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Title	Fibrinogen level deteriorates before other routine coagulation parameters and massive transfusion in the early phase of severe trauma : a retrospective observational study
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Fibrinogen level deteriorates before other routine coagulation parameters and

massive transfusion in the early phase of severe trauma: A retrospective

observational study

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Abstract

Introduction: In trauma, hemostatic functions should be maintained appropriately to prevent massive bleeding. This study elucidated the time-dependent changes in platelet count and coagulation variables, and the effects of disseminated intravascular coagulation (DIC) on these changes during the early phase of trauma.

Methods: Trauma patients with an injury severity score ≥16 were enrolled. The critical levels of platelet count and coagulation variables were defined according to recent trauma guidelines. Massive transfusion was defined as >10 units red cell concentrate. The time from arrival at the emergency department to reaching the critical levels and meeting the criteria for massive transfusion were evaluated.

Results: Eighty trauma patients were enrolled; 35 were diagnosed with DIC on arrival. Among all patients, fibrinogen levels reached the critical level earliest among routine coagulation parameters; other routine coagulation parameters deteriorated after the patients met the criteria for massive transfusion. Routine coagulation parameters reached their critical levels earlier in DIC patients than patients without DIC. Massive transfusion was performed more frequently in

DIC patients, who met the criteria earlier.

Conclusions: During the early phase of trauma, fibrinogen levels deteriorate earlier than other routine coagulation parameters, especially in DIC patients.

Keywords

Disseminated intravascular coagulation, fibrinolysis, fibrinogenolysis, coagulopathy, hemorrhage

Introduction

Trauma-induced coagulopathy (TIC) is a multifactorial condition including hemodilution, hypothermia, and traumatic coagulopathy caused by trauma and traumatic shock [1-3]. We previously reported disseminated intravascular coagulation (DIC) with the fibrinolytic phenotype is the predominant mechanism of TIC [1-3]. We also reported DIC on arrival at the emergency department can predict massive transfusion and poor outcomes in patients with severe trauma [4-6]. Furthermore, we found DIC during the early phase of trauma is characterized by hyper-fibrin(ogen)olysis [4-6]. In DIC with the fibrinolytic phenotype, the consumption of platelets and coagulation factors, and hyper-fibrin(ogen)olysis induces bleeding tendency [4-6].

Fibrinogen plays an important role in clot formation and is substantially diminished as a result of hyper-fibrin(ogen)olysis. Therefore, low fibrinogen levels are associated with hemostatic impairment and induce massive bleeding [7,8]. Several studies indicate low fibrinogen level is a strong risk factor for poor outcomes in trauma patients [9-14]. Schochl et al. evaluated fibrinogen levels by whole-blood thromboelastometry upon arrival at the emergency department and report fibrinogen level predicts massive transfusion in trauma patients [9].

Meanwhile, Chambers et al. report low fibrinogen level is almost always the initial abnormality prompting the implementation of massive transfusion protocols [10].

Previous studies indicate fibrinogen deficiency develops before other hemostatic abnormalities in both major surgery patients [15,16] and animal models [17,18]. Hiippala et al. [15,16] report fibrinogen levels reach 1.0 g/L at 142% blood loss and that hemodilution and fibrinogen deficiency develop before other hemostatic abnormalities in major surgery patients; they carefully monitored blood loss and immediately performed transfusions to ensure stable blood volume [15]. However, massive bleeding in severe trauma patients is very different from the conditions in their study [15,16]. Furthermore, the pathogenesis of TIC differs from that of the coagulation abnormality induced by massive blood loss in major surgery [1-3]. Severe trauma is often accompanied by DIC with the fibrinolytic phenotype due to massive tissue injuries and prolonged hypoperfusion.

Several guidelines indicate fibrinogen levels should be kept ≥1.5 g/L to maintain hemostatic functions [7,19-22]. The updated European trauma guidelines recommend maintaining fibrinogen levels ≥1.5–2.0 g/L [19,23], which was increased from 1.0 g/L in previous guidelines [24-27]. Meanwhile, in our previous report, the optimal cut-off of fibrinogen for the prediction of death and massive transfusion

was 1.9 g/L [5]. Recent studies highlight the importance of fibrinogen

supplementation in trauma patients [28-33]. Stinger et al. indicate transfusion with

a greater fibrinogen/red cell concentrate ratio is associated with better survival of

severe trauma patients with massive transfusion [28].

