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Fibrin/fibrinogen degradation products (FDP) at hospital admission predict neurological outcomes in out-of-hospital cardiac arrest patients

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Abstract

Objective: This study aimed to test the hypothesis that coagulation, fibrinolytic markers and disseminated intravascular coagulation (DIC) score (International Society on Thrombosis and Haemostasis) at hospital admission of out-of-hospital cardiac arrest (OHCA) patients can predict neurological outcomes 1 month after cardiac arrest.

Methods: In this retrospective, observational analysis, data were collected from the Sapporo Utstein Registry and medical records at Hokkaido University Hospital. We included patients who experienced OHCA with successful return of spontaneous circulation (ROSC) between 2006 and 2012 and were transferred to Hokkaido University Hospital. From medical records, we collected information about the following coagulation and fibrinolytic factors at hospital admission: platelet count; prothrombin time; activated partial thromboplastin time; plasma levels of fibrinogen, D-dimer, fibrin/fibrinogen degradation products (FDP), and antithrombin; and calculated DIC score. Favorable neurological outcomes were defined as a cerebral performance category 1−2.

Results: We analyzed data for 315 patients. Except for fibrinogen level, all coagulation variables, fibrinolytic variables, and DIC score were associated with favorable neurological outcomes. In the receiver operating characteristic curve analysis, FDP level had the largest area under the curve (AUC; 0.795). In addition, the AUC of FDP level was larger than that of lactate level. The AUC value of FDP level might indicate that FDP is an independent predictor of favorable neurological outcomes.

Conclusions: All of the coagulation and fibrinolytic markers, except for fibrinogen level, and DIC score at hospital admission, were associated with favorable neurological outcomes. Of all of the variables, FDP level was most closely associated with favorable neurological outcomes in OHCA patients who successfully achieved ROSC.

Introduction

Survival rates and neurological outcomes after out-of-hospital cardiac arrest (OHCA) have long been used as indicators of the effectiveness of prehospital treatments by emergency medical services (EMS) and treatments after hospital arrival by physicians. Well-known prehospital predictors for these post-OHCA outcomes include age, witness of the event by a bystander, bystander-initiated cardiopulmonary resuscitation (CPR), origin of cardiac arrest, primary electrocardiogram (ECG) rhythm, defibrillation, and time to CPR initiation.[1-8] According to a few reports, post-hospital admission predictors for unfavorable neurological outcomes in these patients with ventricular fibrillation (VF) include lactate level elevation at intensive care unit (ICU), and OHCA patients' plasma lactate and serum creatinine levels elevation.[9,10]

Neumar et al.[11] reported that the high mortality rate of patients who initially achieved return of spontaneous circulation (ROSC) after experiencing cardiac arrest could be attributed to the development of post-cardiac arrest syndrome (PCAS), a unique and complex combination of pathophysiological processes. Some of the most important components of PCAS are systemic ischemia and reperfusion.[11]

The mechanisms of unfavorable outcomes after resuscitation from OHCA in patients with PCAS include both myocardial dysfunction and whole-body ischemia and reperfusion syndrome responsible for a systematic inflammatory response similar to that in severe sepsis.[11-14] Whole-body ischemia and reperfusion-induced endothelial injury contributes to thrombotic occlusion of the vessels following activation of coagulation and impairment of fibrinolysis.[13,15-18] These changes lead to disseminated intravascular coagulation (DIC) in patients resuscitated from cardiac arrest.[16,17] DIC causes thrombotic occlusion of vessels, followed by deteriorated oxygen supply to cells and tissues.[19,20] As a result, patients resuscitated after cardiac arrest can experience multiple organ dysfunction syndrome, which causes unfavorable outcomes in OHCA patients.[19-22]

Basal conditions during DIC occasionally cause a simultaneous increase in fibrin(ogen)olysis resulting from tissue-type plasminogen activator (t-PA), which is referred to as DIC with the fibrinolytic phenotype, as opposed to the thrombolytic phenotype.[23] Hyperfibrinolysis is reportedly common in OHCA patients and has been associated with markers of hypoperfusion in these patients.[24,25] If not improved, DIC with the fibrinolytic phenotype during the early stage of OHCA proceeds to the thrombotic phenotype at the later stage of OHCA.[20] Both types of DIC affect the patient outcomes.[19,23] Based on assessment of the mortality rate in OHCA patients one month after cardiac arrest, DIC with the fibrinolytic phenotype predicted the outcome.[26] However, neurological outcomes of OHCA patients were not assessed.

The aim of the present study was to test our hypothesis that coagulation markers, fibrinolytic markers, and the DIC score of OHCA patients at hospital admission can predict neurological outcomes.

