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ORIGINAL ARTICLE

Predictors of hypofibrinogenemia in blunt trauma patients on admission

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Abstract
Purpose Massive bleeding usually leads to critically low levels of clotting factors, including fibrinogen. Although reduced fibrinogen levels correlate with increased mortality, predictors of hypofibrinogenemia have remained poorly understood. We investigated whether findings available on admission can be used as predictors of hypofibrinogenemia.
Methods We retrospectively reviewed serum fibrinogen levels tested on arrival in 290 blunt trauma patients transported to a level I trauma center during a 3-year period. The primary outcome was prehospital predictors for hypofibrinogenemia. Covariates included age, sex, prehospital fluid therapy, prehospital anatomical and physiological scores, time from injury, base excess, and lactate on arrival. All variables with values of $p < 0.10$ in univariate analysis were included in a multivariate logistic regression model. The relationships between the variables and the 7-day mortality rate were evaluated in a Cox proportional hazards model.
Results Patient's age [odds ratio (OR): 0.97, $p < 0.001$], Triage Revised Trauma Score (T-RTS) (OR: 0.81, $p = 0.003$), and prehospital fluid therapy (OR: 2.54, $p = 0.01$) were detected as independent predictors for hypofibrinogenemia in multivariate logistic regression analysis. Serum fibrinogen level [hazard ratio (HR): 0.99, $p = 0.01$] and T-RTS (HR: 0.77, $p < 0.01$) were associated with the 7-day mortality rate.
Conclusion T-RTS is considered to play an important role in predicting hypofibrinogenemia and 7-day mortality in blunt trauma patients.

Keywords Fibrinogen · Mortality · Revised Trauma Score

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Introduction

Massive bleeding is a leading cause of death in trauma patients, and is usually accompanied by critically low levels of clotting factors and coagulopathy [1–4]. Fibrinogen is the first clotting factor to fall to a critically low level during life-threatening bleeding [5, 6]. Importantly, reduced fibrinogen levels have been shown to correlate with increased bleeding and increased mortality [7–9]. For this reason, current guidelines recommend fibrinogen supplementation in all cases of significant bleeding accompanied by thromboelastometric signs of functional fibrinogen deficit or a plasma fibrinogen level <1.5–2.0 g/L [2]. Hypofibrinogenemia from massive bleeding must therefore be addressed without delay in trauma patients, but predictors of hypofibrinogenemia are not well documented [10]. If some prehospital predictors for hypofibrinogenemia leading to traumatic coagulopathy could be identified, it would be possible to take the initiative and stop the

situation from advancing in severity. The aim of the present retrospective comparative study was to determine whether physical findings obtained from prehospital situations can be used as predictive factors for hypofibrinogenemia.

Methods

A retrospective trauma registry review was performed for all blunt trauma admissions to a level I trauma center with 50,000 annual visits and >3000 trauma admissions a year from April 2009 to Match 2012. The setting ranged from trauma scenes to the emergency department (ED) in this trauma center. We registered with the University Hospital Medical Information Network Center (UMIN000013826). The institutional review board of this hospital approved all study protocols. Helicopter emergency medical services (HEMS) cover the entirety of northern Hokkaido, which has a population of about 800,000. Air medical patients account for about 20 % of trauma admissions in our facility, due to the geography of the catchment area.

Study inclusion criteria were all blunt trauma patients who were tested for serum fibrinogen levels on arrival and were admitted to the hospital. Exclusion criteria were arrival at the ED >3 h after injury, New Injury Severity Score (NISS) <4 (because such patients usually had insufficient and inadequate records for evaluation), transfer from another hospital, and cardiopulmonary arrest on arrival. Patients were retrospectively excluded if they were receiving anticoagulant medications (not including aspirin) or had moderate or severe liver disease or known bleeding diathesis. Patients were also excluded if there were transfusions or vasoactive medications before arrival at the hospital. Data collection was based on a retrospective review of all medical records. Data recorded for this study cohort included data for: patient demographics on scene, NISS, Triage Revised Trauma Score (T-RTS), volume of fluid administration by the time the patient arrived at the ED, time from injury to arrival at the ED, mechanism of injury, blood test results including serum fibrinogen level and blood gas analysis on arrival, duration of hospitalization, and in-hospital mortality. NISS is the sum of the squares of the Abbreviated Injury Scale (AIS) scores of a patient's three most severe injuries, regardless of body region [11]. The AIS consists of anatomical trauma scores for individual blunt injuries in each body part, ranging from 1 (minor) to 6 (fatal) on an ordinal scale based on severity [12]. The T-RTS is a physiologic injury severity indicator based on coded intervals of the Glasgow Coma Scale (GCS), systolic blood pressure, and respiratory rate, as shown in Table 1 [13]. T-RTS varies from 0 to 12 and is used for triage and clinical decision-making in the prehospital field or the emergency department.

