

Disseminated Intravascular Coagulation Immediately after Trauma Predicts a Poor Prognosis in Severely Injured Patients: A Sub-analysis of a Multicenter Prospective Study on Disseminated Intravascular Coagulation in Trauma

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Research

Keywords: Coagulopathy, disseminated intravascular coagulation (DIC), mortality, organ dysfunction, transfusion, trauma

Posted Date: December 11th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-125408/v1>

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Abstract

Background: Trauma patients die from massive bleeding due to DIC with a fibrinolytic phenotype in the early phase, which transforms to DIC with a thrombotic phenotype in the late phase of trauma, contributing to the development of MODS and a consequent poor outcome. The aim of this study is to evaluate the effect of a disseminated intravascular coagulation (DIC) diagnosis on the survival probability and predictive performance of DIC scores for massive transfusion, multiple organ dysfunction syndrome (MODS), and hospital death in severely injured trauma patients.

Methods: Severely injured adult patients (Injury Severity Score ≥ 16) were prospectively evaluated for their DIC scores and molecular markers of coagulation and fibrinolysis immediately after emergency department presentation (0 h) and 3 h after admission. Organ dysfunction was assessed by the sequential organ failure assessment (SOFA) score at 24 h after admission. The performance of DIC scores in predicting massive transfusion, MODS, and hospital death, and the effect of a DIC diagnosis on the survival probability were investigated.

Results: The 276 enrolled patients included 121 DIC and 155 non-DIC patients. DIC patients showed larger transfusion volume and higher SOFA scores than non-DIC patients at 24 h after admission. A DIC diagnosis on admission was associated with a lower survival probability (Log Rank $p < 0.001$), higher frequency of massive transfusion and MODS, and higher mortality rate than no such diagnosis. DIC scores at 0 h and 3 h predicted massive transfusion, MODS, and hospital death with significance (all areas under the receiver operating characteristic curves, $p < 0.001$). Markers of thrombin and plasmin generation and fibrinolysis inhibition also showed a good predictive ability for these three items.

Conclusions: A DIC diagnosis on admission was associated with a low survival probability. DIC scores obtained immediately after trauma predicted a poor prognosis of severely injured trauma patients.

Trial registration: UMIN-CTR, UMIN000019588. Registered on 16 November 2015.

Background

The two major insults of trauma and sepsis induce systemic inflammatory response syndrome (SIRS), which affects a patient's outcome due to multiple organ dysfunction syndrome (MODS) [1]. In addition to SIRS, the influence of a compensatory anti-inflammatory response syndrome on the development of organ dysfunction development has been detected [2]. However, all of the randomized controlled trials targeting SIRS failed, and then another hypothesis to improve the outcome of the patients were begun to be explored at the end of 1990s [3]. Tight molecular links between inflammation and coagulation have been described [4], and then crosstalk between innate immune inflammation and coagulation has been considered a leading cause of MODS [5]. Disseminated intravascular coagulation (DIC), defined as dysregulated inflammatory and coagulofibrinolytic responses to the insults like trauma and sepsis, can give rise to MODS via the bidirectional interplay between SIRS and systemic thrombin generation

associated with endothelial injury [6]. Thus, DIC is a representative pathological syndrome embodying the close association of inflammation with coagulation.

Cellular injury due to trauma releases mitochondrial damage-associated molecular patterns (DAMPs) such as mitochondrial DNA, which induce SIRS and then elicits neutrophil-mediated organ injury [7]. Histones are other major DAMPs released from injured cells or from activated neutrophils forming neutrophil extracellular traps (NETs), which lead to inflammation, activation of coagulation, insufficient anticoagulation controls, impaired fibrinolysis and cytotoxic effects causing tissue damage [8]. All of these changes are characteristics of DIC; therefore, histones and NETs are considered major pathomechanisms of DIC [6, 8, 9]. Markedly elevated histones immediately after trauma induced proinflammatory cytokines release, coagulation activation, endothelial damage, and NETs formation, which result in DIC and consequent microvascular thrombosis and MODS [10].

DIC is recognized as thrombohemorrhagic disorder [6]. In clinical settings, two phenotypes of DIC have been noticed: fibrinolytic and thrombotic phenotypes [9]. DIC with a fibrinolytic phenotype at an early phase of trauma contributes to a poor prognosis due to massive bleeding [11]. During the late period of trauma, the combined activation of coagulation and inflammation in DIC plays an important role in the development of MODS and consequent poor outcome after severe trauma [12]. Furthermore, DIC and sustained SIRS for more than 3 days after trauma were found to predict MODS with a likelihood ratio of 11.5 and 6.25, respectively [13]. A database analysis of four published scales showed that the ability to detect polytrauma patients at risk of complications in both the early and late phase improved by adding different scales related to hemorrhage and coagulation [14]. This result suggests significance of hemorrhaging and thrombosis, namely DIC as a thrombohemorrhagic disorder, for predicting the outcome of trauma patients.

The present study evaluated the utility of the DIC scores for detecting massive transfusion and MODS as well as hospital death as results of these events and investigated the influence of the DIC diagnosis on the survival probability in severely injured trauma patients. The ability to detect thrombin and plasmin generation and the inhibition of fibrinolysis on these outcomes was also evaluated.

Methods

Study design, setting, and ethical approval

This is a prognostic study performed as a sub-analysis of a multicenter prospective descriptive cross-sectional study conducted by the Japanese Association for Acute Medicine (JAAM) Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma (FORECAST) study group [15]. The JAAM FORECAST TRAUMA study recruited participants from April 1, 2016, to January 31, 2018, from 39 emergency departments and intensive-care units (ICUs) in tertiary hospitals and was registered at the University Hospital Medical Information Network Clinical Trial Registry. (UMIN-CTR ID: UMIN000019588). This study was approved under the condition that written informed consent to be obtained from the patient or next of kin by the JAAM and the Ethics Committee of each hospital

(JAAM, 2014-01; Hokkaido University Graduate School of Medicine, Head institute of the FORECAST group, 014-0307) and was performed in accordance with Declaration of Helsinki.

Participants

The JAAM FORECAST TRAUMA study enrolled severely injured adult trauma patients (≥ 16 years old) with an Injury Severity Score (ISS) ≥ 16 who were directly transported from the scene by the emergency medical services. Patients with a history of cardiac arrest and resuscitation, who were receiving anticoagulants, who had hemorrhagic diathesis or coagulopathy due to any causes, or who had been transferred from other hospitals were excluded before registration. The size of the study population was dependent on the study period. All patients were followed up until discharge.

Aims And Outcomes

The primary aim of the present study was to confirm the utility of a DIC diagnosis and DIC scores immediately after trauma for detecting massive transfusion, MODS, and hospital death of severely injured trauma patients. In addition, the ability to detect thrombin, plasmin and inhibition of fibrinolysis on the outcomes of trauma patients was investigated. Survival probability and all-cause hospital death were used as primary outcomes. Ventilator-free days and ICU-free days were also obtained as secondary outcomes.

Definition And The Diagnosis

The severity of injury was assessed by an anatomical and physiological bases according to the ISS and revised trauma score, respectively. Severe trauma was defined as an ISS ≥ 16 . A DIC diagnosis was made based on the JAAM DIC diagnostic criteria [16] (Supplementary Table 1. See Additional file 1). In the present study, the prothrombin time International Normalized Ratio (INR) was used as a substitute for the prothrombin time ratio for the diagnosis of DIC. Transfusion of packed red blood cells (PRBCs) more than the estimated circulating blood volume (7.5% of body weight) within 24 h after the presentation to the emergency department (ED) met the definition of massive transfusion. Massive transfusion was also assessed by the rate of transfusion, evaluated by the volume of PRBC administered from the presentation at the ED to 3 h after the admission. Organ dysfunction was evaluated using the sequential organ failure assessment (SOFA) score [17]. To avoid bias arising from overlapping platelet counts regarding both the SOFA and DIC scores, the original SOFA score and SOFA score without the coagulation score were calculated. The Glasgow Coma Scale (GCS) for the SOFA score of central nervous system was used without manipulation. An individual SOFA score ≥ 2 was considered to indicate dysfunction of each organ and cases more than two organs dysfunctions without coagulation dysfunction were defined as MODS. The SIRS criteria were used for the assessment of systemic inflammation [1]. A systolic blood pressure < 90 mmHg at the scene or at the ED and lactate levels > 2 mmol/L at the ED were defined as

shock. The Charlson index was determined for the assessment of comorbidities [18]. Ventilator-free days was defined as the number of days within the first 28 days after admission during which a patient was able to breathe without a ventilator. ICU-free days were calculated in a similar manner.