Methods

Study design

The present study was approved by the institutional review board of the Ethics Committee of Hokkaido University Hospital. This study was a retrospective analysis of prospectively collected data from the Sapporo Utstein Registry of OHCA patients and medical records in Hokkaido University Hospital. Sapporo City started monitoring OHCA patients according to the Utstein template on April 1, 2002. The EMS system in Sapporo has been described in previously published research.[27,28]

Patient selection

This study included OHCA patients transported to Hokkaido University Hospital between January 1, 2006 and December 31, 2012. We excluded patients for whom ROSC was not achieved; for whom spontaneous circulation had been restored before the arrival of EMS personnel; or whose medical records were missing. A portion of the included patients was also included in the study by Wada et al.[26]

Data collection

The durations of all prehospital procedures were recorded using a timekeeping device employed by each EMS system. The device records the times of receipt of the emergency call by EMS, ambulance arrival at the scene, initial contact with the patient, initiation of CPR, and arrival at the hospital. Patient data included sex, age, initial cardiac rhythm, and the time course of resuscitation, as well as whether a bystander had witnessed the episode of cardiac arrest and/or initiated CPR, the patient had been intubated, epinephrine had been administered, and spontaneous circulation had been restored before arrival at the hospital. One month after the event, the EMS staff who initially handled each OHCA patient case collected follow-up data regarding survival and neurological outcomes during a meeting with the medical control director at the hospital. The physicians in charge examined each patients and determined their neurological outcomes. If these patients were transferred other hospital, physicians at the hospital examined them and determined those outcomes. If these patients were discharged from the hospital, the EMS personnel conducted follow-up serach on the phone. A favorable neurological outcome was defined as a Cerebral Performance Category score of 1 (good performance) or 2 (moderate disability). An unfavorable neurological outcome was defined as a score of 3 (severe cerebral disability), 4 (vegetative state), or 5 (death).[29-32] In partnership with the medical control director, emergency personnel summarized the data from each OHCA case according to the standardized Utstein style.

From the medical records of enrolled patients, we collected lactate levels as well as coagulation and fibrinolytic information, including platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and plasma levels of fibrinogen, D-dimer, fibrin/fibrinogen degradation products (FDP), and antithrombin (AT). These variables were measured immediately after arrival at the emergency department. DIC score was calculated by the International Society on Thrombosis and Haemostasis scoring system for overt-DIC.[20]

Statistical analysis

Receiver operating characteristic (ROC) curve analysis, using the Youden Index, was conducted to calculate the optimal cut-off values for the coagulation and fibrinolytic markers at hospital admission of OHCA patients who achieved successful ROSC to predict favorable neurological outcomes. The same analyses ware performed for patients for whom their OHCA was witnessed by bystanders.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of prehospital variables and FDP ≤13.7 mg/L for predicting favorable neurological outcomes were determined.

We used Spearman's rank correlation coefficients to evaluate the correlations between FDP levels and lactate levels or time from calling the EMS to ROSC. Patient characteristics and outcomes were compared between two group using the Mann-Whitney U test (for numerical variables) and the chi-squared test (for categorical variables). These groups included those based on neurological outcome and those based on FDP threshold.

The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for outcomes were assessed using by performing multivariate logistic regression analysis that included the variables of male sex, age, bystander eyewitness, primary ECG rhythm, the time from call EMS to ROSC and FDP ≤ 13.7 μg/mL. SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. A P-value < 0.05 was considered to be statistically significant. Unless otherwise indicated, all data are expressed as the median (interquartile range).

Results

Patient selection

During the study period, 1,848 patients with OHCA were transferred to Hokkaido University Hospital by EMS. Of these patients, there were 1,364 patients who had not experienced ROSC. In addition, there were 79 patients for whom cardiac arrest was not confirmed by EMS. We also excluded 90 patients for whom data were missing. After these exclusions, there were 315 patients who were included in the analysis (Supplemental Figure 1).

Comparison of patient characteristics according to the neurological outcome

Table 1 shows the comparison of prehospital characteristics and laboratory data. There were significant differences in all variables between the groups except frequency of bystander CPR, time from the call to arrival at the scene, and fibrinogen level.

ROC curve analysis

Table 2 shows the results of the ROC curve analysis of coagulation and fibrinolytic variables, DIC score, time from the call to ROSC, and lactate level in OHCA patients who achieved successful ROSC. FDP level had the largest area under the curve (AUC; 0.795), and the cut-off point for FDP level was 13.7 mg/L. Figure 1 shows the ROC curves for FDP, lactate level, and time from the call EMS to ROSC.

In the ROC curve analysis for patients who were witnessed by bystanders, the FDP level had the largest AUC (0.799), and the cut-off point for FDP level was 9.5 mg/L.