Accordingly, the present study elucidated the time-dependent changes in

platelet count and coagulation variables including fibrinogen levels during the

early phase of severe trauma. This study also investigated the influences of DIC

upon arrival at the emergency department on the time-dependent changes in

platelet count and coagulation variables.

Materials and Methods

The present retrospective observational study was approved by the

Institutional Review Board of Hokkaido University Hospital; the need for

informed consent was waived, because this was a retrospective observational

study.

Patient Selection and Data Collection

From January 2010 to December 2012, all trauma patients with an injury

severity score ≥16 [34] admitted to the emergency department were retrospectively

evaluated. Patients were excluded if they were younger than 16 years or

complicated with cardiac arrest, burn, or cervical spine injury caused by a minor

accident. The clinical backgrounds and laboratory test results (i.e., complete blood

counts, coagulation, and biochemistry variables) of the patients were collected

retrospectively from computer-based patient records. Blood samples were drawn

promptly on arrival at the emergency department, and laboratory tests were

immediately performed according to routine protocols. Laboratory tests were

repeated as necessary. The laboratory test results during the first 24 hours were

analyzed.

The patients were divided in 2 groups: those with and without DIC upon

arrival at the emergency department. DIC was evaluated according to the scoring

algorithm of the Japanese Association for Acute Medicine DIC criteria [35]. Massive

transfusion was defined as >10 units of red cell concentrate. We calculated total

fibrinogen administration on the basis of the standard amounts of fibrinogen

contained in each blood component: 1 unit of fresh frozen plasma (FFP, 120 mL)

and platelet concentrate (10 mL) contained 400 and 300 mg fibrinogen,

respectively. The critical levels for platelet count and coagulation variables were

defined on the basis of the European trauma guideline for the management of

bleeding following major trauma [19,23] as follows: platelet count, ≤50 or ≤100 ×

10^9/L (in patients with brain trauma); prothrombin time-international

normalized ratio (PT-INR), ≥1.5; activated partial thromboplastin time (APTT),

≥60 s; fibrinogen, ≤1.5 g/L.

Statistical Analysis

All variables are expressed as median and interquartile range (1st to 3rd

quartile) or number (percent). Kaplan–Meier analyses were performed to

evaluate the time from arrival at the emergency department to reaching the

critical levels for platelet count and coagulation variables. Kaplan–Meier analysis

was also performed to evaluate the time from arrival at the emergency

department to the time when patients met the criteria for massive transfusion.

Intergroup comparisons were made using the Mann–Whitney U-test, χ^2 test, and

the log-rank test in Kaplan–Meier analyses. SPSS 15.0J (SPSS Inc., Chicago, IL,

USA) was used for all statistical analyses. The level of significance was set at $P<$

0.05.

Results

A total of 80 trauma patients were enrolled, and 35 were diagnosed with DIC on arrival at the emergency department. The characteristics of the patients are shown in Table 1. Among all patients, 85% were transferred to the emergency department within 60 minutes after accidents and 75% did not receive fluid resuscitation before arrival. Patients with DIC had higher injury severity scores than patients without DIC. In addition, injuries to the abdomen and extremities were more severe in patients with DIC than those without DIC. The physiologic status (i.e., Glasgow coma scale, blood pressure, and heart rate) of patients with DIC on arrival was more severe than that of patients without DIC.

The results of laboratory tests on arrival at the emergency department are shown in Table 2. Remarkably elevated fibrin/fibrinogen degradation products (FDP) and D-dimer levels were observed in patients with DIC on arrival. Patients with DIC had poorer laboratory test results than those without DIC. The elevation of the FDP/D-dimer ratio, a marker of fibrinogenolysis, was higher in patients with DIC than those without DIC. Laboratory tests were repeated a median of 3 (IQR: 2–4) times/patient during the first 24 hours.

Transfusions during the first 6 and 24 hours are shown in Table 3. Patients with DIC received more transfusions and more units of all blood components than patients without DIC. Most patients with DIC received FFP and

fibrinogen concentrate transfusions during the first 6 hours after arrival at the

emergency department.

Table 4 shows the treatments and outcomes of the patients. Emergency

operations for hemostasis were performed more frequently in patients with DIC

than those without DIC. Most other emergency operations were craniotomies.