Data Collection And Measurements

Immediately after arrival at the ED (0-h timepoint) and 3 h after admission (3-h timepoint), 15 mL of blood was collected in citrated tubes at each sampling point. The samples were immediately centrifuged at 4°C in the laboratories of each hospital, and the obtained plasma was stored at -80°C. All plasma samples were measured at the center laboratory of the LSI Medience Corporation (Tokyo Japan). We measured the following molecular markers: 1) soluble fibrin (marker of direct thrombin generation) (LA, IATRO SFII; LSI Medience, Tokyo, Japan), 2) plasmin and α 2-plasmin inhibitor (antiplasmin) complex (marker of plasmin generation) (LPIA, LPIA-ACE PPI II; LSI Medience, Tokyo, Japan), 3) plasminogen activator inhibitor-1 (PAI-1) (marker of inhibition of fibrinolysis) (LA, LPIA•tPAI test; LSI Medience, Tokyo, Japan), and 4) D-dimer (marker of fibrinolysis) (LPIA, LPIA GENESIS D-dimer; LSI Medience, Tokyo, Japan). In addition to routine laboratory tests and blood gas analysis, measurements of platelet counts, prothrombin time (sec, INR), activated partial thromboplastin time (APTT), fibrinogen, fibrin/fibrinogen degradation products (FDP), and the FDP/D-dimer ratio were performed at 0, 3, and 24 h timepoints after the arrival at the ED. The SIRS criteria and DIC scores were calculated at the 0-, 3-, 24-h timepoints and SOFA scores were obtained at 24 h after admission to the ED.

Statistical Analyses

Measurements are expressed as the median with the 25th -75th interquartile range or number (percentage). Missing values were used without manipulation. Differences in demographics and measured parameters between two groups (DIC vs. non-DIC) were compared with the Mann-Whitney U-test for continuous variables, and either the chi-square test or Fisher's exact test was used for nominal variables when required. Time courses of DIC scores, platelet counts, and global markers of coagulation and fibrinolysis (0 h vs. 3 h and 24 h) were also evaluated using the Mann-Whitney U-test. The receiver operating characteristic (ROC) curve was constructed, and the area under the ROC curve (AUC) was used to assess the predictive ability of DIC scores for massive transfusion, MODS, and hospital death. Survival probability curves with and without a DIC diagnosis were derived based on the Kaplan-Meier method. Differences with a two-tailed p value of < 0.05 were considered statistically significant. The IBM SPSS 26.0 for MAC OSX software program (IBM Japan, Tokyo, Japan) was used for the statistical analyses and calculations.

Results

Characteristics of the patients

A total of 295 patients were registered. After the assessment of eligibility, 276 enrolled patients were divided into 121 DIC and 155 non-DIC patients based on the data immediately on presentation to the ED (0-h timepoint). The flow diagram showing patient screening and registration is presented as Fig. 1. Demographics of the patients are provided in Table 1. Almost all DIC patients (110/121, 90.9%) met the definition of SIRS. Higher ISS and revised trauma scores, and a higher prevalence of shock were observed in DIC patients than in non-DIC patients. The abbreviated injury scale (AIS) for individual organs and GCS at 0, 3, and 24 h are shown in Supplementary Table 2 (See Additional file 1). No differences in the AIS for the head was noted, but DIC patients had a lower GCS than non-DIC patients at presentation to the ED, which markedly worsened at 3 and 24 h after the presentation. The serial changes in DIC scores, platelet counts, and global markers of coagulation and fibrinolysis are shown in Supplementary Table 3 (See Additional file 1). DIC patients showed lower platelet counts, a prolonged prothrombin time and APTT, lower fibrinogen levels, and higher FDP levels and FDP/D-dimer ratios than non-DIC patients at 0, 3, and 24 h after presentation.

Outcomes Of The Patients

DIC patients were transfused with larger volumes of platelet concentrate, fresh-frozen plasma (FFP), and PRBCs at 3 and 24 h after admission to the ED than non-DIC patients (Table 1). As a result, the frequency of massive transfusion in DIC patients was higher than that in non-DIC patients ($p < 0.001$) (Table 2). The total SOFA scores, SOFA scores without coagulation scores, and all individual organ SOFA scores were significantly higher in DIC patients than in non-DIC patients. DIC patients showed a higher incidence of MODS than non-DIC patients ($p = 0.021$) and DIC patients showed more organs with dysfunction than non-DIC patients ($p < 0.001$). A higher mortality rate ($p < 0.001$) and fewer days from both ventilator's use and ICU stay were observed in DIC patients than in non-DIC patients. No patients died within 3 h after admission. All 9 patients who died within 24 h met the DIC diagnosis and their DIC score deteriorated from 0 to 3 h. The frequencies of shock and massive transfusion in 9 patients were 55.6% and 33.3% at 3 h, respectively (Supplementary Table 4. See Additional file 1).

Survival Probability And Outcome Prediction

The survival probability of the patients diagnosed with DIC immediately after the presentation to the ED was significantly lower than that in those without DIC (Log Rank $p < 0.001$) (Fig. 2). As shown in Fig. 3, the DIC scores immediately after presentation to the ED (0-h timepoint) and at 3 h after admission (3-h timepoint) showed a significant predictive ability for hospital death (Fig. 3A), massive transfusion (Fig. 3B) and the development of MODS (Fig. 3C) at 24 h after admission.

The levels of soluble fibrin and plasmin antiplasmin complex at the 0- and 3-h timepoints and PAI-1 at the 3-h timepoint are shown as box plots in Fig. 4. The values were higher in DIC patients than in non-DIC patients. The AUCs of soluble fibrin ($p = 0.001$) and plasmin antiplasmin complex ($p < 0.001$) at the 0- and 3-h timepoints and PAI-1 ($p = 0.015$) at the 3-h timepoint for predicting hospital death of the patients were

all significant (Fig. 5). In addition, the levels of soluble fibrin at the 0-h timepoint, plasmin antiplasmin complex at the 0-h timepoint, and PAI-1 at the 3-h timepoint showed a significant predictive performance for massive transfusion and MODS at 24 h after admission (Supplementary Table 5. See Additional file 1).

Discussion

This sub-analysis of a multicenter prospective study demonstrated the significant performance of DIC scores immediately after trauma for predicting a poor prognosis in severely injured trauma patients. The markedly low survival probability of DIC patients diagnosed immediately after trauma was also confirmed. The massive generation of thrombin and plasmin followed by the inhibition of fibrinolysis by PAI-1 in DIC patients also showed marked predictivity for a poor prognosis.

DIC immediately after trauma represents a fibrinolytic phenotype [6, 9]. In this phenotype of DIC, trauma patients need massive transfusion due to trauma-related bleeding as well as DIC-induced oozing-type bleeding at the surgical-site wounds, mucosal lesions, serosal surfaces and at the sites of indwelling catheters, etc. Massive thrombin formation-induced consumption coagulopathy and the time difference between immediate plasmin generation due to tissue-type plasminogen activator (t-PA) release from the Weibel-Palade bodies and the expression of PAI-1 mRNA leading to plasmin-mediated fibrin(ogen)olysis are main causes of bleeding immediately after trauma [6, 9]. Markedly high levels of soluble fibrin in DIC patients, as well as a reduction in platelet counts, low levels of fibrinogen, and prolonged prothrombin time and APTT, foster the consumption coagulopathy. Low fibrinogen levels as well as elevated FDP levels with high FDP/D-dimer ratios in DIC patients suggest fibrin(ogen)olysis. Immediate increases in the plasmin levels followed by an elevation of PAI-1 levels at 3-h timepoints indirectly support the notion of a time difference between the immediate t-PA release and the PAI-1 mRNA expression. The administration of a median 0 mL of intravenous fluids prior to the ED and significant decreases in platelet counts and fibrinogen levels from 0 to 3-h timepoints despite a large volume of platelet concentrate and FFP transfusion in DIC patients deny dilution coagulopathy.