There were significant differences in all variables between OHCA patients classified according to the FDP threshold except for with physician, time from the call to arrival at the scene, time from the call to CPR initiation, and veno-arterial extracorporeal membrane oxygen (Supplemental Table 1).

Variables accuracy and correlation

Table 3 shows the sensitivity, specificity, PPV, and NPV of prehospital variables and FDP ≤13.7 mg/L for predicting favorable neurological outcomes. The following prehospital variables were considered useful predictors: onset witnessed by a bystander, initial ECG rhythm with VF or ventricular tachycardia (VT), and cardiac arrest of cardiac origin. The sensitivity, specificity, PPV, and NPV of FDP ≤13.7 mg/L compared favorably with those of these prehospital variables.

Figure 2 shows the scatter diagrams and correlations between FDP and lactate level (r = 0.274) or time from the call to ROSC (r = 0.246); these relationships were weak but significant ($P < 0.01$).

Adjusted odds ratios (ORs) for prognoses

According to the logistic regression analyses, primary ECG rhythm (VF/VT), time from the call to ROSC, and FDP ≤13.7 mg/L were statistically significant predictors for favorable neurological outcomes (Table 4).

Discussion

This study evaluated our hypothesis that coagulation variables, fibrinolytic variables, and the DIC score of OHCA patients at hospital admission can predict neurological outcomes. All of the variables, except the fibrinogen variables were significantly associated with favorable neurological outcomes, and FDP level had the largest AUC.

Anoxia and endothelial injury were previously established as triggering stimuli for circulating fibrinolytic activators and increased fibrinolysis.[33-35] Vascular endothelial cells have a considerable amount of t-PA, which causes fibrin(ogen)olysis and subsequently increases the FDP level.[36] Schneiderman et al.[37,38] showed immediate increases in t-PA activity following arterial occlusion-induced ischemia in humans, attributable to release of substantial amounts of t-PA. Endothelial cells secrete t-PA in response to vascular injury, whole body ischemia and reperfusion syndrome and hypoxia owing to cardiac arrest.[36,39] Therefore, FDP levels after cardiac arrest might reflect whole body ischemia and hypoxia.

That explains the close association between low FDP levels at hospital admission and favorable neurological outcomes in OHCA patients with successful ROSC in the present study. A low DIC score at hospital admission was also associated with favorable neurological outcomes for the same reason. However, in the present study fibrinogen levels at hospital admission were not associated with neurological outcomes, although FDP is a degradation product of fibrin and fibrinogen. The different units of mass (FDP, mg/L; fibrinogen, g/L) might explain this.

Elevated lactate levels at ICU admission are closely associated with unfavorable neurological outcomes after OHCA, due to VF.[9,10] In the present study, the optimal cut-off point for lactate level of 6.7 mmol/L was significantly associated with favorable neurological outcomes in OHCA patients who achieved ROSC, with an AUC of 0.726. However, the AUC of FDP (0.795) was greater than that of the lactate level (Figure 1, Table 2). Furthermore, the present study did not restrict the sample to OHCA patients with VF and included patients with any cause of OHCA. In addition, we evaluated the correlation between FDP and lactate level. Figure 2 showed the correlation was weak but significant ($P < 0.01$, correlation coefficient; 0.274). Therefore, as a predictor for neurological outcomes in OHCA patients, FDP level might be more useful than lactate level. We considered that other factors except for whole body ischemia or hypoxia can affect the lactate level in OHCA patients. For example, administration of epinephrine administration for resuscitation can increase lactate levels by an increase in Na^{+}/K^{+}-ATPase activity.[40] In addition, FDP levels might increase in an earlier phase of whole body ischemia and hypoxia than lactate levels.

The duration of cardiac arrest (from witness by a bystander to ROSC) is significantly associated with favorable neurological outcomes; in the subgroup analysis with OHCA patients who achieved ROSC and were witnessed by a bystander, the optimal cut-off points for FDP level, lactate level, and duration of cardiac arrest were significantly associated with favorable neurological outcomes. Surprisingly, even in this subgroup analysis, FDP levels had a larger AUC (0.799) than duration of cardiac arrest (0.765). Therefore, FDP level might reflect the quality of CPR by an eyewitnesses or EMS personnel.

The present study has several limitations. First, the results were based on retrospective analyses of OHCA patients in a single center and limited by an incomplete data set. Second, the lengthy study period meant that the patients were not treated with the same CPR method because of the change in the CPR guidelines. Third, we could use only six variables to determine adjusted ORs owing to the limited number of patients with a favorable neurological outcome.

Conclusion

In the present study, coagulation variables, fibrinolytic variables except fibrinogen, and DIC score at hospital admission were associated with neurological outcomes in OHCA patients who successfully achieved ROSC. In particularly, low FDP level at hospital admission was closely associated with favorable neurological outcomes. In addition, the cut-off point for FDP level to predict favorable neurological outcomes was ≤13.7 mg/L, which might be the most reliable laboratory measurement for predicting favorable neurological outcomes at hospital admission in OHCA patients who successfully achieved ROSC.