During the first 24 hours, 2 patients died from massive bleeding and primary

brain injury. Another 7 patients died from primary brain injury more than 48

hours after hospital admission for a total of 9 in-hospital deaths.

The Kaplan–Meier estimation curves of the time from arrival at the

emergency department to reaching the critical levels for platelet count and

coagulation variables as well as the time to meeting the criteria for massive

transfusion among all patients are shown in Figure 1; the associations between

the Kaplan–Meier analyses are shown in Table 5. Fibrinogen levels reached the

critical level earliest among the routine coagulation parameters. Furthermore,

the other routine coagulation parameters reached their respective critical levels

after the patients met the criteria for massive transfusion. Fibrinogen levels

decreased below 1.5 g/L during the first 12 hours in 42 patients (53%).

The Kaplan–Meier estimation curves for the time from arrival at the

emergency department to reaching the critical levels for platelet count and

coagulation variables as well as the time to meeting the criteria for massive

transfusion in patients with and without DIC are presented separately in Figure

2. Platelet count and all coagulation variables except APTT reached their

respective critical levels earlier in patients with DIC than those without DIC. The

criteria for massive transfusion were met earlier and more frequently in patients

with DIC than those without DIC.

Discussion

The present study demonstrates that fibrinogen reaches its critical level

before the other routine coagulation parameters in trauma patients. Furthermore,

only fibrinogen deterioration was observed before patients met the criteria for

massive transfusion. Patients with DIC received more transfusions and units of

all blood components than patients without DIC. Furthermore, the routine

coagulation parameters deteriorated earlier in patients with DIC than those

without DIC. Fibrin(ogen)olysis was more severe in patients with DIC than those

without DIC.

In trauma patients, DIC with the fibrinolytic phenotype upon arrival at

the emergency department is observed before hemodilution [4-6]. DIC during the

early phase of trauma is characterized by the consumption of platelets and coagulation factors as well as hyper-fibrin(ogen)olysis [4-6]. The present study confirms the consumption of coagulation factors and hyper-fibrin(ogen)olysis on the basis of prolonged PT and APTT, decreased fibrinogen levels, and increased FDP and D-dimer levels. In particular, an increased FDP/D-dimer ratio indicates hyper-fibrinogenolysis. DIC patients already present with a bleeding tendency on arrival at the emergency department.

The active administration of coagulation factors with FFP and fibrinogen concentrate is recommended for damage-control resuscitation in severe trauma patients [1,36]. Fibrinogen supplementation is especially important in severe trauma patients, because fibrinogen plays an important role in clot formation [28-33]. In the present study, patients were administered large quantities of FFP and fibrinogen concentrates during the early phase of trauma. However, we were unable to prevent decreases in fibrinogen levels. We term this phenomenon "DIC-induced consumption coagulopathy."

Although fibrinogen plays an important role in the resuscitation of severe trauma patients, fibrinogen levels are not measured routinely in the emergency departments of many trauma centers [8,37]; in an international survey of clinical practice, Hoyt et al. report that fibrinogen levels are measured routinely when

trauma patients arrive at the emergency department in only 36% of trauma

centers [37]. For 30 years, we have been routinely measuring fibrinogen levels along

with other routine coagulation parameters when trauma patients arrive at the

emergency department. In the present study, fibrinogen levels were measured

along with other routine coagulation parameters a median of 3 (IQR: 2–4)

times/patient during the first 24 hours after arrival at the emergency department.

Routine coagulation parameters, especially fibrinogen level, should be repeatedly

measured in severe trauma patients during the first several hours after arrival at

the emergency department.

Conclusions

During the early phase of trauma, fibrinogen levels deteriorate earlier

and more frequently than other routine coagulation parameters (i.e., PT, APTT,

and platelet count), especially in patients with DIC. Only the deterioration of

fibrinogen levels precedes patients meeting the criteria for massive transfusion.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MH: study design, data acquisition and interpretation, statistical analysis, and drafting of the manuscript; SG: data interpretation and drafting of the manuscript; YO, TW, YY, AS: data interpretation. All authors have read and approved the final manuscript.

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Figure legends

Figure 1

Kaplan–Meier estimation curves for all patients

The curves show the time from arrival at the emergency department to reaching

the critical levels of routine coagulation parameters as well as meeting the

criteria for massive transfusion. The critical levels of the routine coagulation

parameters were as follows: platelet count, ≤50 or ≤100 × 10^9/L; prothrombin

time-internal normalized ratio (PT-INR), ≥1.5; activated partial thromboplastin

time (APTT), ≥60 s; fibrinogen level, ≤1.5 g/L. Massive transfusion was defined as

>10 units red cell concentrates.