The robustness of the present study is based on the confirmation of the results of previous studies using two prospectively obtained data points immediately after trauma. A single center retrospective study showed that DIC with a fibrinolytic phenotype diagnosed within 4 h after arrival at the ED contributed to a poor prognosis due to massive transfusion [11]. A multicenter retrospective study concluded that DIC diagnosed immediately after presentation to the ED could be used to predict massive transfusion for 24 h after admission, with an association between DIC and massive transfusion within 24 h also observed (odds ratio, 4.607, $p = 0.001$) [19]. The Kaplan-Meier curves for the time from presentation to the ED to reaching the critical thresholds of routine parameters for massive bleeding showed that the platelet counts, prothrombin time, and fibrinogen levels in DIC patients were significantly faster than those in non-DIC patients [20]. In addition, the time taken from the arrival at the ED to meet the definition of massive transfusion was shorter in DIC patients than in non-DIC patients. Hayakawa et al. [21] showed that DIC at an early phase of trauma associated with consumption coagulopathy and increased fibrinolysis required

more blood transfusions than was noted in non-DIC patients. Given these previous findings, the present results showing a good performance of DIC scores immediately after trauma to predict massive transfusion seem very reasonable.

The key point of DIC after trauma is that thrombin generation always underlies the changes in fibrinolytic systems as shown in Fig. 4 [6, 9, 22]. Regardless of the phenotype, DIC is always associated with massive thrombin generation; DIC with a fibrinolytic phenotype progresses to thrombotic phenotype along with the elevation of PAI-1 levels [21, 23]. The dynamics of soluble fibrin, plasmin and antiplasmin complex and PAI-1 observed in the present study suggest that this progression occurs approximately 3 h after trauma. Despite the equal severity of brain injury as assessed by the head AIS between the patients with and without DIC, an aggravation of GCS during the 24 h time period in DIC patients may suggest DIC-induced secondary brain injury due to progression of intracranial hemorrhaging or microvascular thrombosis.

The present study is significant for its confirmation that a DIC diagnosis affected the survival probability of severely injured trauma patients. Furthermore, DIC scores obtained immediately after trauma (median 49 min from injury) were proven to predict late-phase MODS and a poor outcome. MODS with a high mortality rate is a characteristic of DIC [6, 8]. Rapid progression of DIC from the fibrinolytic to the thrombotic phenotype by 3 h after arrival to the ED may be the reason for the development of MODS within 24 h after admission. Cabrera et al. [24] showed that trauma patients complicated with MODS had a specific gene expression within 120 min from injury, implicating the participation of innate immune cells, such as neutrophils at this stage of trauma. In addition, previous studies showing immediate changes in mitochondrial DAMPs, histones, neutrophils, and coagulation after trauma may support the results of the present study highlighting the predictive ability of the rapid onset of DIC on the later prognosis of the patients [7, 8, 10].

Another novel finding of the present study was that soluble fibrin, plasmin and antiplasmin complex and PAI-1 were able to predict massive transfusion, MODS and hospital mortality of severe trauma patients. DIC patients were associated with significantly higher levels of soluble fibrin, plasmin and antiplasmin complex and PAI-1 than non-DIC patients. In the main study of our series, increased levels of soluble thrombomodulin, a marker of endothelial injury, were observed in DIC patients [15]. Previous studies showed that MODS was more likely when the markers of endotheliopathy, e.g. soluble thrombomodulin, were increased immediately after trauma [25]. The generations of thrombin and plasmin, inhibition of fibrinolysis by PAI-1, and endothelial injury are the main pathomechanisms of DIC [6, 8], supporting the significant utility of DIC for predicting a poor outcome of trauma patients in the present study.

Trauma-induced coagulopathy is defined as a pre-stage of DIC and progresses to DIC as a result of dysregulated inflammatory and coagulofibrinolytic responses to trauma [26]. When the trauma is sufficiently severe, therefore, DIC develops immediately after trauma without passing through trauma-induced coagulopathy stage [15]. Previous studies have shown that trauma-induced coagulopathy was a significant risk factor of MODS [27], and was an independent predictor of MODS and mortality in severe

trauma [28, 29]. These studies indirectly strengthen the present finding of the significant performance of DIC in predicting MODS and hospital mortality.

Several limitations associated with the present study warrant mention. Although this study was a sub-analysis of prospectively collected data, the data were retrospectively analyzed and included missing values. The use of tranexamic acid was equally distributed between the two groups, but the effects of tranexamic acid on the obtained results were not elucidated. The present study was a single national study conducted in a developed country, which may limit the global generalization of the obtained results worldwide.

Conclusions

The present study showed that the diagnosis of DIC immediately after trauma was associated with a lower survival probability and higher mortality rate than no such diagnosis. DIC scores obtained immediately after presentation to the ED were able to predict massive transfusion, MODS, and hospital death of severe trauma patients. Substantial thrombin and plasmin generation followed by elevation of the PAI-1 levels, the main pathomechanisms of DIC, also predicted massive transfusion, MODS, and hospital mortality. Therefore, the recognition of DIC at a very early phase of trauma is important in order to predict the outcome of severely injured trauma patients.

Abbreviations

DIC: Disseminated intravascular coagulation; MODS: Multiple organ dysfunction syndrome; SOFA: Sequential organ failure assessment; SIRS: Systemic inflammatory response syndrome; DAMPs: Damage-associated molecular patterns; NETs: Neutrophil extracellular traps; JAAM: The Japanese Association for Acute Medicine; FORECAST: Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma; ICUs: Intensive-care units; UMIN-CTR: University Hospital Medical Information Network Clinical Trial Registry; ISS: Injury Severity Score; INR: International Normalized Ratio; PRBCs: Packed red blood cells; ED: Emergency department; GCS: Glasgow Coma Scale; PAI-1: Plasminogen activator inhibitor-1; APTT: Activated partial thromboplastin time; FDP: Fibrin/fibrinogen degradation products; ROC: Receiver operating characteristic; AUC: Area under the ROC curve; AIS: Abbreviated injury scale; FFP: Fresh-frozen plasma; t-PA: Tissue-type plasminogen activator

Declarations

Ethics approval and consent to participate

This study was approved by the JAAM and the Ethics Committee of each hospital (JAAM, 2014-01; Hokkaido University Graduate School of Medicine, Head institute of the FORECAST group, 014-0307) and performed in accordance with Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and/or analyzed in the present study is available from the corresponding author on reasonable request.

Competing interests

None of the authors declare any conflicts of interests in connection with the submitted article. Gando S reported receiving personal fees from Asahi Kasei Pharma America Inc. and Asahi Kasei Pharma Japan Inc. outside the submitted work. Shiraishi A reported receiving personal fees from CSL Behring outside the submitted work. The other authors have no conflict of interest to declare.

Funding

This study was supported by the Japanese Association for Acute Medicine (JAAM, 2014-01).

Authors' contributions

TW, AS, and SG analyzed study results, interpreted the data, drafted the manuscript and equally contributed to this study. AS checked the statistical methods and results. AS, SG, KY, SF, DS, SK, HO, TA, TM, JS, JK, NT, RT, KT, NY, TT, TN, TH, KO, YS, AH, TM, MU, SF, YU, and YO planned the study, decided the methods, developed web-based registration system, discussed the obtained results and critically revised the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

The JAAM FORECST Study Group (email address: jaam-6@bz04.plala.or.jp) thanks Shuta Fukuda for his special assistance in completing the study.

