HIGH D-DIMER LEVELS PREDICT A POOR OUTCOME IN PATIENTS WITH SEVERE TRAUMA, EVEN WITH HIGH FIBRINOGEN LEVELS ON ARRIVAL ; A MULTICENTRE RETROSPECTIVE STUDY

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Abstract

Elevated D-dimer level in trauma patients is associated with tissue damage severity and is an indicator of hyperfibrinolysis during the early phase of trauma. To investigate the interacting effects of fibrinogen and D-dimer levels on arrival at the emergency department for massive transfusion and mortality in severe trauma patients in a multicentre retrospective study. This study included 519 adult trauma patients with an injury severity score ≥16. Patients with ≥10 units of red cell concentrate transfusion and/or death during the first 24 hours were classified as having a poor outcome. Receiver operating characteristic curve analysis for predicting poor outcome showed the optimal cut-off fibrinogen and D-dimer values to be 190 mg/dL and 38 mg/L, respectively. Based on these values, patients were divided into four groups: (1) low D-dimer (<38 mg/L)/high fibrinogen (>190 mg/dL), (2) low D-dimer (<38 mg/L)/low fibrinogen (≤190 mg/dL), (3) high D-dimer (≥38 mg/L)/high fibrinogen (>190 mg/dL), and (4) high D-dimer (≥38 mg/L)/low fibrinogen (≤190 mg/dL). The survival rate was lower in the high D-dimer/low fibrinogen group than in the other groups. Moreover, the survival rate was lower in the high D-dimer/high fibrinogen group than in the low D-dimer/high fibrinogen and low D-dimer/low fibrinogen groups. High D-dimer level on arrival is a strong predictor of early death or requirement for massive transfusion in severe trauma patients, even with high fibrinogen levels.

Keywords: coagulopathy, disseminated intravascular coagulation, fibrinolysis, transfusion, multiple trauma, fibrin fibrinogen degradation products.

INTRODUCTION

In patients with severe trauma, trauma-induced coagulopathy is observed during the early phase, frequently develops into severe haemorrhage due to coagulation abnormalities, and contributes to a poor outcome (1-4). Although trauma-induced coagulopathy is mainly caused by tissue injuries and shock with complex underlying mechanisms, consumptive coagulopathy and hyperfibrinolysis are the predominant mechanisms.(1, 5-9).

During the early phase of trauma, fibrinogen plays an important role in clot formation (10, 11). Therefore, many previous studies have indicated that low fibrinogen levels were associated with haemostatic impairment and induced massive bleeding as well as predicted a poor outcome (7, 12-17). Furthermore, fibrinogen levels tend to deteriorate more quickly than other coagulation factors during the early phase of trauma (14, 18, 19).

Previous studies have indicated that elevated D-dimer levels are also associated with a poor outcome (5-7, 20) as well as the severity of tissue damage (21-23). Gando and colleagues recently reported that high D-dimer levels on arrival at the emergency department (ED) indicated hyperfibrinolysis and predicted massive bleeding and death (5-7).

Although low fibrinogen levels on arrival at the ED have been shown to be associated with coagulopathy and a poor outcome (7, 10-17), the predictive value of the interaction between fibrinogen and D-dimer levels in the early phase of severe trauma has never been evaluated. Therefore, we hypothesized that high D-dimer levels would predict trauma-induced coagulopathy

and a poor outcome in patients with severe trauma, even with high fibrinogen levels on arrival at the ED. The aim of the present study was to investigate the interacting effects of fibrinogen and D-dimer levels on arrival at the ED for massive transfusion and mortality in patients with severe trauma in a multicentre retrospective study.

MATERIALS AND METHODS

This retrospective study was conducted at 15 tertiary emergency and critical care centres in Japan (Japanese Observational Study for Coagulation and Thrombolysis in Early Trauma, J-OCTET) and was approved by the Institutional Review Board of each hospital. No consent was needed because of the retrospective study.

Patient Selection and Data Collection

J-OCTET was a retrospective multicentre study to investigate disorders of coagulation and thrombolysis in patients with severe trauma. J-OCTET recruited consecutive trauma patients with an injury severity score (ISS) ≥ 16 admitted to EDs from January to December 2012. Patients were excluded if they were younger than 18 years or complicated with cardiac arrest, burn, cervical spine injury not caused by a high-energy accident, pregnancy, or liver cirrhosis. The clinical backgrounds, laboratory test results (i.e., complete blood counts, coagulation, and biochemistry variables),

treatments, and outcomes of the patients were retrospectively collected.

Definitions

Trauma-induced coagulopathy may induce massive bleeding during the early phase of trauma and may be associated with death before massive transfusion (1-4). Furthermore, in patients with severe brain injuries, trauma-induced coagulopathy may induce early death unrelated to massive bleeding and massive transfusion (24, 25). Therefore, we defined a poor outcome associated with trauma-induced coagulopathy as patients with more than 10 units of red cell concentrate transfusion or death during the first 24 hours; all other patients were defined as having a good outcome.

Statistical Analysis

All variables are expressed as median and interquartile range (i.e., 1st to 3rd quartile) or number (percent). Intergroup comparisons were made using the Mann-Whitney *U*-test or χ^2 test. To compare more than two groups, the Kruskal-Wallis test was applied with a Bonferroni correction. The receiver operating characteristic (ROC) curves of fibrinogen and D-dimer were constructed to determine the relationship to a poor outcome. Cut-off values were defined based on the Youden Index. Based on the cut-off values for fibrinogen and D-dimer to differentiate the outcomes, patients were divided into four groups, and the amount of transfusion, haemostatic procedures, and survival rates

were compared. Kaplan-Meier analyses were performed to evaluate survival time, and the log-rank test was used to compare differences between groups. 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

Patient characteristics

A total of 796 severe trauma patients were enrolled in J-OCTET (Supplemental Table). Of these, 277 patients, in which fibrinogen and/or D-dimer levels were not measured on arrival at the ED, were excluded from the present analysis, thus 519 patients were analysed (Figure 1). The patient characteristics are shown in Table 1. Patients with a poor outcome were anatomically, physiologically, and haematologically more severe than those with a good outcome. Time from accident to sample collection was statistically different between the two groups. Patients with a more severe condition may promptly transfer to the ED and have blood samples taken immediately after arrival. The precise duration from accident to sample collection was not indicated in some patients, because the time of the accidents was unclear.