Figure 2

Kaplan–Meier estimation curves in patients with and without DIC

Figure 1
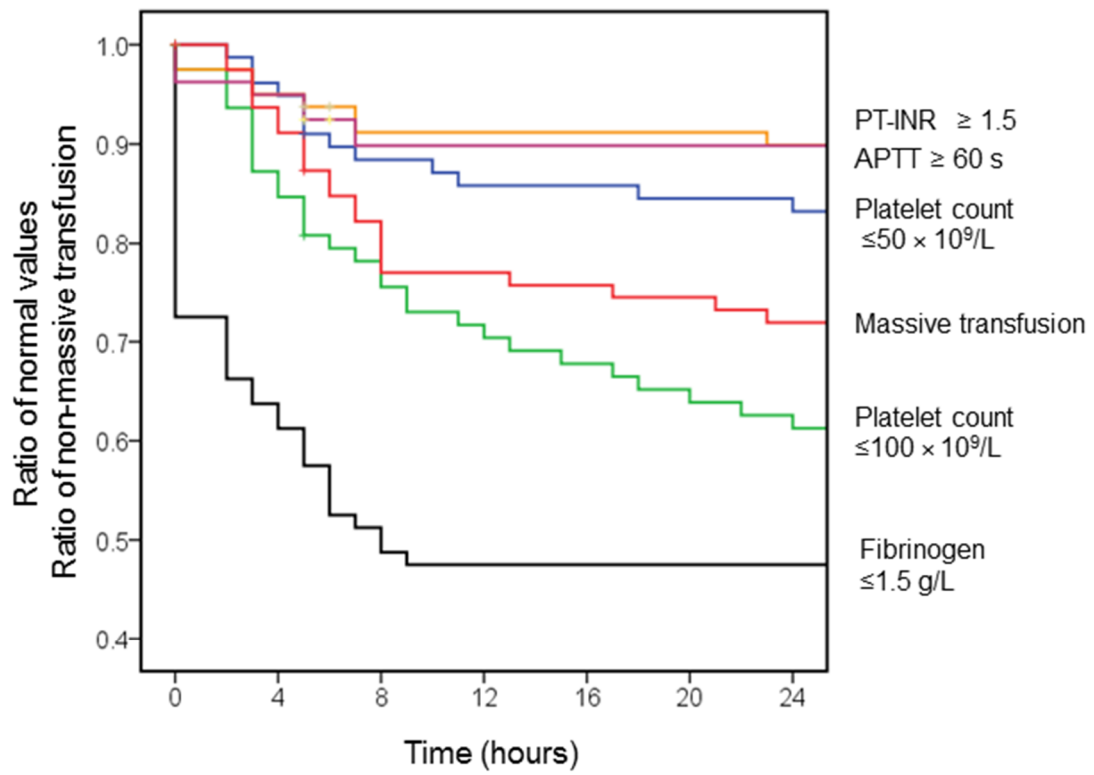
Figure 2
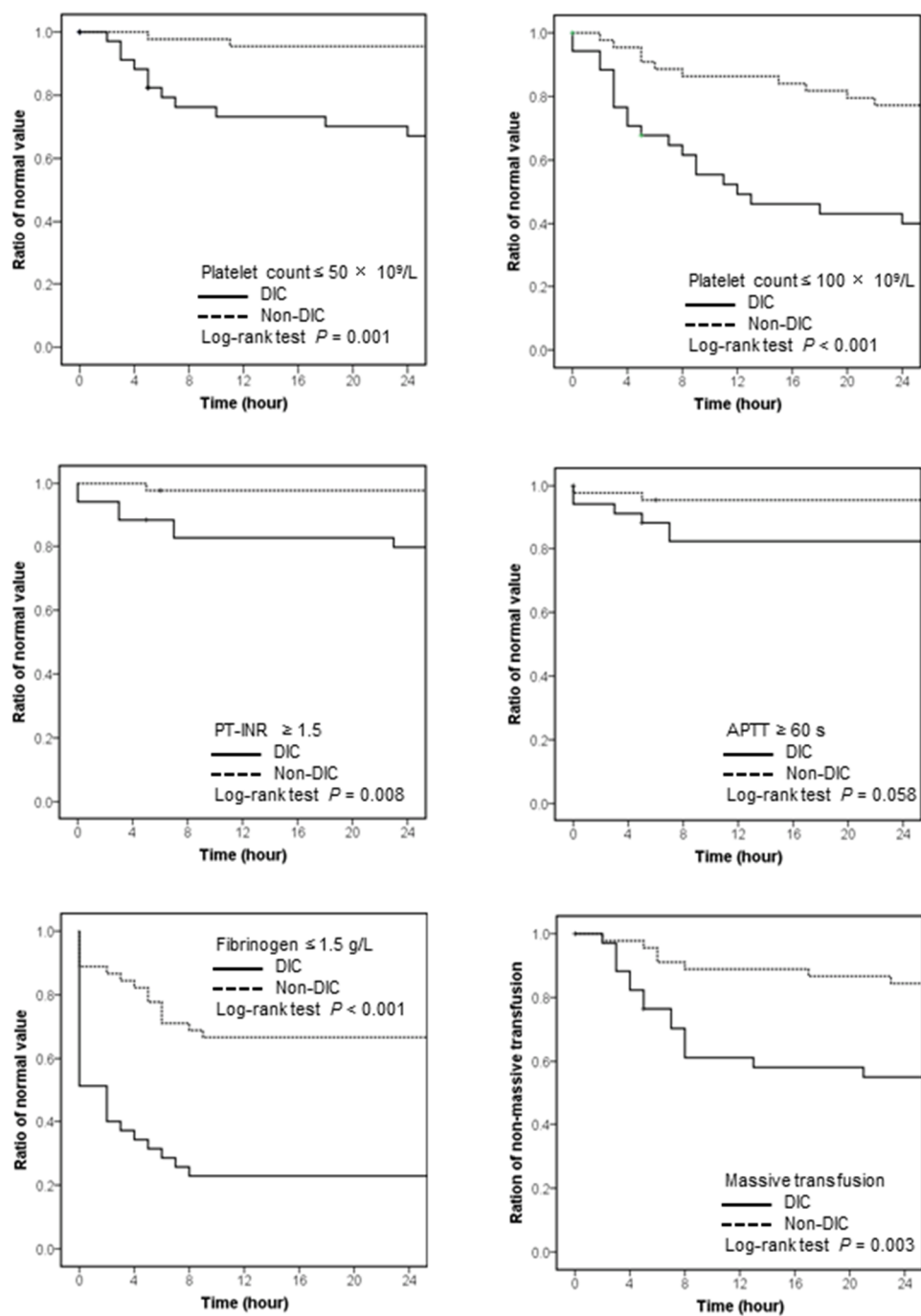
Tables