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Kameda Medical Center (Atsushi Shiraishi); Sapporo Higashi Tokushukai Hospital (Satoshi Gando); Osaka Medical College (Kazuma Yamakawa); Keio University School of Medicine (Seitaro Fujishima, Junichi Sasaki); National Defence Medical College (Daizoh Saitoh); Tohoku University Graduate School of Medicine (Shigeki Kushimoto), Osaka University Graduate School of Medicine (Hiroshi Ogura); Tsukuba Memorial Hospital (Toshikazu Abe); University of Occupational and Environmental Health (Toshihiko Mayumi); Kobe University Graduate School of Medicine (Joji Kotani); Aichi Medical University Hospital (Naoshi Takeyama); Yamaguchi University Hospital (Ryosuke Tsuruta); Kawasaki Municipal Hospital (Kiyotsugu Takuma); Kurume University (Norio Yamashita); Aizu Chuo Hospital (Shin-ichiro Shiraishi); Teikyo University School of Medicine (Hiroto Ikeda); Kawasaki Medical School (Yasukazu Shiino); Kyorin University School of Medicine (Takehiko Tarui); Chiba University Graduate School of Medicine (Takaaki Nakada); St. Luke's International Hospital (Toru Hifumi); Kitakyushu City Yahata Hospital (Kohji Okamoto); Saga University Hospital (Yuichiro Sakamoto); Center Hospital of the National Center for Global Health and Medicine (Akiyoshi Hagiwara); Nippon Medical School (Tomohiko Masuno); Community Healthcare Organization, Chukyo Hospital (Masashi Ueyama); Osaka General Medical Center (Satoshi Fujimi, Yutaka Umemura), Tokyo Medical and Dental University, (Yasuhiro Otomo)