Division of patients based on D-dimer and fibrinogen levels

Figure 2 shows the ROC curves for predicting a poor outcome according to fibrinogen and D-dimer levels as fibrinolytic variables, and the results of the ROC curve analysis are shown in Table 2. The optimal cut-off values for fibrinogen and D-dimer were 1.9 g/L and 38 mg/L, respectively.

Based on the cut-off values for fibrinogen and D-dimer, 519 patients, who had both fibrinogen and D-dimer levels measured on arrival at the ED, were divided into the following four groups: (1) 267 patients in low D-dimer (<38 mg/L)/high fibrinogen (>190 mg/dL), (2) 53 patients in low D-dimer/low fibrinogen (≤190 mg/dL), (3) 113 patients in high D-dimer (≥38 mg/L)/high fibrinogen, and (4) 86 patients in high D-dimer/low fibrinogen. The characteristics of the patients in the four groups are shown in Table 3. Although Glasgow Coma Scale scores were statistically different among the four groups, anatomical severities of head trauma (abbreviated injury score of the head) were not different. Table 4 shows haemostatic procedures (including emergency surgery and interventional radiology for haemostasis) and transfusion data. The rate of haemostatic procedures and amount of transfusion increased gradually from group (1) to (4). Furthermore, the mortality rate increased gradually from group (1) to (4) (Figure 3). Kaplan-Meier survival curves in the four groups are presented in Figure 4. The survival rate in group (4) was lower than that in the other three groups ($P < 0.001$ vs. group (1), $P < 0.001$ vs. group (2), and $P = 0.011$ vs. group (3). Moreover, the survival rate in group (3) was statistically lower than that in groups (1) and (2) ($P < 0.001$ and $P = 0.007$, respectively).

DISCUSSION

In the present study, the outcome of patients with high D-dimer/low fibrinogen was poorest

among the severe trauma patients. Moreover, mortality was significantly higher in patients with high D-dimer levels than in those with low D-dimer levels among patients without fibrinogen deficiency on arrival at the ED.

D-dimer is a fibrin degradation product and reflects fibrinolysis after coagulation activation in the vessels before blood sampling (26). Fibrinolysis is induced by plasmin, which is activated from plasminogen by tissue type-plasminogen activator (t-PA) (26). Recent studies have indicated that hyperfibrinolysis, detected as clot lysis using thromboelastometry, was an important component in trauma-induced coagulopathy and induced haemostatic impairments and a poor outcome (27-30). Traumatic shock and tissue hypoperfusion induce acute release of t-PA from endothelial cells (1, 2, 31). The released t-PA causes hyperfibrinolysis, which is detected as clot lysis using thromboelastometry, in severe trauma patients (1, 2). In thromboelastometry, the clot lysis is observed when fibrinolytic activation by t-PA overrides fibrinolytic suppression by α2-antiplasmin in the blood sample after the start of thromboelastometry (30, 32). Therefore, hyperfibrinolysis indicated by elevation of D-dimer levels is different from that indicated by thromboelastometry. Moreover, several studies have suggested that elevation of D-dimer levels is usually observed in trauma patients with thromboelastometry-indicated hyperfibrinolysis (30, 33, 34), but thromboelastometry-indicated hyperfibrinolysis may not always be observed in trauma patients with elevation of D-dimer levels (30). Raza at al. indicated that thromboelastometry-indicated hyperfibrinolysis was observed in only 5% of patients with severe trauma, although elevation of

D-dimer levels was observed in most patients with severe trauma (30). Therefore, elevated D-dimer level may indicate hyperfibrinolysis and predict massive transfusion, which is an important outcome of this study.

Previous reports have indicated that high D-dimer levels on arrival at the ED were associated with a poor outcome in patients with traumatic brain injury (21-23). However, several studies demonstrated that high D-dimer levels were associated with a poor outcome in all trauma patients regardless of brain injury complications (5-7, 30, 33, 34). In the present study, anatomical severities of head trauma were not different among the four groups (Table 3). Although Glasgow Coma Scale scores were statistically different among groups, physiological factors might affect the consciousness levels regardless of the anatomical severities of head trauma.

Gando and colleagues previously reported a relationship between fibrin/fibrinogen degradation products (FDP) and outcome in trauma patients (5-7). FDP levels reflect not only fibrinolysis, but also fibrinogenolysis, unlike D-dimer levels (26). Therefore, FDP levels are more ideal for evaluating hyperfibrinolysis during the early phase of trauma than D-dimer levels (5-7). However, in the present multicentre study, we could not analyse FDP levels because they were not measured on arrival at the ED in many patients.

There has been much discussion in recent years regarding ratios of packed red cells and plasma in massive transfusion, with debate over whether a 1:1 ratio should be achieved (35). In the present study, almost all of the physicians adopted the transfusion practice, which was close to a 1:1

ratio of red cells to plasma, in the involved centres. Thus, the transfusions were close to a 1:1 ratio of red cells to plasma (Table 4).