Table 1 Patient characteristics

	All patients	DIC	Non-DIC	P value
	n = 80	n = 35	n = 45	
Male	57 (71.3)	24 (68.6)	33 (73.3)	0.641
Age, years	50 (33–67)	43 (29–68)	52 (41–66)	0.225
Anticoagulant/antiplatelet use	3 (3.8)	1 (2.9)	2 (4.4)	0.711
Cirrhosis	2 (2.5)	2 (5.7)	0 (0.0)	0.104
Fluid administration before arrival	20 (25)	7 (20)	13 (29)	0.440
Fluid amounts before arrival, mL	0 (0–38)	0 (0–0)	0 (0–75)	0.467
Time from accident to arrival at ED				

0–30 minutes	33 (41.3)	16 (45.7)	17 (3.78)	
31–60 minutes	35 (43.8)	14 (40.0)	21 (46.7)	
>61 minutes	10 (12.5)	3 (8.6)	7 (15.6)	0.279
Unknown	2 (2.5)	2 (5.7)	0 (0.0)	
SIRS score	2 (1–3)	3 (2–3)	2 (1–29	< 0.001
DIC score	3 (3–4)	4 (4–5)	3 (1–3)	< 0.001
Blunt injury	79 (98.8)	35 (100.0)	44 (97.8)	0.375
ISS	26 (20–34)	30 (20–36)	24 (20–29)	0.047
Head/neck AIS ≥3	55 (68.7)	27 (77.1)	28 (62.2)	0.153
Face AIS ≥3	3 (3.8)	1 (2.9)	2 (4.4)	0.711
Chest AIS ≥3	41 (51.3)	16 (45.7)	25 (55.6)	0.382
Abdomen AIS ≥3	13 (16.3)	10 (28.6)	3 (6.7)	0.008