Conflicts of Interest

None to declare

Acknowledgments

None to declare

References

1. Spaite DW, Stiell IG, Bobrow BJ, et al. Effect of transport interval on out-of-cardiac arrest survival in the OPALS study: implications for triaging patients to specialized cardiac arrest centers. *Ann Emerg Med*. 2009;54:248−255.

2. Ma MH, Chiang WC, Ko PC, et al. Outcomes from out-of-hospital cardiac arrest in Metropolitan Taipei: does an advanced life support service make a difference? *Resuscitation.* 2007;74:461−469.

3. Colquhoun MC, Chamberlain DA, Newcombe RG, et al. A national scheme for public access defibrillation in England and Wales: early results. *Resuscitation.* 2008;78:275−280.

4. Iwami T, Nichol G, Hiraide A, et al. Continuous improvement in "chain of survival" increased survival after out-of-hospital cardiac arrests: a large-scale population-based study. *Circulation.* 2009;119:728−734.

5. Herlitz J, Svensson L, Engdahl J, et al. Characteristics of cardiac arrest and resuscitation by age group: an analysis from the Swedish Cardiac Arrest Registry. *Am J Emerg Med.* 2007;25:1025−1031.

6. Eisenberg MS. Improving survival from out-of-hospital cardiac arrest: back to the basics.

Ann J Emerg Med. 2007;49:314−316.

7. Fairbanks RJ, Shah MN, Lerner EB, et al. Epidemiology and outcomes of out-of-hospital cardiac arrest in Rochester, New York. *Resuscitation*. 2007;72:415−424.

8. Ono Y, Hayakawa M, Wada T, et al. Effects of prehospital epinephrine administration on neurological outcomes in patients with out-of-hospital cardiac arrest. *J Intensive Care.* 2015;3:29.

9. Müller M, Sterz F, Domanovits H, et al. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. *Intensive Care Med.* 1997;23:1138−1143.

10. Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: OHCA score. *Eur Heart J.* 2006;27:2840−2845.

11. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council,

Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation.* 2008;118:2452−2483.

12. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis like" syndrome. *Circulation*. 2002;106:562−568.

13. Adrie C, Monchi M, Laurent I, et al. Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: implication of the protein C anticoagulant pathway. *J Am Coll Cardiol.* 2005;46:21−28.

14. Hékimian G, Baugnon T, Thuong M, et al. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. *Shock.* 2004;22:116−119.

15. Gando S, Kameue T, Nanzaki S, et al. Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest. *Thromb Haemost.* 1997;77;278−282.

16. Gando S, Nanzaki S, Morimoto Y, et al. Tissue factor and tissue factor pathway inhibitor

levels during and after cardiopulmonary resuscitation. *Thromb Res.* 1999;96:107−113.

17. Böttiger BW, Martin E. Thrombolytic therapy during cardiopulmonary resuscitation and the role of coagulation activation after cardiac arrest. *Curr Opin Crit Care.* 2001;7:176−183.

18. Petzelbauer P, Zacharowski PA, Miyazaki Y, et al. The fibrin-derived peptide Bbeta 15-42 protects the myocardium against ischemia-reperfusion injury. *Nat Med.* 2005;11:298-304.

19. Levi M, Ten Cate H. Disseminated intravascular coagulation. *N Eng J Med.* 1999;341:586−592.

20. Wada T, Gando S, Mizugaki A, et al. Coagulofibrinolytic changes in patients with disseminated intravascular coagulation associated with post-cardiac arrest syndrome—fibrinolytic shutdown and insufficient activation of fibrinolysis lead to organ dysfunction. *Thromb Res.* 2013;132:e64−69.

21. Taylor FB Jr, Toh CH, Hoots WK, et al; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost.*

2001;86:1327−1330.

22. Gando S. Microvascular thrombosis and multiple organ dysfunction syndrome. *Crit Care Med.* 2010;38:S35-42. doi: 10.1097/CCM.0b013e3181c9e31d.

23. Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. *J Intensive Care.* 2014;2:20.

24. Viersen VA, Greuters S, Korfage AR, et al. Hyperfibrinolysis in out of hospital cardiac arrest is associated with markers of hypoperfusion. *Resuscitation.* 2012;83:1451−1455. doi: 10.1026/j-resuscitation.2012.05.008.

25. Schöchl H, Cadamuro J, Seidl S, et al. Hyperfibrinolysis is common in out-of-hospital cardiac arrest: results from a prospective observational thromboelastometry study. *Resuscitation.* 2013;84:454−459. doi: 10.1016/j.resuscitation.2012.08.318.