The present retrospective study has several limitations. First, although 796 patients with severe trauma were included, some patients did not have fibrinogen and D-dimer levels measured on arrival at the ED. Therefore, in the analysis comparing the four groups based on fibrinogen and D-dimer levels, 227 patients were excluded because of missing values. Second, time from accident to sample collection varied in each patient, and the time was statistically different between the poor and good outcome groups (Table 1). Patients with a more severe condition may have been promptly transferred to the ED to have blood samples taken immediately after arrival. However, there was no statistically significant difference among the four groups (those separated by D-dimer and fibrinogen levels) in the timing following accident (Table 3). During the early phase of trauma, coagulation and fibrinolytic variables change dramatically, thus differences in the time from injury to blood collection may have some effect on the results. This is especially true in patients with hyperfibrinolysis, as fibrinogen levels may decrease gradually just after injury owing to consumption by coagulation activation and degradation by hyperfibrinolysis. Third, in the participating institutions, D-dimer level was measured using the latex coagulating method, which employed different reagents at the three companies. The sensitivity and range differ among the three reagents and may affect the results of the present study.

In conclusion, high D-dimer levels on arrival at the ED are a strong predictor of early death

or a requirement for massive transfusion in severe trauma patients, regardless of fibrinogen levels, which may indicate hyperfibrinolytic status. This indicates the need to recognize patients with high D-dimer levels to allow better preparation for immediate haemostatic resuscitation.

Authorship

MH, S Kushimoto, HK, JS, HO, TM, TU, NM, HI, AH, MT, and NK designed the study. MH interpreted the data and drafted the manuscript. DS and AS supported the statistical analysis. MH, DK, TK, TS, HO, YH, TU, SF, YN, GM, AY, K Murata, S Kim, OT, and NK collected and assessed the data. All authors revised the manuscript for important intellectual content. All authors also read and approved the final manuscript.

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The following Institutional Review Board of each hospital approved the present study: Institutional Review Board of Hokkaido University Hospital for Clinical Research; Ethics Committee of Tohoku University School of Medicine; Institutional Review Board of National Hospital Organization Disaster Medical Center; Keio University School of Medicine, ETHICS COMMITTEE; Ethics Committee of Osaka University Medical School; Institutional Review Board of Rinku General

Medical Center; Ethics Committee of Kinki University Faculty of Medicine; Institutional Review Board of Yokohama City University Medical Center; Institutional review board of Fukuoka University Hospital; Ethical committee of National Center for Global and Medicine; Ethics Committee of Tokyo Women's Medical University; Medical Research Ethics Committee of Tokyo Medical and Dental University; Nippon Medical School Hospital Institutional Review Board; The Ethical Committee of Kurume University; Ethics Committee, Juntendo University, Urayasu Hospital.

Figure legends

Figure S1

Definition of categories.

A poor outcome category was defined as patients requiring more than 10 units of red cell concentrate transfusion or death during the first 24 hours; the remaining patients were defined as having a good outcome.

Figure 1

Receiver operating characteristic (ROC) curves for predicting a poor outcome based on fibrinogen and D-dimer levels.

Dotted line, D-dimer; Solid line, fibrinogen.

Figure 2

Mortality rate 24 and 48 hours after arrival at the emergency department.

The mortality rate 24 and 48 hours after arrival at the emergency department was statistically different among the groups ($P < 0.001$ and < 0.001, respectively). Low and high D-dimer levels were defined as <38 mg/L and ≥38 mg/L, respectively, on arrival at the emergency department. Low and

high fibrinogen levels were defined as ≤1.9 g/L and >1.9 g/L, respectively, on arrival at the emergency department. Fbg, fibrinogen

*P< 0.0083 (after Bonferroni correction) versus the low D-dimer/high fibrinogen group.

†P< 0.0083 (after Bonferroni correction) versus low D-dimer/low fibrinogen group.

‡P< 0.0083 (after Bonferroni correction) versus high D-dimer/high fibrinogen group.

Figure 3

Kaplan-Meier survival curves.

The survival rate in the (4) high D-dimer/low fibrinogen group was lower than that in the other three groups (P< 0.001 vs. (1), P< 0.001 vs. (2), and P= 0.011 vs. (3) based on log-rank tests). The survival rate in the (3) high D-dimer/high fibrinogen group was lower than that in (1) and (2) groups (P< 0.001 and P= 0.007, respectively based on log-rank tests). Fbg, fibrinogen.

Low D-dimer (<38 mg/L) and high D-dimer (≥38 mg/L) and low Fbg (≤1.9 g/L) and high Fbg (>1.9 g/L) levels are values on arrival at the emergency department.

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Supplment Table Patient characteristics in J-OCTET

	Poor outcome n = 164	Good outcome n = 632	*P* values
Age, year	56 (36-72)	59 (39-72)	0.977
Male, n (%)	111 (68)	478 (76)	0.039
Blunt trauma, n (%)	162 (98)	628 (99)	0.439
Anti-coagulant/platelet, n (%)	9 (6)	52 (8)	0.240
Prehospital infusion, n (%)	23 (14)	62 (10)	0.119
ISS	30 (25-41)	21 (17-26)	<0.001
Head/neck AIS	4 (2-4)	4 (0-5)	0.978
Face AIS	0 (0-0)	0 (0-0)	0.056
Chest AIS	3 (0-4)	0 (0-3)	<0.001
Abdomen AIS	1 (0-3)	0 (0-0)	<0.001
Extremity/pelvic AIS	2 (0-3)	0 (0-2)	<0.001
External AIS	0 (0-1)	0 (0-1)	0.881
Revised Trauma Score	7.60 (4.09-7.11)	7.84 (6.90-7.84)	<0.001
Heart rate, /min	103 (83-122)	83 (72-94)	<0.001
Systolic BP, mmHg	113 (84-143)	137 (114-159)	<0.001
Respiratory rate, /min	22 (18-29)	20 (18-24)	<0.001
Body temperature, °C	36.0 (35.3-36.4)	36.4 (35.8-36.8)	<0.001
Glasgow coma scale	9 (3-13)	14 (11-15)	<0.001
Time from accident to sample collection			
- 30 minutes, n (%)	68 (42)	163 (26)	
31 - 60 minutes, n (%)	62 (38)	292 (46)	
61 - 90 minutes, n (%)	18 (11)	85 (13)	0.002
91minutes -, n (%)	12 (7)	78 (12)	
Unknown, n (%)	4 (2)	14 (2)	
Arterial blood gas analyses			
pH	7.346 (7.242-7.400)	7.387 (7.344-7.422)	<0.001
$PaCO_2$, mmHg	38.3 (32.3-44.9)	39.3 (35.0-43.9)	0.430
Base deficit, mmol/L	5.0 (2.2-9.5)	1.2 (0.7-3.2)	<0.001
Lactate, mmol/L	4.1 (2.5-6.9)	2.2 (1.4-3.3)	<0.001
Laboratory tests			
White blood cell, $x10^9$/L	11.8 (8.5-16.6)	10.4 (7.5-14.3)	0.002
Hemoglobin, g/dL	11.7 (10.0-13.5)	13.5 (12.0-14.6)	<0.001
Platelet, $x10^9$/L	184 (142-237)	204 (166-253)	<0.001
AST, U/L	86 (49-205)	39 (27-74)	<0.001
ALT, U/L	59 (31-121)	29 (18-51)	<0.001
LDH, U/L	513 (337-820)	319 (240-462)	<0.001
CK, U/L	361 (221-608)	202 (131-345)	<0.001
PT-INR	1.15 (1.05-1.34)	1.02 (0.97-1.10)	<0.001
APTT, sec	31.4 (26.4-39.2)	25.3 (23.0-28.0)	<0.001
Fibrinogen, mg/dL	183 (137-309)	244 (200-290)	<0.001
D-dimer, mg/L	62.8 (29.1-131.4)	19.6 (6.8-44.6)	<0.001