Extremity AIS ≥3	25 (31.3)	15 (42.9)	10 (22.2)	0.048
External AIS ≥3	1 (1.3)	1 (2.9)	0 (0.0)	0.254
Glasgow coma scale	12 (6–14)	8 (4–13)	13 (8–14)	0.025
Systolic blood pressure, mmHg	120 (90–140)	106 (83–106)	132 (95–1051)	0.011
Heart rate, beats/min	82 (70–105)	100 (72–121)	80 (69–85)	0.003
Respiratory rate, breaths/min	24 (18–28)	24 (19–29)	24 (18–26)	0.322
Body temperature, ℃	36.0 (35.5–36.7)	36.0 (35.2–37.2)	36.1 (35.5–36.6)	0.703
Revised trauma score	6.90 (4.79–7.84)	5.97 (4.09–7.84)	7.11 (5.97–7.84)	0.024

All measurements are expressed as the median (IQR) or number (%).

ED, emergency department; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular

coagulation; ISS, injury severity score; AIS, abbreviated injury score.

Table 2 Laboratory results on arrival at the emergency department

	All patients	DIC	Non-DIC	P value
	$n = 80$	$n = 35$	$n = 45$	
Laboratory tests				
White blood cell (×10⁹ cells/L)	12.6 (9.0–16.4)	15.8 (10.4–17.7)	10.9 (8.8 14.7)	0.010
Hemoglobin (g/dL)	12.8 (11.1–14.6)	12.2 (9.9–14.1)	13.1 (11.8–14.9)	0.033
Platelet count (×10⁹ cells/L)	201 (151–236)	198 (135–221)	202 (159–248)	0.252
Aspartate aminotransferase (U/L)	50 (35–118)	101 (42–215)	42 (32–86)	0.002
Alanine aminotransferase (U/L)	42 (29–73)	68 (38–164)	33 (26–47)	0.012
Lactate dehydrogenase (U/L)	431 (321–597)	521 (375–751)	365 (283–489)	0.004
Creatine kinase (U/L)	273 (176–517)	290 (211–654)	254 (167–420)	0.118

Prothrombin time (s)	12.2 (11.4–14.0)	13.7 (12.1–15.0)	11.6 (11.1–12.7)	<0.001
PT-INR	1.06 (0.98–1.17)	1.15 (1.06–1.30)	1.00 (0.97–1.09)	<0.001
Activated partial thromboplastin time (s)	31.5 (28.5–38.0)	36.2 (31.6–47.2)	29.6 (27.1–31.9)	<0.001
Fibrinogen (g/L)	1.81 (1.42–2.07)	1.59 (1.13–1.83)	1.96 (1.73–2.37)	<0.001
Fibrin/fibrinogen degradation products (μg/mL)	73.9 (28.8–123.3)	99.5 (49.2–211)	46.0 (13.7–89.7)	<0.001
D-dimer (μg/mL)	50.3 (19.7–83.3)	69.1 (37.4–124.8)	35.4 (11.1–64.5)	<0.001
FDP/D-dimer ratio	1.39 (1.29–1.56)	1.50 (1.31–1.72)	1.33 (1.27 1.48)	0.008
Antithrombin (%)	86 (71–95)	74 (65–92)	89 (79–97)	0.010
Patients with critical hemostatic abnormality on arrival				
PT-INR ≥ 1.5	2 (2.5)	2 (5.7)	0	0.188
APTT ≥ 60 s	3 (3.8)	2 (5.7)	1 (2.2)	0.578
Platelet count ≤ 50 × 10^9 cells/L	0	0	0	-

Platelet count ≤ 100 × 10^9 cells/L	2 (2.5)	2 (5.7)	0	0.188
Fibrinogen ≤1.5 g/L	22 (27.5)	17 (48.6)	5 (11.1)	<0.001

All measurements are expressed as the median (IQR) or number (%).

DIC, disseminated intravascular coagulation; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin

degradation product; APTT, activated partial thromboplastin time.