Table 1 Coded categories of physiological parameters used for calculation of the Triage Revised Trauma Score

GCS	SBP	RR	Coded value
13–15	>89	10–29	4
9–12	76–89	>29	3
6–8	50–75	6–9	2
4–5	1–49	1–5	1
3	0	0	0

GCS Glasgow Coma Scale, *SBP* systolic blood pressure (mmHg), *RR* respiratory rate (/min)

Patients were managed according to clinical protocols known as Japan Advanced Trauma Evaluation and Care before and after arrival at the ED. These protocols recommend that up to 2 L of crystalloids should be rapidly administered to a traumatized patient with hypovolemic shock. Only in the case of HEMS, prehospital fluid therapy was performed using acetate ringer solution with two large-bore intravenous routes in order to obtain hemodynamic stability, and a blood sample was therefore taken after initiating fluid therapy. Other than in these cases, fluid therapy was started after taking blood samples in the ED because emergency medical services (EMS) in Japan are not permitted to initiate fluid therapy except for patients in cardiopulmonary arrest. On the other hand, HEMS include an emergency physician and a nurse, and fluid therapy can therefore usually be initiated for trauma patients during transport from the scene.

Blood samples, including samples for serum fibrinogen level measurement and blood gas analysis, were drawn on arrival at the ED before the initiation of fluid therapy or transfusion in the ED. The Clauss fibrinogen assay based on thrombin clotting time was used in all patients. In Japan, fibrinogen concentrate or cryoprecipitate is not permitted for use in patients with acquired hypofibrinogenemia. Therefore, we usually used fresh frozen plasma for those patients instead. Massive transfusions were performed on the basis of results from the repeated blood tests of the patient and vital signs. No recommended ratio (plasma:platelet:red blood cell) was aimed at.

The primary outcome evaluated in this investigation was prehospital predictors for hypofibrinogenemia, and the secondary outcome was 7-day mortality rate. Variables used in this study were patient's age, gender, serum fibrinogen level, NISS, T-RTS, initiation of fluid therapy, volume of fluid therapy in a prehospital situation, base excess, lactate, time from injury, and 7-day mortality rate. The number of cases in this area during the study period determined the sample size. Hypofibrinogenemia was

defined as serum fibrinogen level <2 g/L on admission, according to previous reports [7, 14–18]. T-RTS was defined as the score that was evaluated by the EMS on scene. Volume of fluid administration was defined as the volume until the patient underwent blood sampling after arrival at our hospital. Time from injury was defined as the time of injury to the time at arrival at the ED. The time of injury was noted from EMS records. In cases for which no such records were available, the time at which the EMS was notified (EMS call time) was used instead. The NISS was noted from medical records in our hospital. In cases in which this value was not evaluated, we retrospectively evaluated and recorded it with reference to medical records and interpretation of computed tomography by radiologists. As we cannot hypothesize a linear relationship between the outcome variable and T-RTS score as well as NISS, we decided to use crude data in order not to limit our analysis by dictomization. First, we divided patients into two groups: a hypo group with hypofibrinogenemia and a normal group without hypofibrinogenemia.

Univariate analyses were performed to identify factors associated with hypofibrinogenemia. All variables with a value of $p < 0.10$ in univariate analysis were included in multivariate analysis using binary logistic regression to identify independent risk factors for hypofibrinogenemia.

An initial univariate Cox regression analysis was performed to compare the frequencies of possible risk factors associated with the 7-day mortality rate. To control for possible confounding factors, a multivariate Cox regression analysis was performed to analyze factors that were significant in univariate models ($p < 0.05$) and met the assumptions of a proportional hazards model.

The normality of the data distribution was tested using the Kolmogorov–Smirnov test. Normally distributed data are reported as mean values (with SD), and non-normally distributed data are reported as median values. Comparison of two means was performed using Student's t test, comparison of two medians was performed using the Mann–Whitney U test, and comparison of two proportions was performed using Fisher's exact test.