ISS, injury severity score; AIS, abbreviated injury score; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; PT-INR, prothrombin time-International normalized ratio ; APTT, activated partial thromboplastin time.

Table 1 Patient characteristics

	Poor outcome n = 107	Good outcome n = 412	*P* values
Age, year	55 (36-72)	60 (39-72)	0.834
Male, n (%)	71 (66)	311 (76)	0.056
Blunt trauma, n (%)	105 (98)	408 (99)	0.439
Anti-coagulant/platelet, n (%)	6 (6)	34 (8)	0.361
Prehospital infusion, n (%)	15 (14)	46 (11)	0.414
ISS	29 (25-38)	22 (17-26)	<0.001
Head/neck AIS	4 (1-5)	4 (0-4)	0.749
Face AIS	0 (0-0)	0 (0-0)	0.072
Chest AIS	3 (0-4)	0 (0-3)	0.061
Abdomen AIS	2 (0-3)	0 (0-0)	<0.001
Extremity/pelvic AIS	2 (0-3)	0 (0-2)	<0.001
External AIS	0 (0-1)	0 (0-1)	0.627
Revised Trauma Score	5.967 (4.094-7.108)	7.840 (6.900-7.841)	<0.001
Heart rate, /min	103 (83-120)	84 (71-95)	<0.001
Systolic BP, mmHg	116 (86-141)	137 (113-160)	<0.001
Respiratory rate, /min	22 (18-30)	20 (18-25)	0.013
Body temperature, °C	36 (35.3-36.4)	36.4 (35.9-36.8)	<0.001
Glasgow coma scale	10 (3-13)	14 (10-15)	<0.001
Time from accident to sample collection			
- 30 minutes, n (%)	44 (41)	102 (25)	
31 - 60 minutes, n (%)	43 (40)	198 (48)	
61 - 90 minutes, n (%)	12 (11)	57 (14)	0.016
91minutes -, n (%)	6 (6)	45 (11)	
Unknown, n (%)	2 (2)	10 (2)	
Arterial blood gas analyses			
pH	7.35 (7.24-7.41)	7.39 (7.35-7.43)	<0.001
$PaCO_2$, mmHg	38.3 (32.4-45.6)	38.6 (34.4-42.8)	0.892
Base deficit, mmol/L	4.7 (1.3-8.3)	1.2 (-0.7-3.1)	<0.001
Lactate, mmol/L	4.1 (2.4-6.3)	2.2 (1.4-3.1)	<0.001
Laboratory tests			
White blood cell, $x10^9$/L	11.7 (8.5-16.5)	10.5 (7.5-14.7)	0.040
Hemoglobin, g/dL	11.6 (9.9-13.5)	13.3 (11.9-14.5)	<0.001
Platelet, $x10^9$/L	186 (152-235)	202 (161-252)	0.013
AST, U/L	86 (51-221)	43 (29-80)	<0.001
ALT, U/L	57 (33-121)	33 (20-59)	<0.001
LDH, U/L	515 (332-825)	338 (252-493)	<0.001
CK, U/L	353 (221-621)	221 (141-387)	<0.001
PT-INR	1.15 (1.06-1.38)	1.03 (0.98-1.1)	<0.001
APTT, sec	31.7 (26.5-39.1)	25.5 (23.1-28.1)	<0.001
Fibrinogen, mg/dL	182 (127-229)	240 (199-287)	<0.001
D-dimer, mg/L	60 (28.2-120.4)	19.6 (7.4-46.1)	<0.001

ISS, injury severity score; AIS, abbreviated injury score; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; PT-INR, prothrombin time-International normalized ratio ; APTT, activated partial thromboplastin time.

Table 2 The receiver operating characteristic (ROC) curve analysis of fibrinolytic variables

	AUC	95% confidence interval		*P* value	Cutoff value
		lower	upper		
Fibrinogen	0.726	0.668	0.784	<0.001	190 mg/dL
D-dimer	0.751	0.698	0.804	<0.001	38 mg/L

AUC, area under curve.