Table 3 Transfusions during the first 6 and 24 hours

	All patients	DIC	Non-DIC	P
	n = 80	n = 35	n = 45	value
Transfusions during the first 6 hours				
RCC transfusion	30 (37.5)	19 (54.3)	11 (24.4)	0.010
RCC, unit	0 (0–6)	4 (0–25)	0 (0–1)	0.002
Massive transfusion	18 (22.5)	13 (31.1)	5 (11.1)	0.007
FFP transfusion	31 (38.8)	20 (57.1)	11 (24.4)	0.005
FFP, unit	0 (0–8)	4 (0–34)	0 (0–2)	0.001
Platelet concentrate transfusion	12 (15.0)	12 (34.4)	0 (0.0)	<0.001
Platelet, unit	0 (0–0)	0 (0–20)	0	<0.001

Fibrinogen concentrate administration	26 (32.5)	19 (54.3)	7 (15.6)	<0.001
Fibrinogen concentrate, g	0 (0–3)	3 (0–3)	0 (0–0)	<0.001
Total fibrinogen administration, g	0.0 (0.0–6.4)	5.4 (0–22.6)	0.0 (0.0–1.6)	0.001
Transfusions during the first 24 hours				
RCC transfusion	32 (40.0)	20 (57.1)	12 (26.7)	0.006
RCC, unit	0 (0–10)	12 (3–45)	0 (0–4)	0.001
Massive transfusion	22 (27.5)	15 (42.9)	7 (15.6)	0.007
FFP transfusion, n	30 (37.5)	21 (60.0)	9 (20.0)	<0.001
FFP, unit	0 (0–13)	18 (5–63)	0 (0–0)	<0.001
Platelet concentrate transfusion	15 (18.8)	13 (37.1)	2 (4.4)	<0.001
Platelet, unit	0 (0–0)	0 (10–20)	0 (0–0)	<0.001

Fibrinogen concentrate administration	30 (37.5)	20 (57.1)	10 (22.2)	0.001
Fibrinogen concentrate, g	0 (0–3)	3 (3–6)	0 (0–3)	0.001
Total fibrinogen administration, g	0.0 (0.0–7.7)	6.2 (0.0–28.2)	0.0 (0.0–3.0)	<0.001

All measurements are expressed as the median (IQR) or number (%). Total fibrinogen administration

was calculated according to standard amounts of fibrinogen contained in each blood components (1 unit

FFP: 400 mg fibrinogen; 1 unit platelet concentrate: 300 mg fibrinogen.

DIC, disseminated intravascular coagulation; RCC, red cell concentrate; FFP, fresh frozen plasma.

Table 4 Treatments and outcomes

	All patients	DIC	Non-DIC	
	$n = 80$	$n = 35$	$n = 45$	P value
Emergency operation for hemostasis	9 (11.3)	7 (20.0)	2 (4.4)	0.029
Interventional radiology for hemostasis	7 (8.8)	5 (14.3)	2 (4.4)	0.122
Other emergency operation	21 (26.3)	9 (25.7)	12 (26.7)	0.923
Tranexamic acid administration during the first 3 hours	30 (37.5)	15 (42.9)	15 (33.3)	0.383
Outcome				
Death within 24 hours	2 (2.5)	2 (5.7)	0 (0.0)	0.104
Death within 48 hours	2 (2.5)	2 (5.7)	0 (0.0)	0.104
In-hospital death	9 (11.3)	6 (17.1)	3 (6.7)	0.141

All measurements are expressed as number (%).

DIC, disseminated intravascular coagulation

Table 5 Associations among routine coagulation parameters in Kaplan–Meier curves

P value (Log-rank test)	PT-INR ≥1.5	APTT ≥60 s	Platelet count ≤50 × 10⁹/L	Platelet count ≤100 × 10⁹/L	Fibrinogen ≤1.5 g/L	Massive transfusion
PT-INR ≥ 1.5	—	0.831	0.349	<0.001	<0.001	0.005
APTT ≥ 60 s	0.831	—	0.260	<0.001	<0.001	0.007
Platelet count ≤ 50 × 10⁹ cells/L	0.349	0.260	—	0.001	<0.001	0.095
Platelet count ≤ 100 × 10⁹ cells/L	<0.001	<0.001	0.001	—	0.023	0.121
Fibrinogen ≤1.5 g/L	<0.001	<0.001	<0.001	0.023	—	<0.001
Massive transfusion	0.005	0.007	0.095	0.121	<0.001	—

P values are the results of the log-rank tests between each curve in Kaplan–Meier analysis in Figure 1.

PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time