Results of multivariate logistic regression analysis are presented as adjusted odds ratios with 95 % confidence intervals. Interactions between variables were searched for systematically, and collinearity was considered for values of $r > 0.8$ (Spearman's coefficient matrix correlation). The discriminatory abilities of the final models with and without hypofibrinogenemia were assessed by the likelihood ratio χ^2 statistic and C statistic. Calibration of models was tested using the Hosmer–Lemeshow statistic.

All statistical comparisons were two-tailed, and values of $p < 0.05$ were required to reject the null hypothesis. Statistical analysis was performed using a computer and the R statistical package (version 2.14.2, http://www.R-project.org; Free Software Foundation's GNU General Public License, Wien, Austria).

Results

During the study period, 491 trauma patients were enrolled in the study. Of those patients, 201 were excluded: 106 for ISS <4, 78 for insufficient data, 11 for cardiopulmonary arrest on arrival, and 6 for being transported from another hospital. This left a total of 290 patients for evaluation (Fig. 1). Serum fibrinogen level on admission was 2.36 ± 0.89 g/L. Time of injury was missing from EMS records in 4 cases (1.3 %). The rate of NISS as calculated retrospectively was 77 %. Mechanisms of blunt trauma

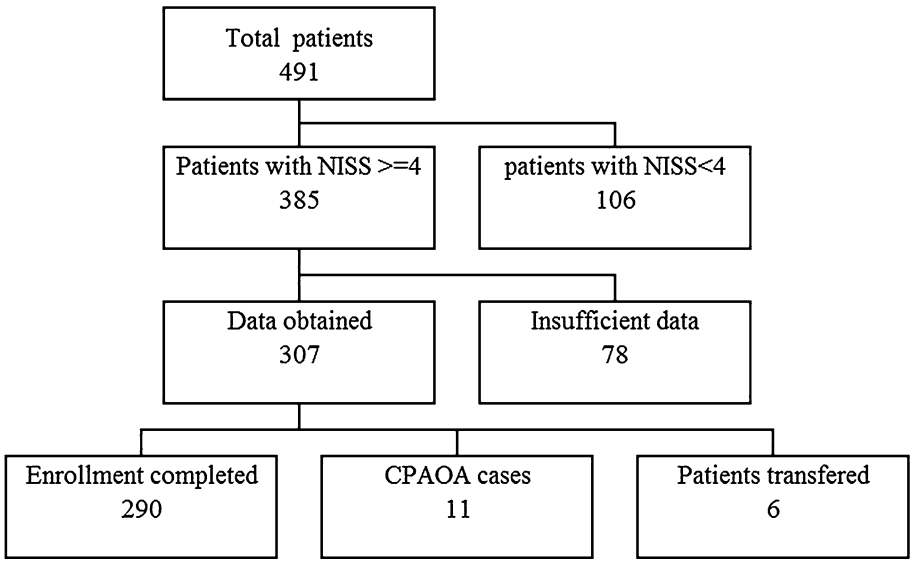

Fig. 1 Patient flow chart. *NISS* New Injury Severity Score, *CPAOA* cardiopulmonary arrest on arrival

Table 2 Patient characteristics and findings in all enrolled patients ($N = 290$) and fluid volume in patients with prehospital fluid therapy ($N = 58$)

	Hypofibrinogenemia ($N = 96$)	Normal ($N = 194$)	p
Age (years)	48 ± 23	61 ± 20	<0.001*
Male (*N*)	60	133	0.35
NISS	18	16	<0.001*
TRTS	10	12	<0.001*
Fluid therapy (*N*)	28	30	0.008*
Base excess (mEq/L)	−5.3 ± 6.5	−0.5 ± 4.3	<0.001*
Lactate (mg/dL)	41 ± 26	22 ± 17	<0.001*
Time since injury (min)	57 ± 36	47 ± 33	0.026*
Duration of hospitalization (day)	27 ± 39	28 ± 41	0.48
7-day mortality (%)	21.9	2.1	<0.001*
	Hypofibrinogenemia ($N = 28$)	Normal ($N = 30$)	p
Fluid volume (mL)	1078 ± 675	886 ± 398	0.2

Hypofibrinogenemia means <2.0 g/L. Age, base excess, lactate, time from injury, and fluid volume are presented as the mean ± SD. NISS and T-RTS are presented as medians. Male and fluid therapy are presented as actual numbers