26. Wada T, Gando S, Ono Y, et al. Disseminated intravascular coagulation with the fibrinolytic phenolype predicts outcome of patients with out-of-hospital cardiac arrest. *Thrombosis Journal.* 2016 doi: 10.1186/s12959−016−0116−y.

27. Hayakawa M, Gando S, Mizuno H, et al. Effects of epinephrine administration in out-of-hospital cardiac arrest based on a propensity analysis. *J Intensive Care.* 2013;1:12.

28. Ono Y, Hayakawa M, Maekawa K, et al. Should laryngeal tubes or masks be used for out-of-hospital cardiac arrest patients? *Am J Emerg Med.* 2015;33:1360−1363.

29. Hayakawa M, Gando S, Okamoto H, et al. Shortening of cardiopulmonary resuscitation time before the defibrillation on worsens the outcome in out-of-hospital VF patients. *Am J Emerg Med.* 2009;27:470−474.

30. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation.* 1991;84:960−975.

31. Jacobs I, Nadkarni V, Bahr J, et al; International Liaison Committee on Resuscitation; American Heart Association; European Resuscitation Council; Australian Resuscitation Council; New Zealand Resuscitation Council; Heart and Stroke Foundation of Canada; InterAmerican Heart Foundation; Resuscitation Councils of Southern Africa; ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals

from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resusuciation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resusciation Councils of Southern Africa). *Circulation.* 2004;110:3385−3397.

32. Cummins RO, Chamberlain D, Hazinski MF, et al. Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: the in-hospital "Utstein style." *Circulation.* 1997;95:2213-2239.

33. Clarke RL, Cliffton EE. Oxygen saturation and spontaneous fibrinolytic activity. *Am J Med Sci.* 1962;244:466-471.

34. Todd AS. Endothelium and fibrinolysis. *Atherosclerosis.* 1972;15:137-140.

35. Batsch P, Haeberli A, Hauser K, et al. Fibrinogenolysis in the absence of fibrin formation in severe hypobaric hypoxia. *Aviat Space Environ Med*. 1988;59:428-432

36. Lowenstein CJ, Morrell CN, Yamakuchi M. Regulation of Weibel-Palade body exocytosis. *Trends Cardiovasc Med.* 2005;15:302−308.

37. Schneiderman J, Adar R, Savion N. Changes in plasma tissue-type plasminogen activator and plasminogen activator inhibitor activity during acute arterial occlusion associated

with ischemia. *Thromb Res.* 1991;62:401-408

38. Schneiderman J, Eguchi Y, Adar R, et al. Modulation of fibrinolytic system by major peripheral ischemia. *J Vasc Surg.* 1994;19:516-524.

39. Kooistra T, Schrauwen Y, Arts J, et al. Regulation of endothelial cell t-PA synthesis and release. *Int J Hematol.* 1994;59:233−255.

40. Levy B, Gibot S, Franck P, et al. Relation between muscle Na+K+ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet.* 2005;365:871−875.

