Effects of tranexamic acid on coagulofibrinolytic markers during the early stage of severe trauma

A propensity score–matched analysis

Satoshi Gando, MDb,e,*, Atsushi Shiraishi, MDc, Takeshi Wada, MDa, Kazuma Yamakawa, MDb, Seitaro Fujisawa, MDa, Daizoh Saitoh, MDa, Shigeki Kushimoto, MDa, Hiroshi Ogura, MDa, Toshikazu Abe, MDi, Toshihiko Mayumi, MDa, Junichi Sasaki, MDa, Joji Kotani, MDm, Naoshi Takeyama, MDa, Ryosuke Tsuruta, MDa, Kiyotsugu Takuma, MDa, Shin-ichiro Shiraishi, MDd, Yasuhashi Shino, MDa, Taka-aki Nakada, MDh, Kohji Okamoto, MDh, Yuichiro Sakamoto, MDh, Akiyoshi Hagiwara, MDh, Satoshi Fujimi, MDh, Yutaka Umemura, MDh, Yasuhiro Otomo, MDh, for the JAAM FORECAST TRAUMA Study Group

Abstract
Tranexamic acid (TXA) reduces the risk of bleeding trauma death without altering the need for blood transfusion. We examined the effects of TXA on coagulation and fibrinolysis dynamics and the volume of transfusion during the early stage of trauma. This subanalysis of a prospective multicenter study of severe trauma included 276 patients divided into propensity score–matched groups with and without TXA administration. The effects of TXA on coagulation and fibrinolysis markers immediately at (time point 0) and 3 hours after (time point 3) arrival at the emergency department were investigated. The transfusion volume was determined at 24 hours after admission. TXA was administered to the patients within 3 hours (median, 64 minutes) after injury. Significant reductions in fibrin/fibrinogen degradation products and D-dimer levels from time points 0 to 3 in the TXA group compared with the non-TXA group were confirmed, with no marked differences noted in the 24-hour transfusion volumes between the 2 groups. Continuously increased levels of soluble fibrin, a marker of thrombin generation, from time points 0 to 3 and high levels of plasminogen activator inhibitor-1, a marker of inhibition of fibrinolysis, at time point 3 were observed in both groups. TXA inhibited fibrin(ogen)olysis during the early stage of severe trauma, although this was not associated with a reduction in the transfusion volume. Other confounders affecting the dynamics of fibrinolysis and transfusion requirement need to be clarified.

Abbreviations: DIC = disseminated intravascular coagulation, ED = emergency department, FDP = fibrin/fibrinogen degradation product, FORECAST = Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma, ISS = Injury Severity Score, JAAM = Japanese Association for Acute Medicine, PAI-1 = plasminogen activator inhibitor-1, SOFA = sequential organ failure assessment, TAFI = thrombin-activatable fibrinolysis inhibitor, TPA = tissue-type plasminogen activator, TXA = tranexamic acid, uPA = urokinase-type plasminogen activator.

Keywords: coagulation, fibrinolysis, propensity score, tranexamic acid, trauma
1. Introduction

The CRASH-2 trial confirmed a significant reduction in the risk of death due to bleeding in trauma patients administered tranexamic acid (TXA).\[1\] A subsequent exploratory analysis of the CRASH-2 study showed that early administration of TXA within 3 hours was more effective than its later use after trauma.\[2\]

The synthetic lysine analogue TXA exerts antifibrinolytic activity by binding to the lysine-binding site of plasminogen, thereby preventing plasminogen binding to the lysine residue on fibrin. Plasminogen conversion to plasmin by tissue-type plasminogen activator (tPA) occurs even after TXA binding to plasminogen; however, TXA-bound plasminogen (can) neither bind to fibrin nor degrade fibrin.\[3\] The main mechanism underlying the effects of TXA within the CRASH-2 trial is, therefore, considered to involve the inhibition of fibrin clot degradation at injury sites.\[4\]

However, the original study failed to demonstrate any marked differences in the transfusion rate of blood products.\[1\] Based on this result, other mechanisms underlying the ability of TXA to reduce the rate of death due to bleeding trauma have been speculated.\[5\] The nonfibrinolytic actions of TXA, including its anti-inflammatory properties, following severe trauma have been extensively reviewed.\[6\] Although the target population was the patients undergoing cardiac surgery, TXA showed immunomodulatory effects associated with reduced postoperative infection rates, independent of its effects on the inhibition of fibrinolysis.\[7\]

While several viewpoints have been proposed concerning the ability of TXA to reduce the rate of death due to bleeding, the actual dynamics of coagulation and fibrinolysis during TXA use in trauma patients have not yet been elucidated. The present study explored the effects of TXA on the dynamics of coagulation and fibrinolysis in patients administered the agent immediately after severe trauma. We hypothesized that TXA would inhibit fibrin(ogen)olysis and reduces the transfusion requirements in these patients.