NISS New Injury Severity Score, *T-RTS* Triage Revised Trauma Score

* $p < 0.05$

Table 3 Multivariate logistic regression analysis of independent risk factors for hypofibrinogenemia (<2.0 g/L) in all enrolled patients

Risk factor	Odds ratio	95 % confidence interval		p	VIF
		Lower	Upper		
Age	0.97	0.96	0.98	<0.001*	1.1
NISS	1.01	0.99	1.03	0.360	1.4
T-RTS	0.81	0.70	0.92	0.003*	2.0
Fluid therapy	2.54	1.22	5.32	0.010*	1.2
Base excess	0.89	0.79	1.01	0.080	3.6
Lactate	1.00	0.97	1.03	0.930	3.9
Time from injury	1.00	0.99	1.01	0.440	1.2

NISS New Injury Severity Score, *T-RTS* Triage Revised Trauma Score, *VIF* variance inflation factor

* $p < 0.05$

were as follows: traffic accidents, 228 cases (79 %); falls, 56 cases (19 %); sports, 4 cases (1 %); and fights, 2 cases (1 %). The demographics of all patients are shown in Table 2. Fluid volume in patients with prehospital fluid therapy in each group is also shown. Age, NISS, T-RTS, fluid therapy, base excess, lactate, time from injury, and 7-day mortality were significantly different between these groups.

The results of multivariate analysis in all patients are shown in Table 3. We identified age [odds ratio (OR): 0.97, $p < 0.001$], T-RTS (OR: 0.81, $p = 0.003$), and fluid therapy (OR: 2.54, $p = 0.01$) as independent predictors for hypofibrinogenemia. The likelihood ratio χ^2 statistic was significant ($p < 0.01$). The Hosmer–Lemeshow statistical goodness-of-fit test was not significant ($p = 0.47$).

As for the analysis of the 7-day mortality rate using a Cox proportional hazards model, univariate analysis showed that serum fibrinogen level, NISS, T-RTS, base excess, and lactate were significant variables (Table 4). Then multivariate analysis showed that serum fibrinogen level [hazard ratio (HR): 0.99, $p = 0.01$] and T-RTS (HR: 0.77, $p < 0.01$) were associated with the 7-day mortality rate (Table 5). The assumption of proportional hazards was supported for all covariates ($p = 0.46$).

Discussion

This retrospective comparative study provided some important findings. Patient's age and T-RTS on scene were identified as independent risk factors for hypofibrinogenemia in blunt trauma patients. In addition, serum fibrinogen level on admission was an independent predictor for 7-day mortality. Since preventable trauma deaths mostly occur under conditions of uncontrolled bleeding with a low serum fibrinogen concentration [1, 2], we believe that one of the solutions to this problem is to avoid hypofibrinogenemia in advance.

In the present study, T-RTS on scene was significantly associated with hypofibrinogenemia. To our knowledge, this is the first report showing a relation between hypofibrinogenemia and T-RTS. Although anatomical severity scores such as NISS correlate well with patient survival

[14], we showed that a physiologic severity score such as T-RTS is a better score for predicting hypofibrinogenemia. The reason for this may be that a low physiologic severity score often implies a decompensated state caused by uncontrolled bleeding or severe injuries, which leads to massive loss of fibrinogen [19]. Our results agree with the results of a previous study showing that T-RTS scores were able to predict massive bleeding [20]. Fibrinogen is the first clotting factor to fall to a critically low level during life-threatening bleeding [5, 6]. Therefore, hypofibrinogenemia in blunt trauma patients is considered a preliminary state for acute traumatic coagulopathy due to massive bleeding, which is the major cause of preventable trauma death [21–23]. To treat blunt trauma patients with a low T-RTS, we should perform repeated examinations of patient data, including measurements of serum fibrinogen level. Then we should perform a therapeutic intervention such as an emergency procedure or fibrinogen supplementation at an appropriate time.

Our study also showed that T-RTS was associated with 7-day mortality. This is understandable since several investigations have shown that T-RTS is an excellent index for predicting the mortality of trauma patients [13, 24]. Since only T-RTS has the ability to predict hypofibrinogenemia and 7-day mortality, we should make better use of this score in trauma care.