Table 3 Patient characteristics

	Low D-dimer		High D-dimer		
	High Fbg	**Low Fbg**	**High Fbg**	**Low Fbg**	***P* value**
	n = 267	**n = 53**	**n = 113**	**n = 86**	
Age, year	60 (40-70)	32 (24-60) *	68 (46-77) *	52 (32-70) *†‡	<0.001
Male, n (%)	205 (77)	44 (83)	73 (65)	60 (70)	0.027
Blunt trauma, n (%)	263 (99)	51 (96)	113 (100)	86 (100)	0.123
Anti-coagulant/platelet, n (%)	28 (11)	1 (2)	7 (6)	4 (5)	0.075
Prehospital infusion, n (%)	25 (9)	4 (8)	12 (11)	20 (23) *	0.004
ISS	21 (17-26)	25 (19-30) *	25 (21-30) *†	28 (25-38) *†	<0.001
Head/neck AIS	4 (0-4)	4 (0-4)	3 (1-5)	4 (1-5)	0.439
Face AIS	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.925
Chest AIS	0 (0-3)	0 (0-3)	1 (0-3) †	3 (0-4)	0.006
Abdomen AIS	0 (0-0)	0 (0-2) *	0 (0-2) *	0 (0-2)	0.012
Extremity/pelvic AIS	0 (0-2)	0 (0-3)	2 (0-3) †	2 (0-3) *	<0.001
External AIS	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0.712
Revised Trauma Score	7.84 (6.90-7.84)	7.84 (6.08-7.84)	7.11 (5.56-7.84) †	6.39 (4.09-7.55) *†‡	<0.001
Heart rate, /min	84 (73-94)	92 (78-111)	86 (70-105) †	92 (77-110)	0.004
Systolic BP, mmHg	137 (112-160)	120 (96-146) *	130 (99-170) *	128 (109-142)	0.021
Respiratory rate, /min	20 (17-24)	23 (19-29) *	22 (18-28) *	22 (17-29) *	0.005
Body temperature, °C	36.4 (35.8-36.8)	36.2 (36.0-37.0)	36.1 (35.6-36.6) †	36.1 (35.5-36.6)	0.009
Glasgow coma scale	14 (12-15)	14 (12-15)	13 (7-15) *†	9 (3-13) *†‡	<0.001
Time from accident to sample collection					
- 30 minutes, n (%)	70 (26)	18 (34)	31 (27)	27 (31)	
31 - 60 minutes, n (%)	125 (47)	25 (47)	58 (51)	33 (38)	
61 - 90 minutes, n (%)	36 (14)	6 (11)	11 (10)	16 (19)	0.764
91minutes -, n (%)	29 (11)	3 (6)	10 (9)	9 (11)	
Unknown, n (%)	7 (3)	1 (2)	3 (3)	1 (1)	
Arterial blood gas analyses					
pH	7.393 (7.348-7.430)	7.380 (7.316-7.421)	7.380 (7.344-7.417)	7.360 (7.274-7.406)	0.002
$PaCO_2$, mmHg	38.6 (34.2-42.4)	37.0 (30.9-42.8)	39.5 (33.9-45.6)	40.2 (35.2-44.0)	0.105
Base deficit, mmol/L	0.8 (1.1-3.1)	2.4 (0.9-5.7) *	1.4 (0.3-4.5) *†	3.1 (0.7-7.1) *	<0.001
Lactate, mmol/L	2.1 (1.4-3.1)	3.0 (2.33.4) *	2.4 (1.5-3.5) *†	3.3 (2.2-5.5) *‡	<0.001
Laboratory tests					
White blood cell, $x10^9$/L	9.3 (6.8-13.4)	11.6 (7.65-16.4)	11.9 (7.9-16.5) †	13.4 (9.8-17.2) *	<0.001
Hemoglobin, g/dL	13.5 (12.1-14.8)	13.6 (11.8-14.5)	12.4 (11.2-13.9) †	11.9 (9.8-13.7) *†	<0.001
Platelet counts, $x10^9$/L	21.2 (17.1-25.8)	20.0 (15.9-24.2)	18.8 (15.2-24.4) †	17.9 (13.9-23.1) *	<0.001
AST, U/L	39 (27-75)	60 (28-146)	62 (36-129) †	69 (43-145) *	<0.001
ALT, U/L	29 (18-55)	42 (22-87)	40 (25-84) †	49 (32-99) *	<0.001
LDH, U/L	305 (237-415)	348 (213-565)	473 (328-654) †	507 (362-741) *†	<0.001
CK, U/L	199 (128-320)	262 (146-421)	294 (174-507)	383 (218-622) *	<0.001
PT-INR	1.01 (0.96-1.07)	1.07 (1.01-1.13) *	1.08 (1.00-1.14) *†	1.18 (1.09-1.42) *†‡	<0.001
APTT, sec	25.0 (22.9-27.2)	25.4 (23.2-27.7)	28.0 (25.0-31.6) †	30.4 (27.2-38.0) *†‡	<0.001
Fibrinogen, mg/dL	256 (224-296)	169 (150-180) *	249 (220-281) *†	151 (109-174) *‡	<0.001
D-dimer, mg/L	11.0 (4.5-21.2)	17.6 (7.6-24.1)	62.3 (49.4-100.7) †	85.4 (59.6-180.7) *‡	<0.001

**P* <0.0083 (after Bonferroni correction) versus low D-dimer/high Fbg group.
†*P* <0.0083 (after Bonferroni correction) versus low D-dimer/low Fbg group.
‡*P* <0.0083 (after Bonferroni correction) versus high D-dimer/high Fbg group.
Fbg, fibrinogen; ISS, injury severity score; AIS, abbreviated injury score; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; PT-INR, prothrombin time-international normalised ratio ; APTT, activated partial thromboplastin time.