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Figures

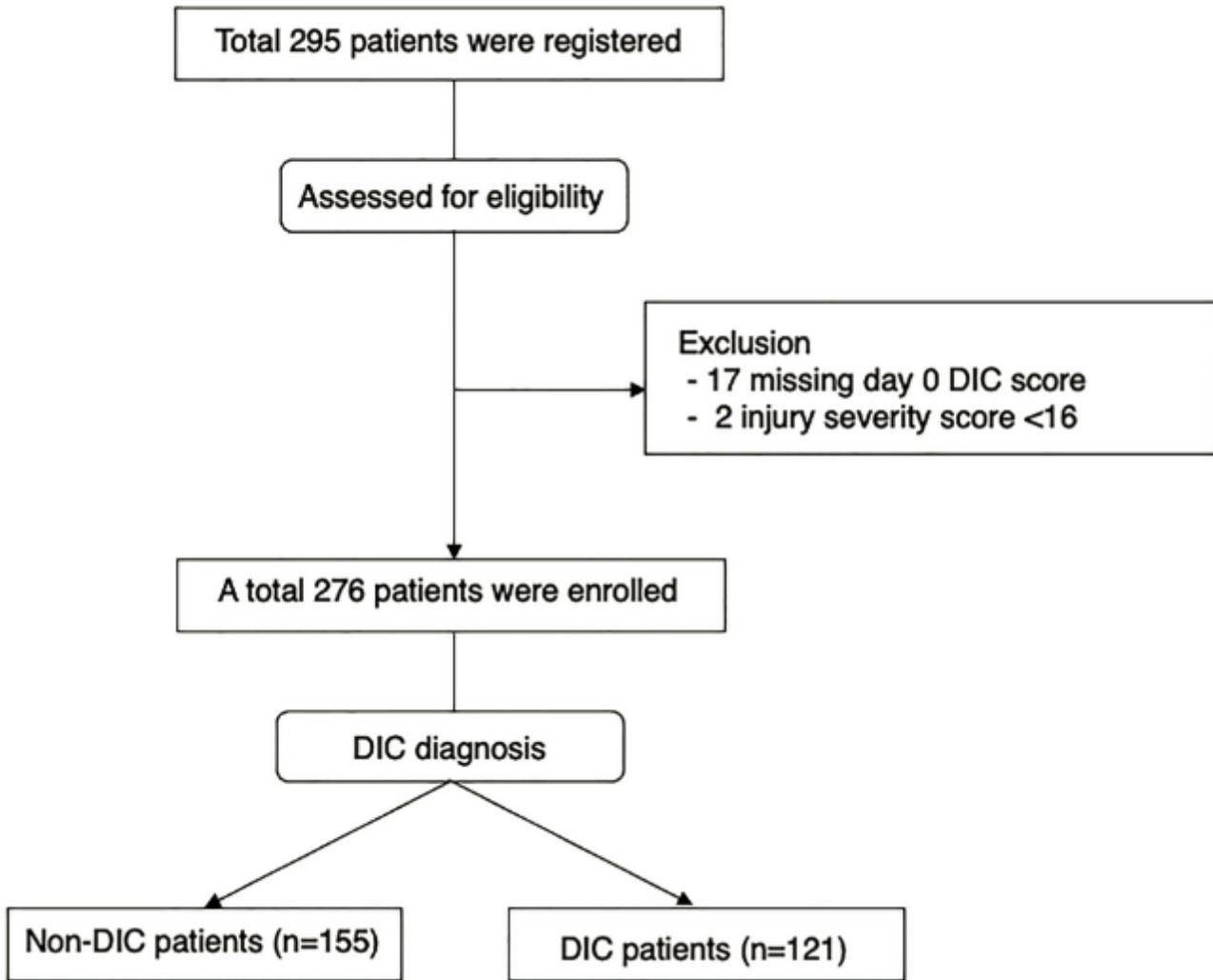


Figure 1

Flow diagram showing patients screening and enrollment

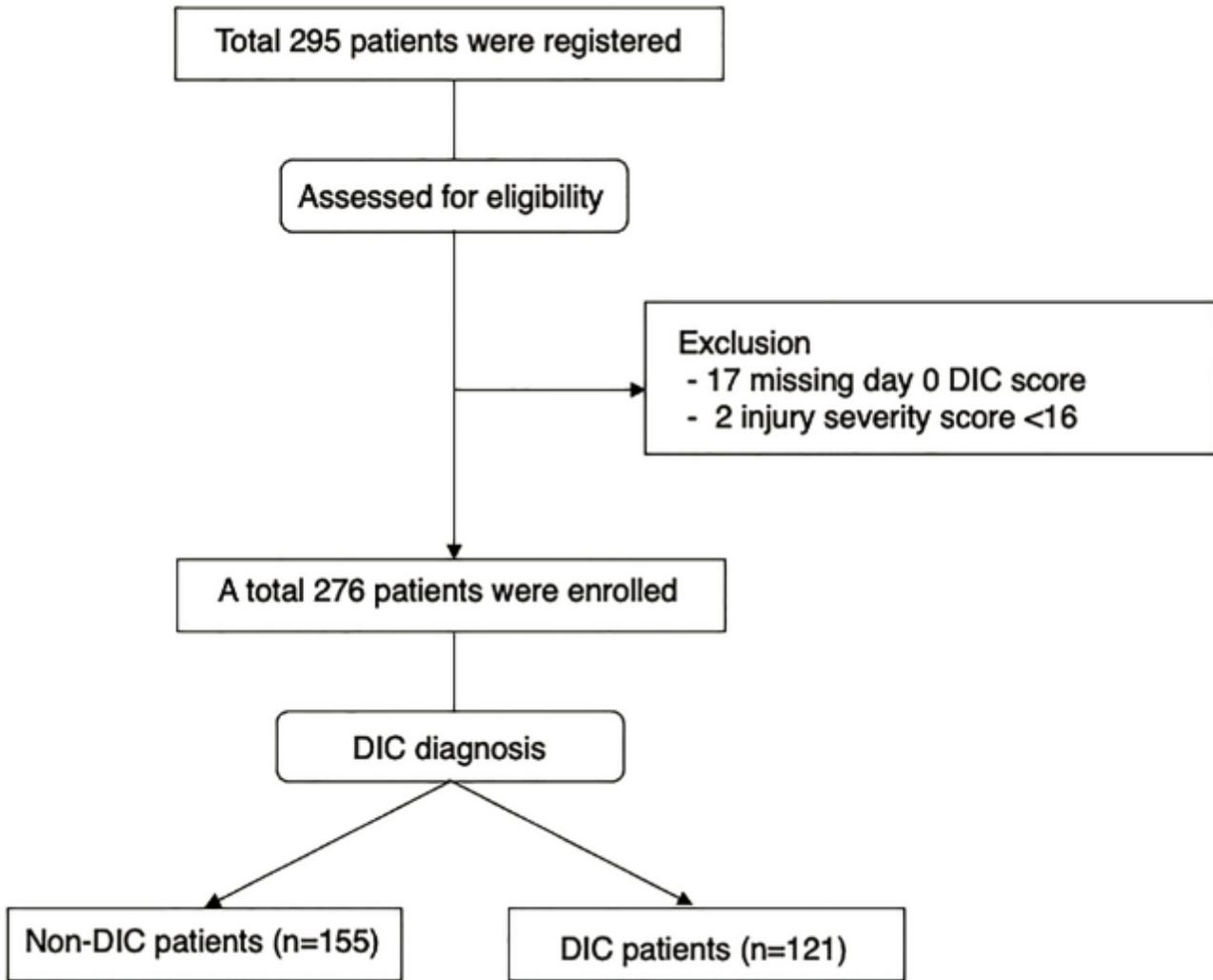


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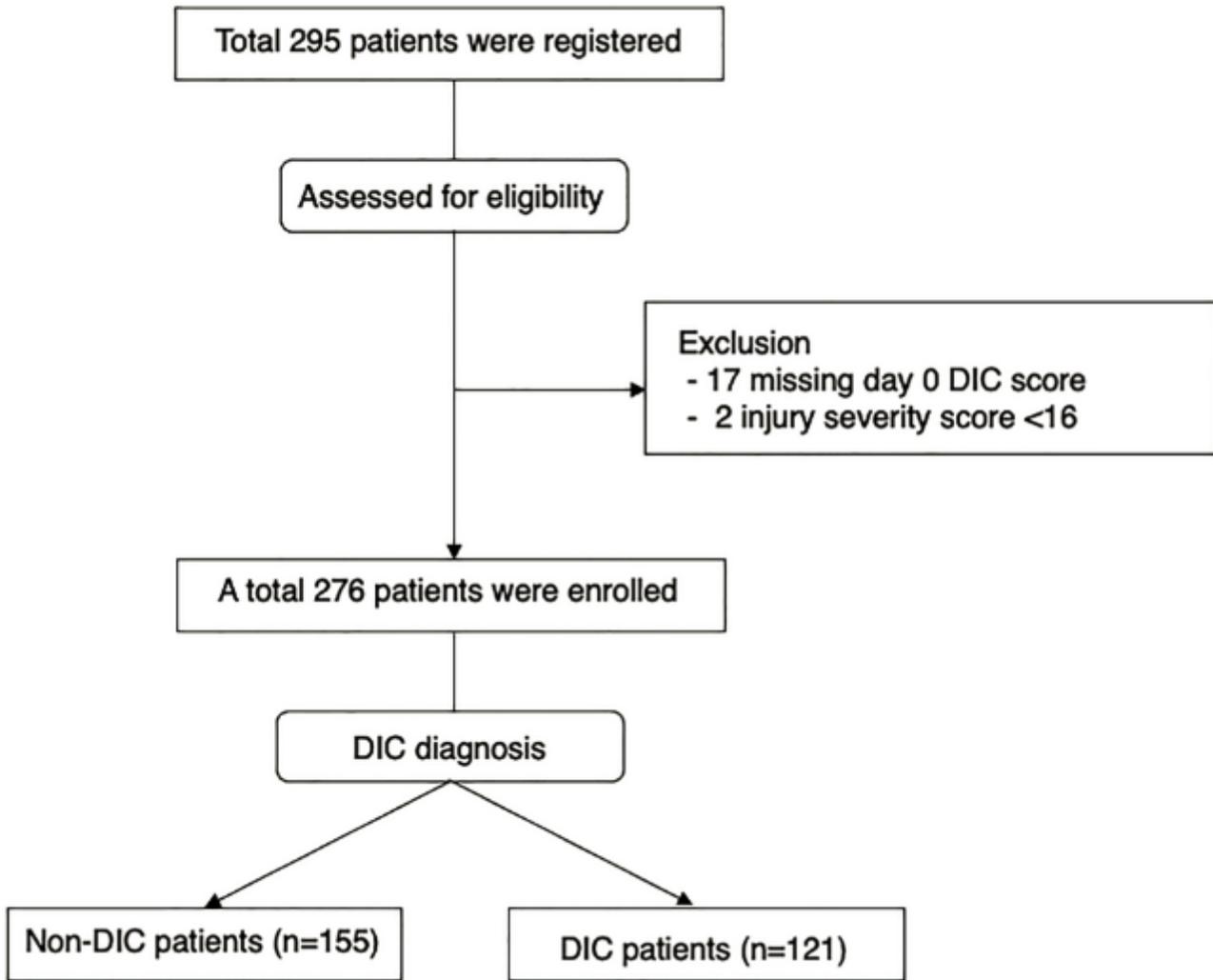


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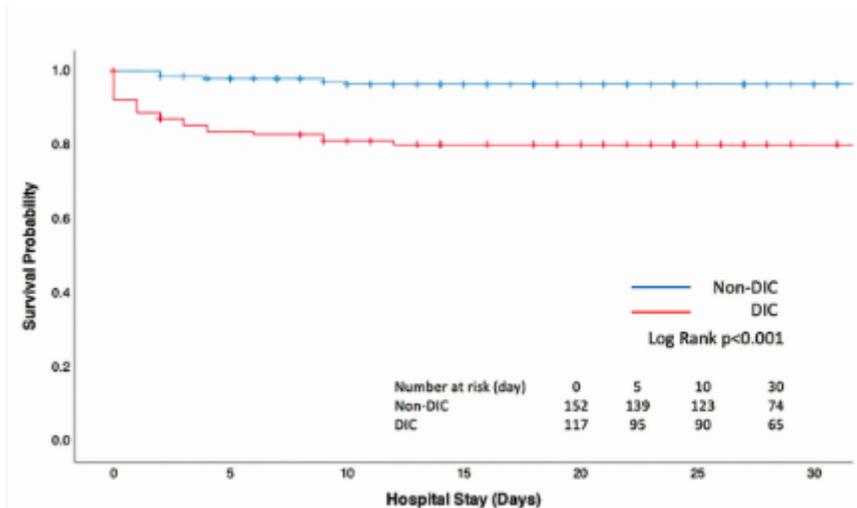


Figure 2

Kaplan-Meier survival probability curves for mortality during hospitalization. Numbers at risk represent the number of the patients with or without disseminated intravascular coagulation (DIC) at risk of death at the indicated days.

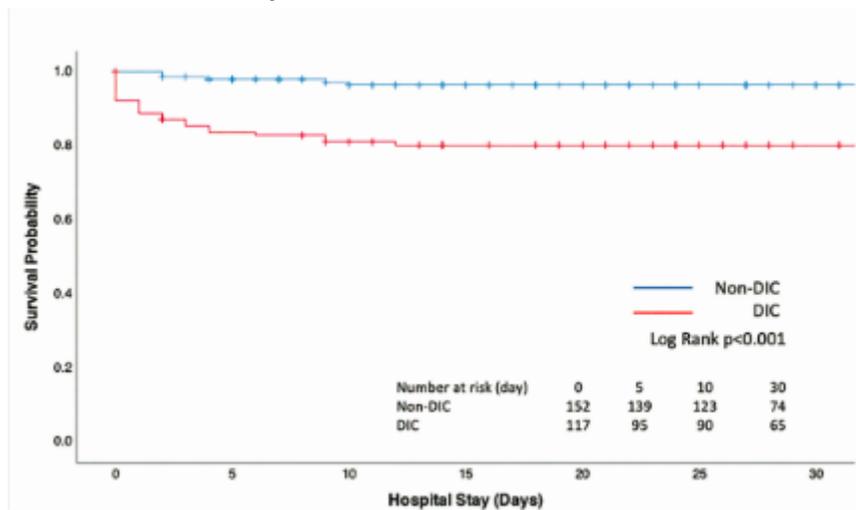


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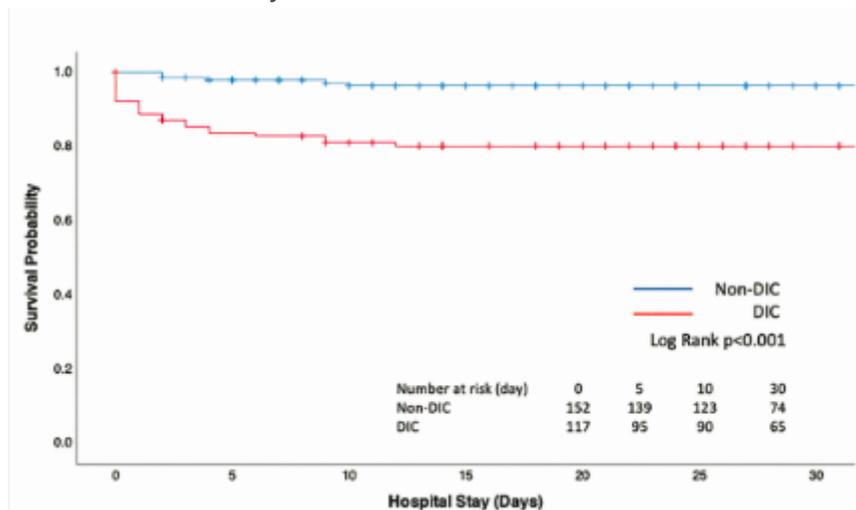