We demonstrated that hypofibrinogenemia occurred more frequently in younger patients. This difference may arise from the mechanism of trauma, but there was no statistical difference in this respect between the younger and older patients in this study (data not shown). Another study showed that older individuals have higher plasma concentrations of fibrinogen [25]. Moreover, increasing injury severity reportedly shows a correlation with biomarker response indicative of traumatic coagulopathy only in younger trauma patients, whereas older patients show a nonadaptive response regardless of injury severity [26]. These differences may partly explain our results.

The present study showed that fluid therapy was one predictor of hypofibrinogenemia. The mechanisms are assumed to be hemodilutional change and increased blood loss due to fluid resuscitation. The same results were also obtained in previous studies [27]. Although the benefit of permissive hypotension had been reported [28–30], our clinical protocol in those days recommended 2 L of rapid fluid resuscitation when hemorrhagic shock was suspected. Resuscitation to a normal systolic blood pressure with a massive volume of crystalloids might have led to hypofibrinogenemia.

As noted above, EMS are not permitted to perform fluid therapy in Japan. Therefore, we included cases in which HEMS were performed at or en route from the scene. Because of this limitation, we did not have a sufficient number of cases with prehospital fluid therapy and could not perform parametric statistical analysis such as analysis using Student's *t* test. Further study is needed to elucidate the relation between fluid therapy and serum fibrinogen level.

The present study showed that serum fibrinogen level on admission was an independent predictor for 7-day mortality. It can be assumed that trauma patients with hypofibrinogenemia on admission have massive trauma or uncontrolled bleeding. A previous study showed the same results and significant associations with both 24-h and 28-day mortality rates [27]. However, it is controversial whether fibrinogen supplementation after admission to trauma patients with hypofibrinogenemia contributes to an improvement in prognosis [9, 27, 31, 32]. Although recent reports have denied the effectiveness of fibrinogen supplementation [27, 32], we did not investigate it in the

Table 4 Hazard ratio (HR) of 7-day mortality in univariate analysis for all enrolled patients ($N = 290$)

Risk factor	HR	95 % confidence interval		p
		Lower	Upper	
Fibrinogen	0.98	0.975	0.987	<0.001*
Age	0.99	0.98	1.01	0.670
Gender	0.54	0.25	1.20	0.130
NISS	1.06	1.05	1.08	<0.001*
T-RTS	0.66	0.60	0.72	<0.001*
Fluid therapy	1.20	0.48	3.00	0.700
Base excess	0.80	0.76	0.85	<0.001*
Lactate	1.05	1.04	1.06	<0.001*
Time from injury	1.00	0.99	1.01	0.770

Five factors shown above were significant in the univariate models ($p < 0.05$). Fibrinogen is presented as g/L

NISS New Injury Severity Score, *T-RTS* Triage Revised Trauma Score

* $p < 0.05$

Table 5 Hazard ratio (HR) of 7-day mortality for all enrolled patients ($N = 290$)

Risk factor	HR	95 % confidence interval		p
		Lower	Upper	
Fibrinogen	0.99	0.98	0.998	0.01*
NISS	1.02	0.99	1.04	0.12
T-RTS	0.77	0.68	0.88	<0.01*
Base excess	0.92	0.84	1.01	0.09
Lactate	1.00	0.98	1.03	0.80

NISS New Injury Severity Score, *T-RTS* Triage Revised Trauma Score

* $p < 0.05$

present study because of the retrospective design. Since many factors are considered to be responsible for a trauma patient's prognosis, further studies, including studies on the effects of fibrinogen supplementation, are required.

In this retrospective study, we did not include amount of blood loss as a covariate because a clear determination of the amount of blood loss from the time when the trauma occurred is not possible. Therefore, we included the values of base excess and lactate on arrival instead.

Some limitations of the present study must be considered. First, since patient data were collected retrospectively, the timing of measurements such as T-RTS cannot be considered uniform. Second, since the patient data derived from a predominantly rural state, the ability to generalize to a wider population is limited. Finally, as we mentioned before, we did not have a sufficient number of cases with fluid therapy because of the law in Japan.

In conclusion, low T-RTS at the scene and a young age are considered to play important roles in predicting a devastating state with hypofibrinogenemia in blunt trauma patients. Taking these two factors into consideration, we should prevent hypofibrinogenemia in blunt trauma patients by performing repeated measurements of serum fibrinogen levels and providing appropriate fibrinogen supplementation using fresh frozen plasma or fibrinogen concentrate.

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