Figure legends

Figure 1. Receiver operating characteristic curves

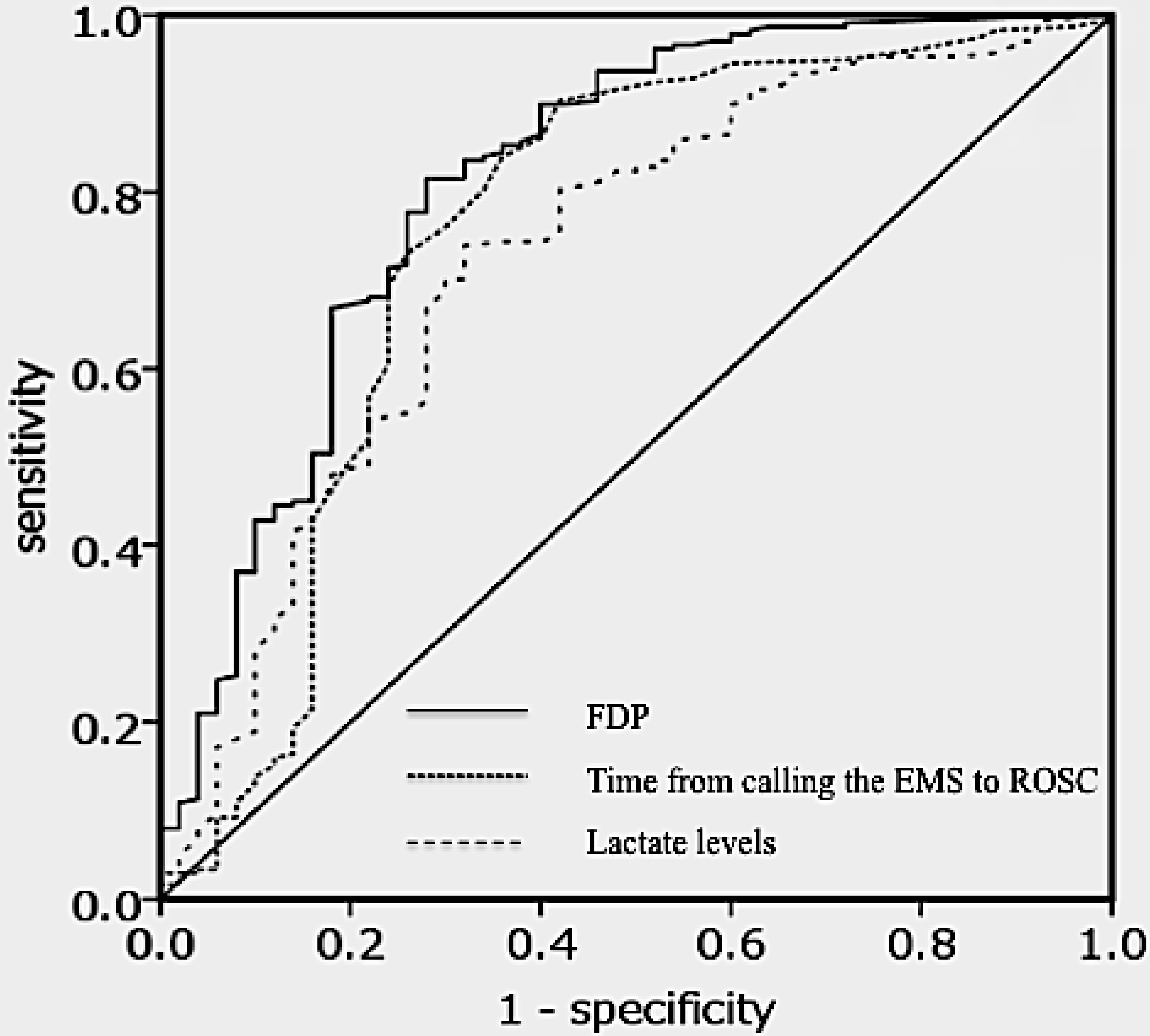
Receiver operating characteristic (ROC) curves of fibrin/fibrinogen degradation product (FDP) level, time from calling the emergency medical services (EMS) to return of spontaneous circulation (ROSC), and lactate level for the prediction of favorable neurological outcomes in out-of-hospital cardiac arrest (OHCA) patients who successfully achieved ROSC

Figure 2. Scatter diagrams and correlations between fibrin/fibrinogen degradation product (FDP) level and lactate level and time from calling emergency medical services (EMS) to return of spontaneous circulation (ROSC)

The left vertical line in the left scatter diagram represents lactate level and the left vertical line in the right diagram shows time from call EMS to ROSC. The horizontal lines in both diagrams represent FDP level. In the bottom of this figure, the correlation between FDP and lactate or time from call EMS to ROSC is showed.