2. Methods

2.1. Study design and setting

We conducted a retrospective analysis of a multicenter prospective study by the Japanese Association for Acute Medicine (JAAM) Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST).\[8\] The JAAM FORECAST TRAUMA was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR ID: UMIN00019588). The participants were prospectively recruited from April 2016 to January 2018 from 39 emergency departments (EDs) and intensive care units in tertiary hospitals.

This study was approved under the condition that written informed consent be obtained from each patient or next of kin by the JAAM and the Ethics Committee of each hospital (JAAM, 2014-01; Hokkaido University Faculty of Medicine, head institute of the FORECAST group, 014-0307) and was performed in accordance with the Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines was applied in the reporting of this study.

2.2. Participants

The JAAM FORECAST TRAUMA study enrolled severely injured 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. In addition, 27 healthy volunteers without age or sex matching were enrolled to obtain control values of measured markers.

2.3. Aims

The primary aim of this study was to compare the dynamics of coagulation and fibrinolysis markers between the patients administered TXA (TXA group) and control patients without TXA administration (non-TXA group). The second aim was to evaluate the effects of TXA on the needs for transfusion within 24 hours after admission.

2.4. Definitions and diagnoses

The severity of injury was assessed on anatomical and physiological bases according to the ISS and revised trauma score, respectively. Severe trauma was defined as an ISS >16. Isolated brain injury was defined as an abbreviated injury scale of the head and neck of ≥4 and an abbreviated injury scale of other body parts of ≤2. Disseminated intravascular coagulation (DIC) was diagnosed at time point 0 based on the JAAM DIC diagnostic criteria using the prothrombin time international normalized ratio as a substitute for the prothrombin time ratio.\[9\] Organ dysfunction was evaluated using the sequential organ failure assessment (SOFA) score.\[10\] A systolic blood pressure <90 mm Hg at the scene or at the ED and lactate levels >2 mmol/L at the ED were defined as being in shock. TXA was administered based on the protocol of the CRASH-2 trial depending on each institution’s discretion.\[1,2\]

2.5. Data sources and measurements

Immediately after arrival at the ED (0-hour time point, time point 0) and 3 hours after admission (3-hour time point, time point 3), 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 central laboratory of the LSI Medience Corporation (Tokyo Japan). The following markers were measured:

- Soluble fibrin (marker of direct thrombin generation; LA, IATRO SFII; LSI Medience), Plasmin and α2-plasmin inhibitor (antiplasmin) complex (marker of plasmin generation; LPIA, LPIA-ACE PPI II; LSI Medience), α2-plasmin inhibitor (antiplasmin; HemosII. Plasmin Inhibitor; Instrumental Laboratory, Bedford, MA), Plasminogen activator inhibitor-1 (PAI-1; LA, LPIA•PAI test; LSI Medience), and D-dimer (LPIA, LPIA GENESIS D-dimer; LSI Medience).

Blood gas analyses were used to measure lactate levels. In addition, measurements of the platelet counts, prothrombin time (seconds, international normalized ratio), activated partial thromboplastin time, fibrinogen levels, and fibrin/fibrinogen degradation product (FDPs; marker of fibrin(ogen)olysis) levels were performed at 0-, 3-, and 24-hour time points after the arrival at the ED. The DIC scores were calculated at the 0-, 3-, 24-hour time points, and SOFA scores were obtained at 24 hours after admission to the ED.

2.6. Propensity score matching

To avoid bias, the clinically relevant potential confounders for the exposure of TXA and non-TXA were defined as follows: age, sex, intravenous fluid volume prior to ED, time from injury...
to ED, shock, DIC, Glasgow Coma Scale, systolic blood pressure, body temperature, pH, lactate level, and revised trauma score at time point 0, the diagnosis of isolated brain injury, ISS, emergency operation, time from admission to the operation, 3-hour transfusion volumes of packed red blood cells, fresh frozen plasma, platelet concentrate, and fibrinogen concentrates.

The propensity score was derived using a binary logistic regression model with forced entry method including the above potential confounders and baseline characteristics of the TXA and non-TXA groups with $P < .05$. Model fitness was confirmed by the Hosmer-Lemeshow statistic ($P = .836$ and C statistic (area under the receiver operating characteristic curve, 0.750; $P = .000$). One-to-one propensity score matching was performed by nearest neighbor matching using 25% of the standard deviation of the propensity scores (0.036). The balance of variables were estimated using the $P$ value and standardized mean difference.