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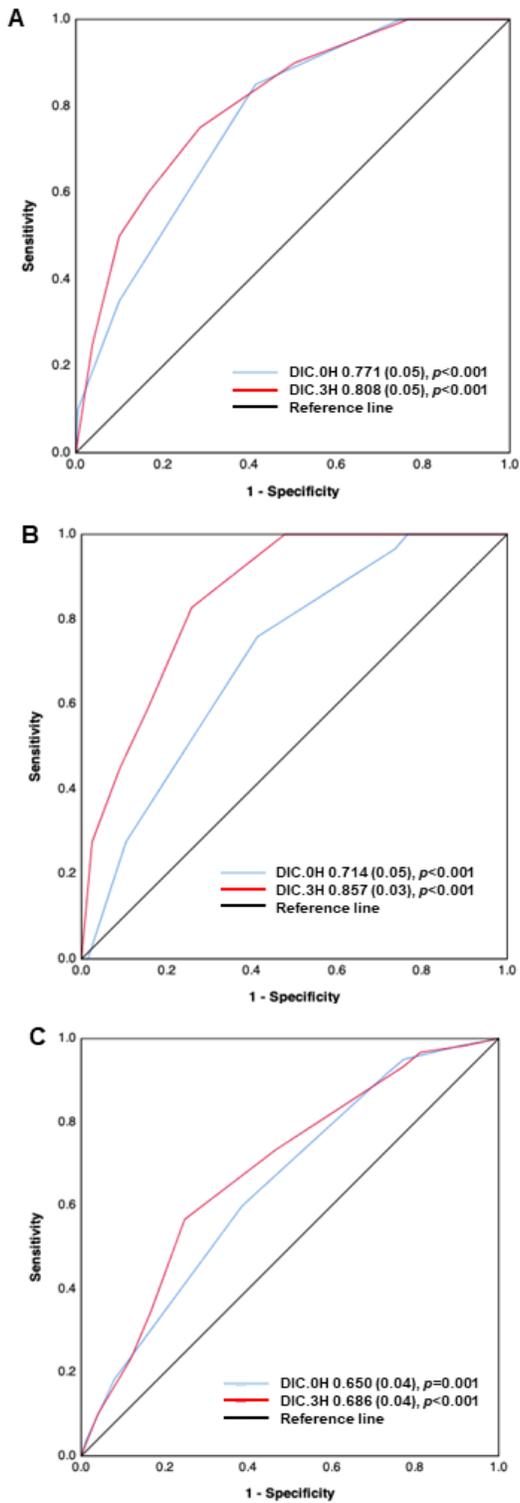


Figure 3

Receiver operating characteristics (ROC) curves of disseminated intravascular coagulation (DIC) scores at 0 h and 3 h after presentation to the emergency department (ED) to predict hospital death (A), massive transfusion (B) and multiple organ dysfunction syndrome (MODS) (C) at 24 h after presentation to the ED. The number indicates the area under the ROC curve (AUC) (standard error).

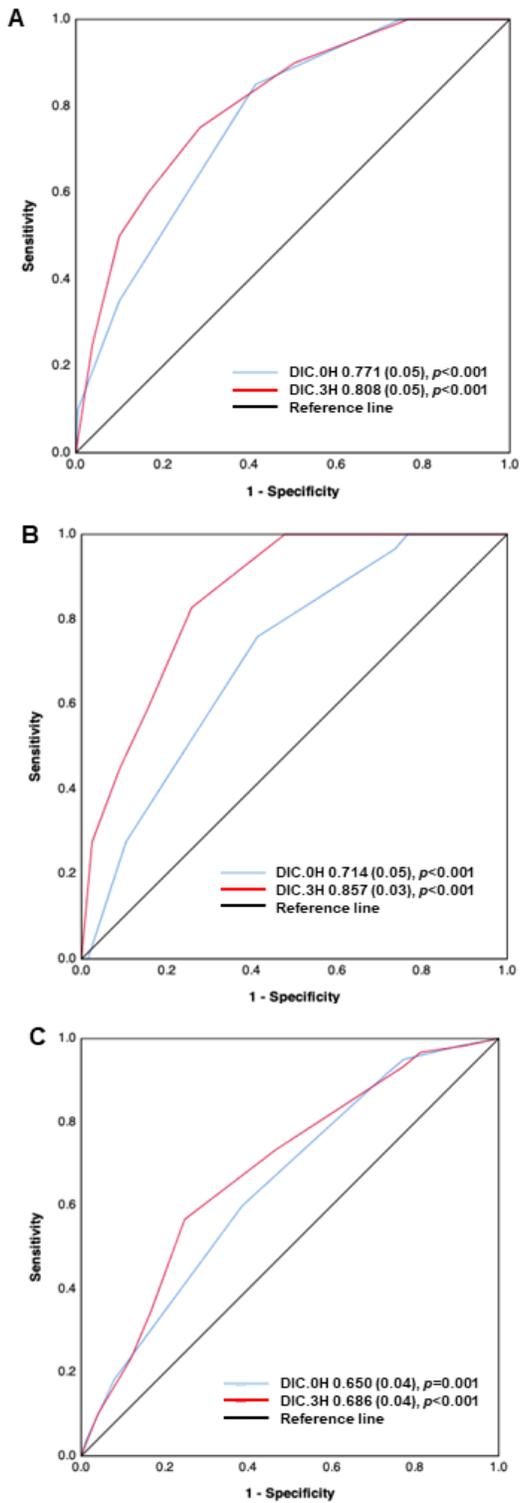


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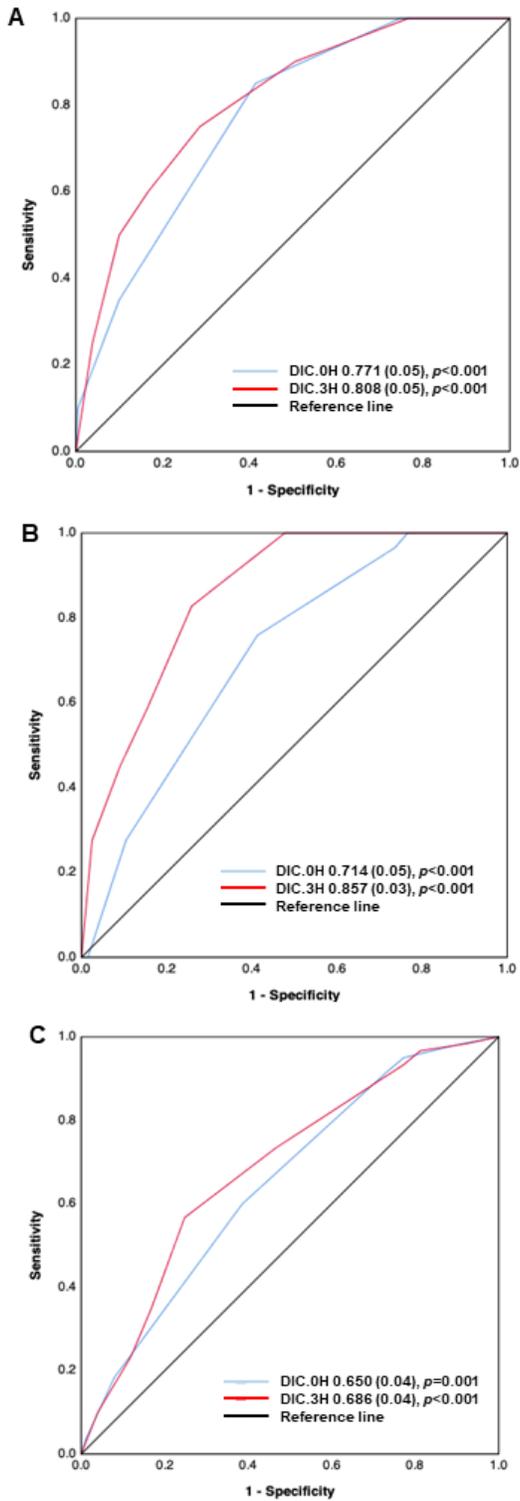