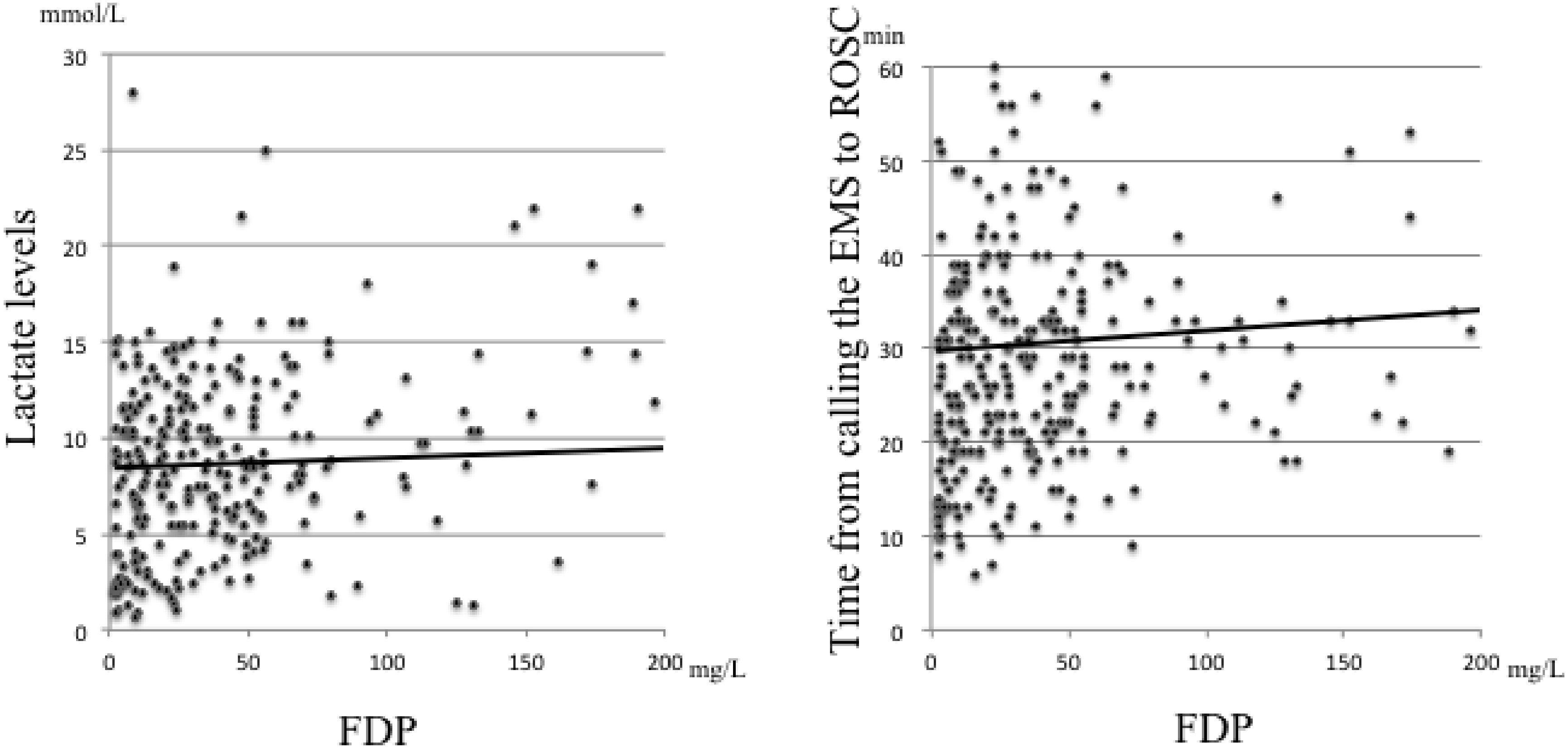
FDP, fibrin/fibrinogen degradation products; ROSC, return of spontaneous circulation; EMS, emergency medical services

Figure 1



sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0
FDP
Time from calling the EMS to ROSC
Lactate levels

Figure 2



	Lactate levels	Time from calling the EMS to ROSC
FDP		
correlation coefficient	0.274	0.246
P value	<0.001	<0.001

Table 1. Characteristics of out-of-hospital cardiac arrest patients according to neurological outcomes

Neurological outcome	CPC 1 or 2 n = 51	CPC 3-5 n = 264	P value
Age, years, median (IQR)	61 (56−72)	74 (60−82)	< 0.001
Male sex	40 (78.4)	140 (53.0)	0.001
Witness by a bystander	45 (88.2)	152 (57.6)	< 0.001
With physician	46 (90.2)	186 (70.5)	0.003
CPR initiated by a bystander	14 (27.5)	95 (36.0)	0.241
Origin of cardiac arrest			
Cardiac	47 (92.2)	106 (40.2)	< 0.001
Not cardiac	4 (7.8)	158 (59.8)	
Primary ECG rhythm			
VF/VT	38 (74.5)	38 (14.4)	< 0.001
PEA/Asystole	13 (25.5)	226 (85.6)	
Life support by EMS personnel			
Defibrillation	40 (78.4)	51 (19.3)	< 0.001
Advanced airway management	40 (78.4)	257 (97.3)	< 0.001
Intravenous line inserted	42 (82.4)	255 (96.6)	< 0.001
Epinephrine administerd	18 (35.3)	219 (83.0)	< 0.001
Time, minutes, median (IQR)			
Time from calling EMS to arrival at the scene	5 (4−7)	6 (5−7)	0.078
Time from calling EMS to CPR initiation	6 (5−8)	7 (6−9)	< 0.001
Time from calling EMS to ROSC	17 (13−24)	30 (23−39)	< 0.001
Time from calling EMS to arrival at the hospital	32 (25−36)	34 (28−39)	< 0.001
Time from CPR initiation to ROSC	10 (6−20)	23 (16−30)	< 0.001
Duration of cardiac arrest	16 (11−24)	31 (23−37)	< 0.001
Laboratory data, median (IQR)			
FDP (mg/L)	7.2 (2.6−24.6)	37.4 (18.4−69.3)	< 0.001
D-dimer (mg/L)	4.20 (1.17−14.57)	21.16 (10.64−43.03)	< 0.001
AT (%)	83.0 (71.0−91.0)	71.0 (60.0−81.0)	< 0.001
Fibrinogen (g/L)	2.34 (2.03−2.96)	2.38 (1.87−3.00)	0.663
PT (sec)	12.4 (11.8−14.0)	14.2 (12.8−16.4)	< 0.001
APTT (sec)	32 (29−41)	48 (37−65)	< 0.001
Platelet count (10^4/μL)	20.8 (16.1−25.4)	18.1 (14.6−22.8)	0.01
Lactate (mmol/L)	5.2 (2.2−8.7)	9.2 (6.4−12.2)	< 0.001
DIC score, median (IQR)	0 (0−3)	3 (2−4)	< 0.001
V-A ECMO	10 (19.6)	21 (8.0)	0.011
Therapeutic hypothermia	35 (68.6)	60 (22.7)	< 0.001