Table 4 Hemostatic procedures and transfusions

	Low D-dimer		High D-dimer		
	High Fbg	Low Fbg	High Fbg	Low Fbg	*P* value
	n = 267	n = 53	n = 113	n = 86	
Hemostatic procedures, n (%)	48 (18)	16 (30)	38 (34)	31 (36)	0.001
Transfusion during 6 hours					
RCC, units	0 (0-0)	0 (0-3)*	0 (0-5)*	4 (0-10)*†	<0.001
FFP, units	0 (0-0)	0 (0-3)*	0 (0-6)*	4 (0-10)*†	<0.001
PC, units	0 (0-0)	0 (0-0)	0 (0-0)*	0 (0-0)*	<0.001
Massive transfusion, n (%)	7 (2.6)	10 (18.9)	18 (15.9)	28 (32.6)	<0.001
Transfusion during 24 hours					
RCC, units	0 (0-0)	0 (0-9)	0 (0-8)*	6 (0-16)*†‡	<0.001
FFP, units	0 (0-0)	0 (0-6)	0 (0-10)*	5 (0-20)*†	<0.001
PC, units	0 (0-0)	0 (0-0)	0 (0-0)*	0 (0-10)*	<0.001
Massive transfusion, n (%)	16 (6)	13 (25)	22 (19)	37 (43)	<0.001

Massive transfusion was defined as over 10 units of red cell concentrate transfusion during the first 24 hours.
**P* <0.0083 (after Bonferroni correction) versus low D-dimer/high Fbg group.
†*P* <0.0083 (after Bonferroni correction) versus low D-dimer/low Fbg group.
‡*P* <0.0083 (after Bonferroni correction) versus high D-dimer/high Fbg group.
RCC, red cell concentrate; FFP, fresh frozen plasma; PC, platelet concentrate; Fbg, fibrinogen.

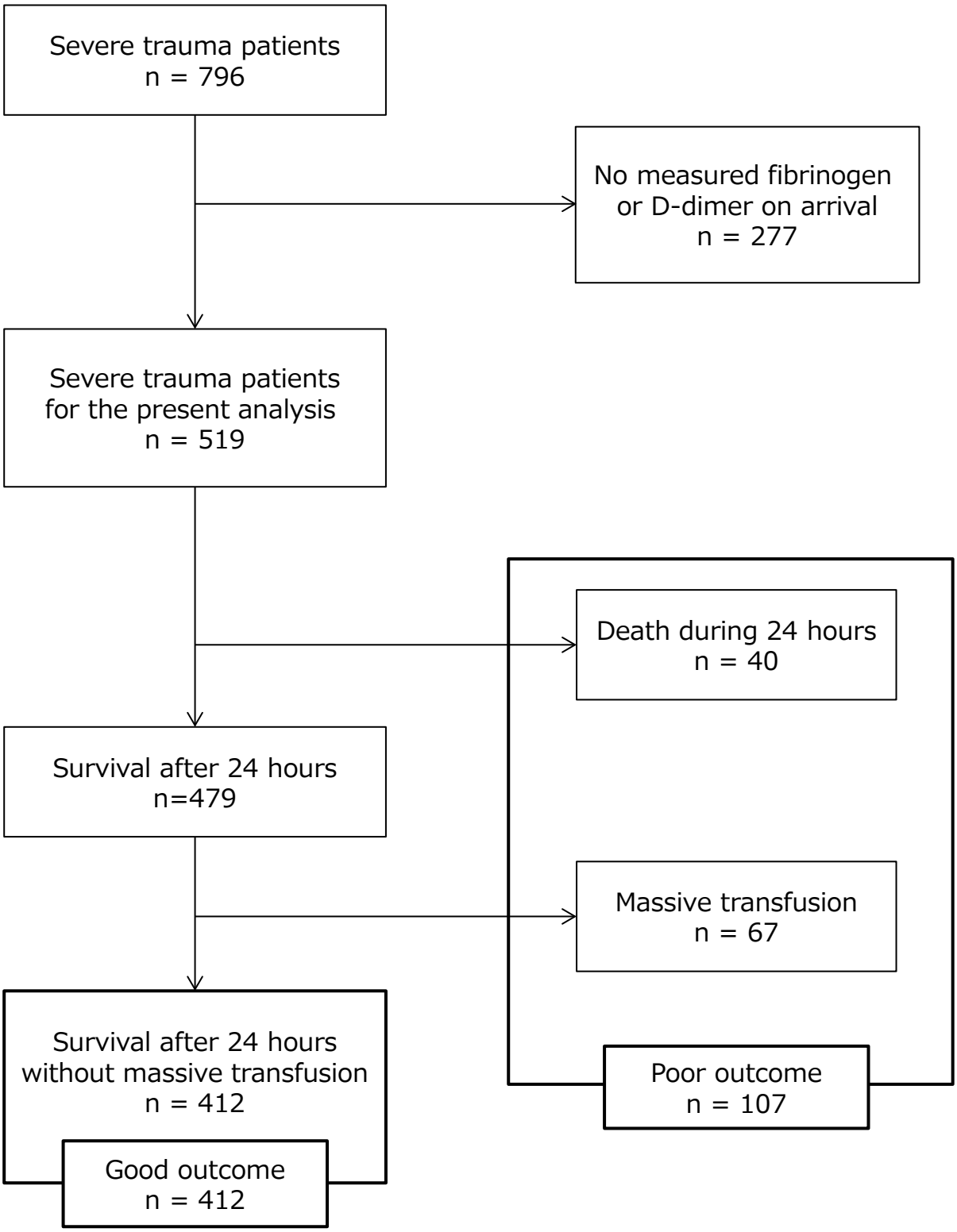

Severe trauma patients
n = 796
No measured fibrinogen
or D-dimer on arrival
n = 277
Severe trauma patients
for the present analysis
n = 519
Death during 24 hours
n = 40
Survival after 24 hours
n=479
Massive transfusion
n = 67
Survival after 24 hours
without massive transfusion
n = 412
Poor outcome
n = 107
Good outcome
n = 412