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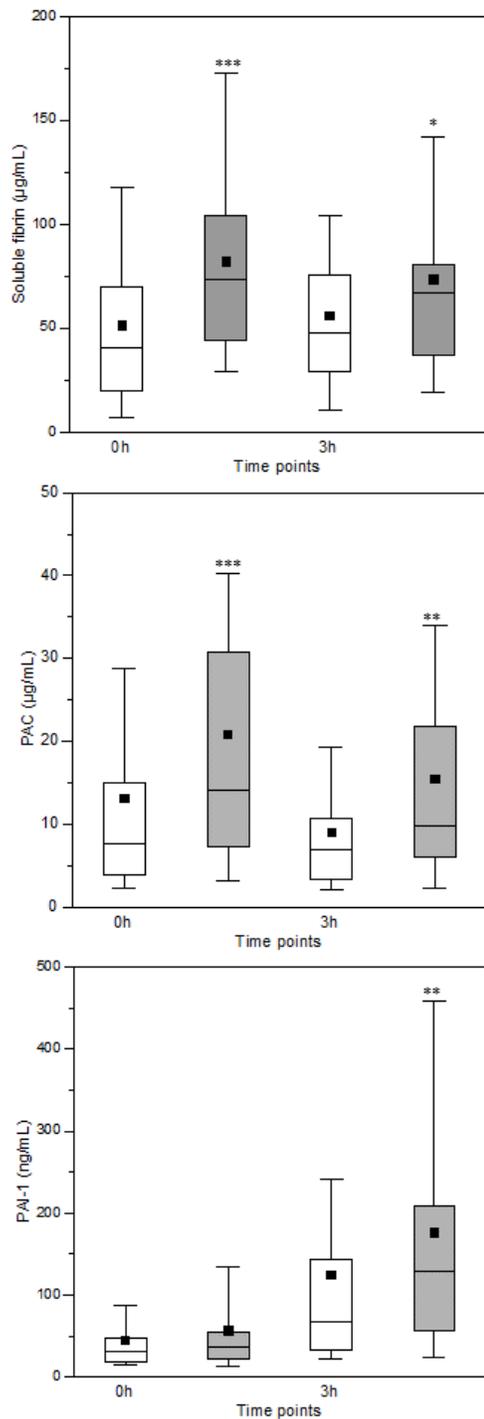


Figure 4

Box plots for soluble fibrin, plasmin and antiplasmin complex (PAC), and plasminogen activator inhibitor-1 (PAI-1) at 0 h and 3 h after presentation to the emergency department. Disseminated intravascular coagulation (DIC) patients showed significantly higher values of soluble fibrin and PAC at 0 and 3 h and PAI-1 at 3 h than those of non-DIC patients. White box, non-DIC patients; grey box, DIC patients. Horizontal

bars in the box indicate the median (middle) and interquartile ranges (upper 25% and lower 75%). Black boxes are mean values. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. non-DIC patients.

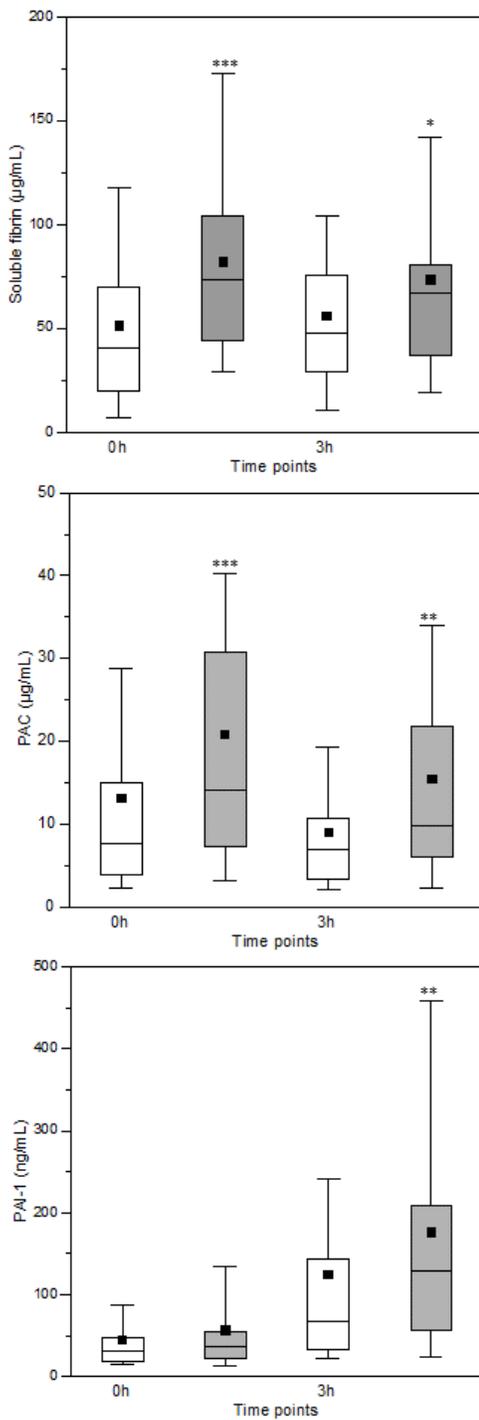


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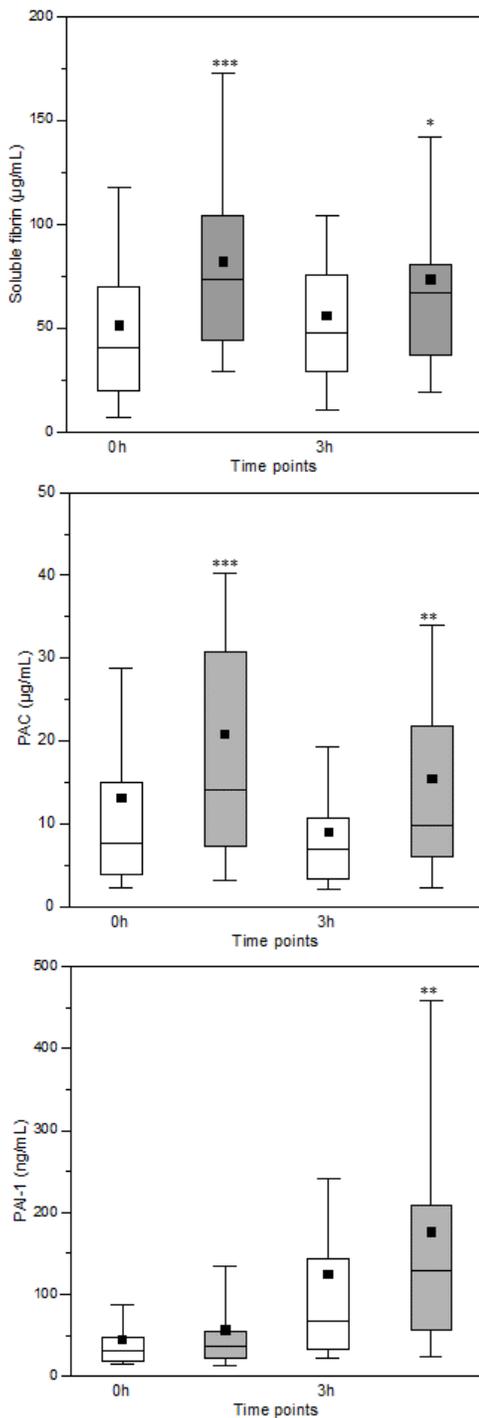