Data are expressed as n (%), unless otherwise indicated.

CPC, Cerebral Performance Category; IQR, interquartile range; CPR, cardiopulmonary resuscitation; ECG, electrocardiography; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; EMS, emergency medical services; ROSC, return of spontaneous circulation; FDP, fibrin/fibrinogen degradation products; AT, antithrombin; PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; V-A ECMO, veno-arterial extracorporeal membrane oxygenation

Table 2. Receiver operating characteristic curve analysis

	AUC	95% confidence interval		P value	cutoff value
		lower	upper		
all OHCA patients who achieved ROSC					
FDP (mg/L)	0.795	0.719	0.872	< 0.001	13.7
D-dimer (mg/L)	0.768	0.69	0.846	< 0.001	9
AT (%)	0.708	0.631	0.785	< 0.001	80.5
Fibrinogen (g/L)	0.481	0.4	0.561	0.663	1.92
PT (sec)	0.707	0.624	0.789	< 0.001	13.3
APTT (sec)	0.74	0.661	0.818	< 0.001	41
Platelet count ($10^4/\mu L$)	0.613	0.531	0.696	0.01	19.1
DIC score	0.755	0.674	0.836	< 0.001	0.5
Time from calling EMS to ROSC (min)	0.759	0.67	0.847	< 0.001	18.5
Lactate levels (mmol/L)	0.726	0.644	0.808	< 0.001	6.7
OHCA patients witnessed by bystanders and who achieved ROSC					
FDP (mg/L)	0.799	0.715	0.884	< 0.001	9.5
D-dimer (mg/L)	0.771	0.683	0.859	< 0.001	7.7
AT (%)	0.712	0.628	0.797	< 0.001	81.5
Fibrinogen (g/L)	0.547	0.457	0.636	0.343	2.3
PT (sec)	0.698	0.606	0.79	< 0.001	13
APTT (sec)	0.724	0.638	0.81	< 0.001	36.7
Platelet count ($10^4/\mu L$)	0.628	0.535	0.72	0.009	19.1
DIC score	0.77	0.681	0.859	< 0.001	0.5
Duration of cardiac arrest (min)	0.765	0.67	0.859	< 0.001	18.5
Lactate levels (mmol/L)	0.716	0.626	0.807	< 0.001	6.7

AUC, area under the curve; ROSC, return of spontaneous circulation; FDP, fibrin/fibrinogen degradation products; AT, antithrombin; PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; EMS, emergency medical services

Table 3. Accuracy of variables to predict favorable neurological outcomes in out of hospital cardiac arrest patients who successfully achieved return of spontaneous circulation

	sensitivity	specificity	positive predictive value	negative predictive value
Witnessed by a bystander	0.882	0.424	0.228	0.949
ECG rhythm(Vf/VT)	0.745	0.848	0.5	0.945
Cardiac origin	0.922	0.598	0.307	0.975
FDP ≤13.7 mg/L	0.725	0.803	0.416	0.828

ECG, electrocardiograph; Vf, ventricular fibrillation; VT, ventricular tachycardia; FDP, fibrin/fibrinogen degradation products

Table 4. Logistic regression analyses for the prediction of favorable neurological outcomes in out of hospital cardiac arrest patients who successfully achieved return of spontaneous circulation (ROSC)

Variables	regression coefficient	OR	95% CI	P-value
Male sex	0.42	1.52	0.61−3.80	0.367
Age	−0.013	0.99	0.96−1.01	0.311
Witnessed by a bystander	1.003	2.73	0.92−8.06	0.07
Primary ECG rhythm (Vf/VT)	2.203	9.05	3.98−20.60	<0.001
Time from calling EMS to ROSC	−0.042	0.96	0.93−0.99	0.005
FDP ≤ 13.7 mg/L	1.606	4.98	2.18−11.40	<0.001

OR, odds ratio; CI, confidence interval; ECG, electrocardiograph; Vf, ventricular fibrillation; VT, ventricular tachycardia; EMS, emergency medical services; FDP, fibrin/fibrinogen degradation products