Fig. 1

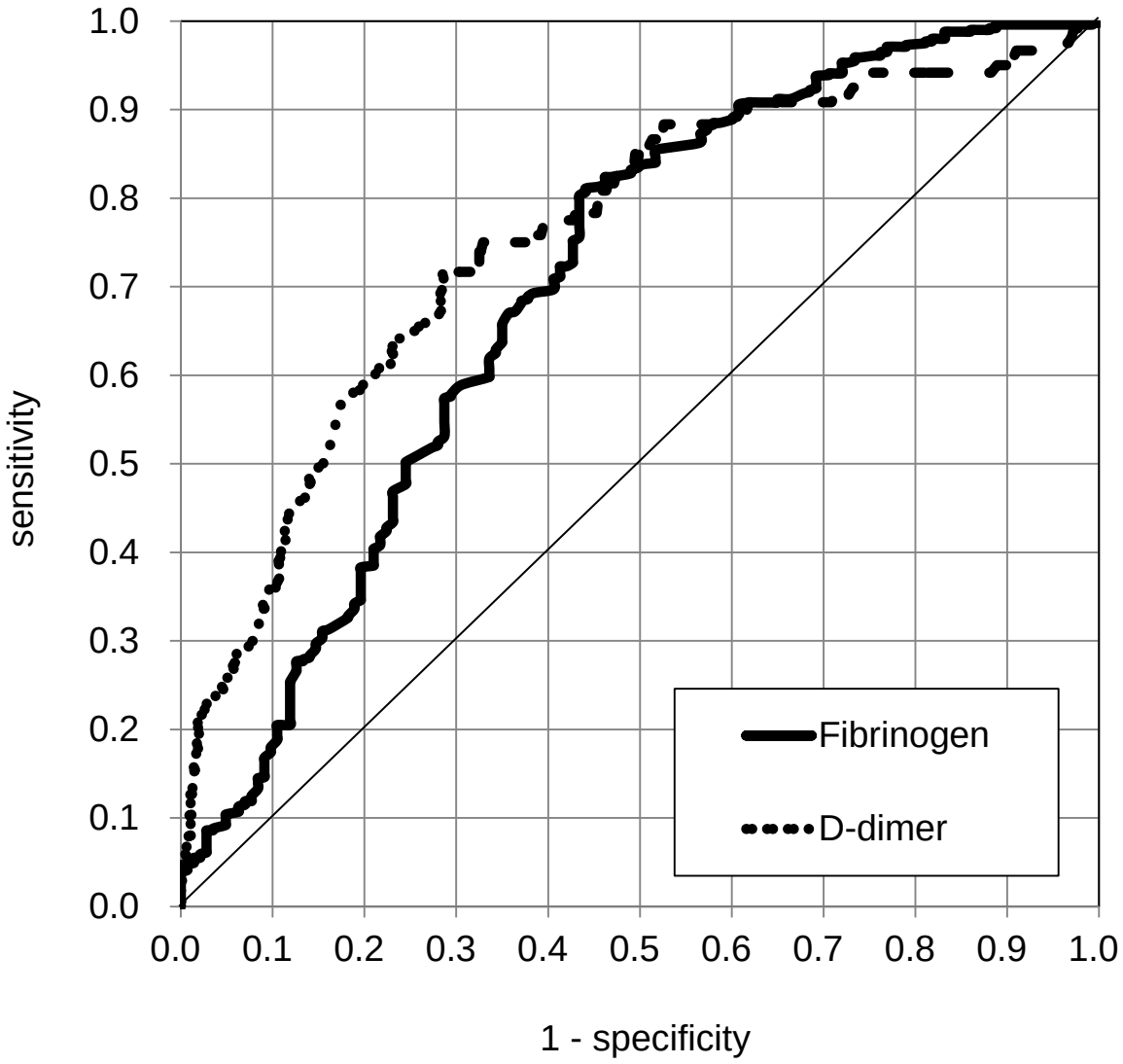

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
sensitivity
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1 - specificity
Fibrinogen
D-dimer