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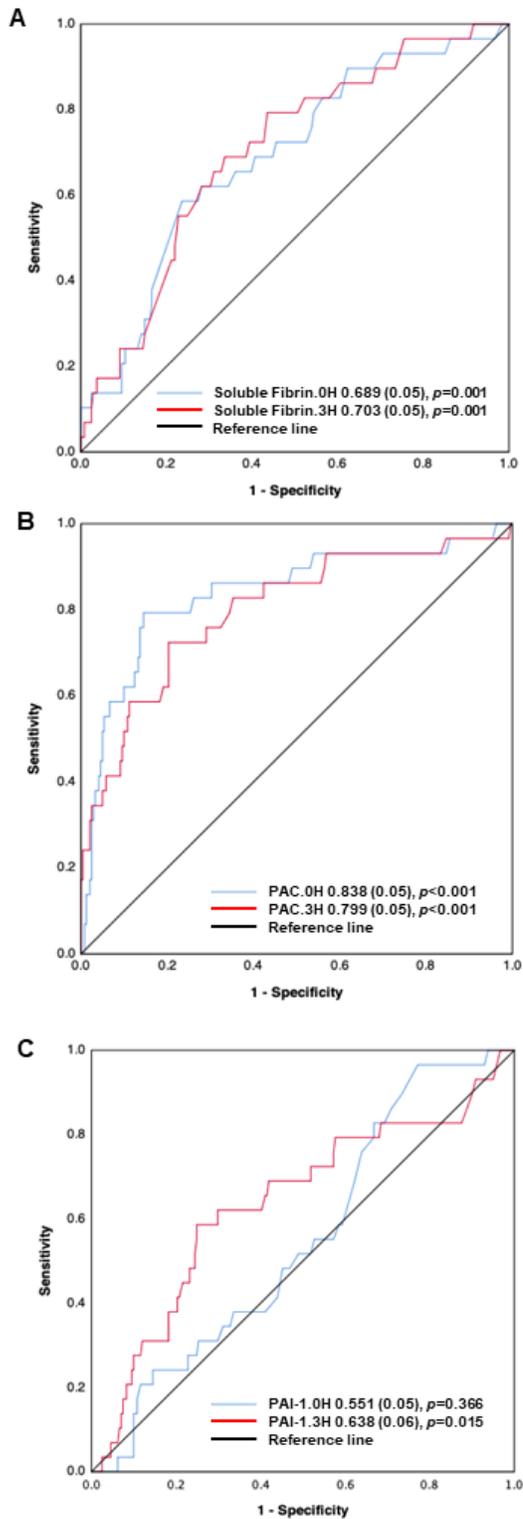


Figure 5

Receiver operating characteristics (ROC) curves of soluble fibrin, plasmin and antiplasmin complex (PAC) and plasminogen activator inhibitor-1 (PAI-1) at 0 h and 3 h after presentation to the emergency department to predict hospital death. The number indicates the area under the ROC curve (AUC) (standard error).

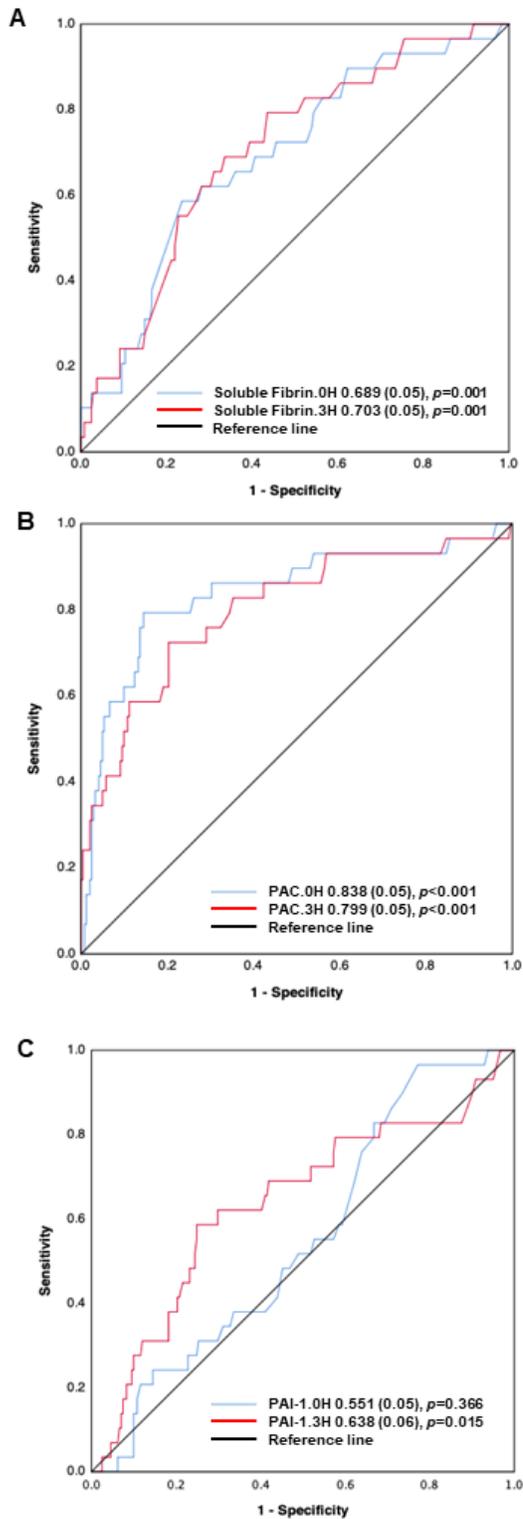


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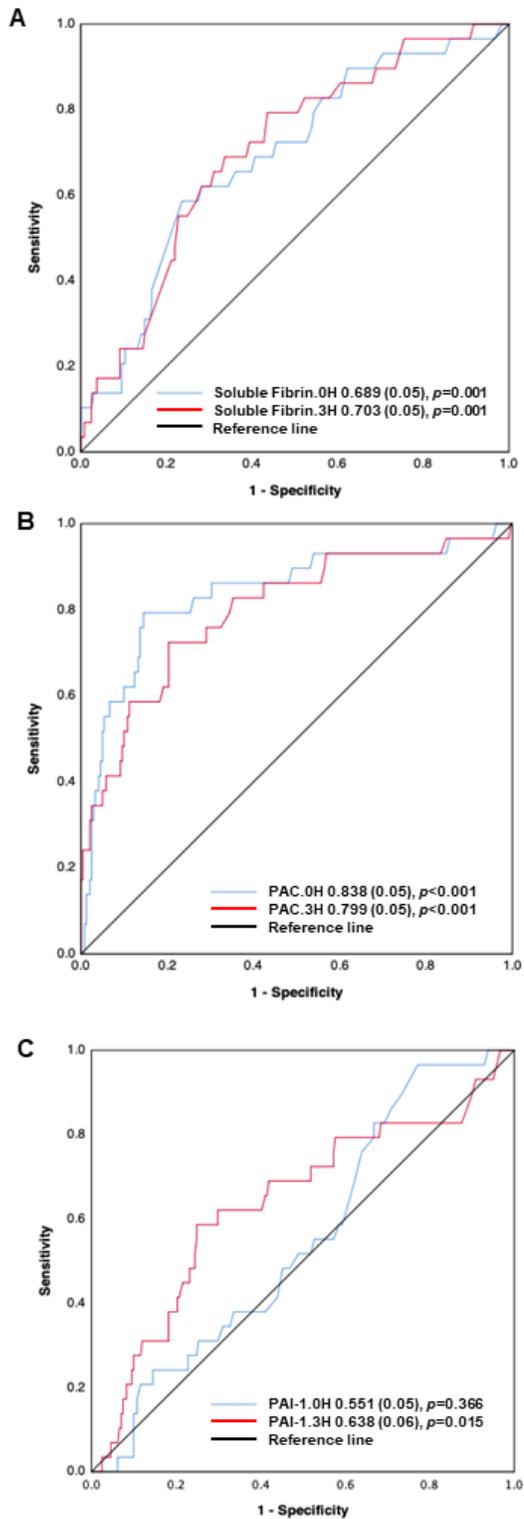


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