, BE, and lactate) is conceivable, although these indexes were treated as independent factors. Finally, organ specificity was not considered in this study. Additional research that takes into consideration the trauma sites that strongly reflect coagulopathy and cause a high bleeding volume (*e.g.*, head and pelvis, respectively) is needed.

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Conflicts of interest

The authors declare no conflicts of interest for this article.

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Appendix 1 A list of the participating centers in this study

1. Advanced Critical Care and Emergency Center, Yokohama City University Medical Center
2. Kurume University Hospital Advanced Emergency Medical Service Center
3. Department of Emergency and Critical Care Medicine, Keio University Hospital
4. Department of Emergency Medicine & Critical Care, Center Hospital of the National Center for Global Health and Medicine
5. Emergency Medical Care Center, National Disaster Medical Center
6. Department of Emergency and Critical Care Medicine, Juntendo University Urayasu Hospital
7. Critical Care Medical Center, Tokyo Women's Medical University
8. Emergency Medical Care Center, Rinku General Medical Center
9. Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine
10. Trauma and Acute Critical Care Medical Center, Tokyo Medical and Dental University, Medical Hospital
11. Tohoku University Hospital Emergency Center
12. Advanced Critical Care Center, Nippon Medical School Hospital
13. Emergency and Critical Care Center, Fukuoka University Hospital
14. Hokkaido University Hospital Emergency and Critical Care Center
15. Emergency and Disaster Center, Kinki University Hospital