Fig. 2

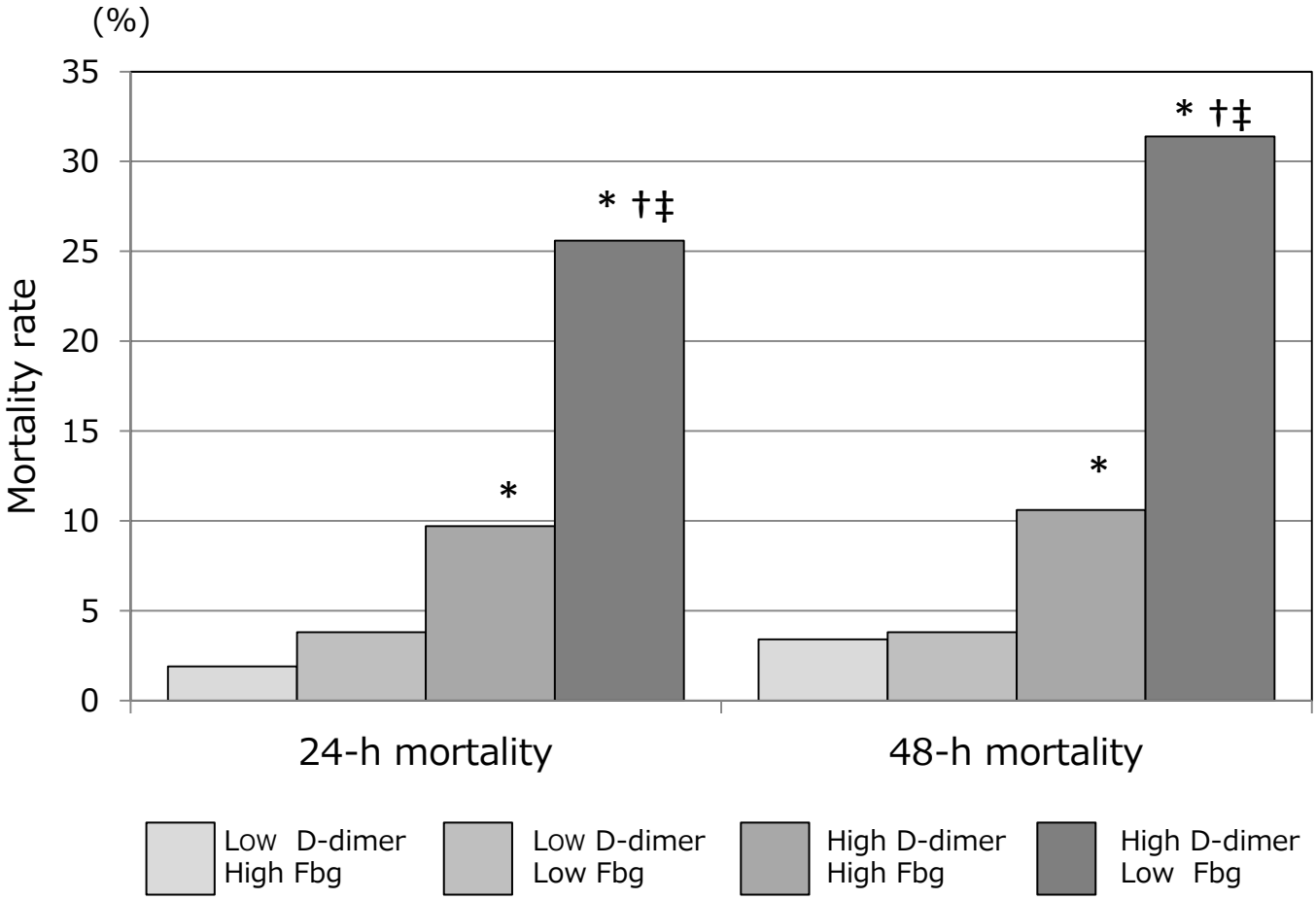
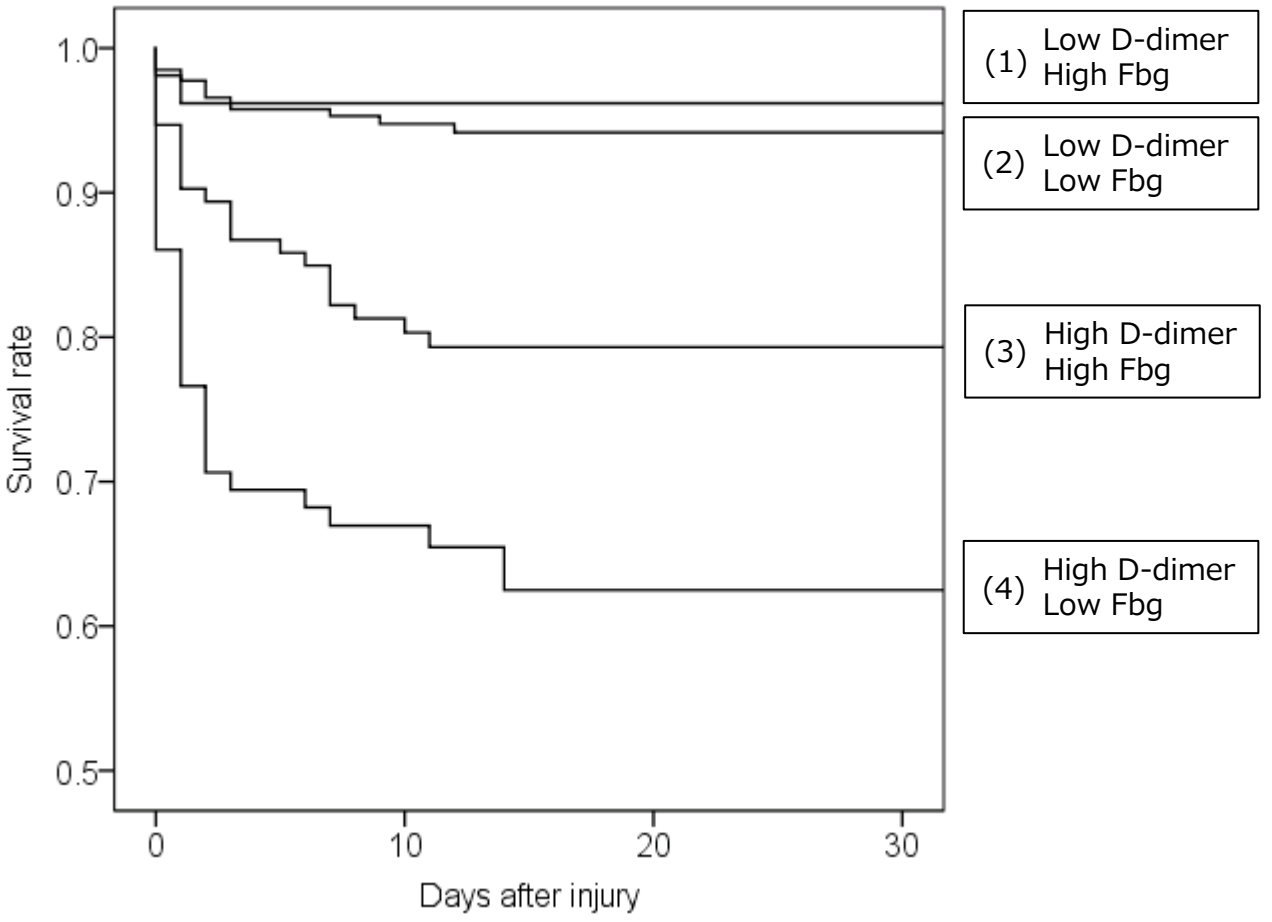

(%)
35
30
25
20
15
10
5
0
Mortality rate
* †‡
*
* †‡
*
24-h mortality
48-h mortality
Low D-dimer
High Fbg
Low D-dimer
Low Fbg
High D-dimer
High Fbg
High D-dimer
Low Fbg

Fig. 3



Number at risk

267	167	103	74	Low D-dimer & High Fbg
53	40	27	20	Low D-dimer & Low Fbg
113	83	63	43	High D-dimer & High Fbg
86	47	35	25	High D-dimer & Low Fbg

Fig. 4