2.7. Statistical analyses

Measurements are expressed as the median to 75th interquartile range or number (percentage). Missing values were used without manipulation, and the sensitivity analysis was not applied. Differences between TXA and non-TXA were analyzed in the propensity-matched group. Differences in demographics and measured parameters between the 2 groups were compared with the Mann-Whitney $U$ test for continuous variables, and either the $\chi^2$ test or Fisher exact test was used for nominal variables. Intragroup differences in coagulofibrinolytic markers between time points 0 and 3 were analyzed using the Wilcoxon rank-sum test. All authors as statistical expertise checked the statistical analyses. Differences with a 2-tailed $P$ value of $<.05$ were considered statistically significant. The IBM SPSS 27.0 for MAC OSX software program (IBM Japan, Tokyo, Japan) was used for the statistical analyses, calculations, and propensity score matching.

### Table 1

| Demographics | Before propensity score matching | After propensity score matching |
|--------------|----------------------------------|----------------------------------|
| **Non-TXA**  | **TXA**                           | **Non-TXA**  | **TXA**                           |
| (n = 141)    | (n = 135)                         | (n = 36)    | (n = 36)                         |
| **P** value  | SMD                              | **P** value  | SMD                              |
| Age (yr)     | 60 (42–69)                       | 58 (39–74)  | .856                             | 0.059                         |
| Male gender, n(%) | 93 (66)                         | 90 (67)    | .901                             | 0.042                         |
| Time from injury to TXA (min) | -                             | 64 (40–96) | -                                | -                             |
| Blunt Injury, n (%) | 135 (95.7)                     | 133 (98.5) | .279                             | 0.167                         |
| Isolated brain injury, n (%) | 20 (14.2)                       | 14 (10.4)  | .325                             | 0.155                         |
| ISS          | 25 (18–29)                       | 29 (22–38) | .000                             | −0.325                        |
| Revised trauma score | 7.8 (6.9–7.8)                 | 6.9 (5.2–7.8) | .000                             | 0.565                         |
| DIC, n (%)   | 55 (39.0)                        | 66 (48.9)  | .098                             | 0.200                         |
| DIC score   | 3 (1–4)                          | 3 (3–4)    | .016                             | −0.290                        |
| Shock, n (%) | 25 (17.9)                        | 36 (26.7)  | .079                             | 0.216                         |
| Operation within 24 h after admission, n (%) | 64 (47.1)                      | 86 (64.7)  | .004                             | −0.36                         |
| Time from admission to operation (min) | 148 (100–263)                 | 137 (89–250) | .476                             | −0.068                        |
| Time from injury to ED (min) | 46 (35–74)                      | 46 (31–68) | .216                             | 0.206                         |
| Intravenous fluids prior to ED (mL) | 0 (0–100)                      | 0 (0–200)  | .002                             | −0.377                        |

At the emergency department

| Glasgow Coma Scale | 14 (12–15) | 12 (6–14) | .000 | 0.599 | 14 (9–15) | 14 (11–14) | .765 | −0.035 |
| Systolic blood pressure (mm Hg) | 129 (103–153) | 132 (103–154) | .538 | −0.108 | 131 (97–153) | 132 (102–143) | .875 | 0.043 |
| Diastolic blood pressure (mm Hg) | 76 (62–93) | 78 (62–96) | .393 | −0.096 | 79 (52–95) | 76 (59–89) | .827 | 0.129 |
| Heart rate (beats/min) | 88 (73–105) | 91 (76–106) | .269 | −0.154 | 89 (72–99) | 92 (79–110) | .333 | 0.201 |
| Respiratory rate (breath/min) | 20 (16–26) | 21 (18–27) | .133 | −0.283 | 20 (17–25) | 23 (20–28) | .055 | −0.483 |
| Body temperature (°C) | 36.5 (35.8–36.8) | 36.4 (35.9–36.8) | .568 | 0.131 | 36.8 (36.0–36.9) | 36.6 (36.0–36.9) | .730 | −0.019 |
| Lactate (mmol/L) | 2.4 (1.7–3.8) | 2.8 (1.9–4.0) | .212 | −0.080 | 2.5 (1.7–3.9) | 2.9 (1.6–4.4) | .735 | −0.002 |
| pH | 7.38 (7.34–7.43) | 7.36 (7.32–7.40) | .002 | 0.298 | 7.37 (7.34–7.42) | 7.38 (7.33–7.40) | .693 | 0.117 |

3-h transfusion

| Packed red blood cells (U) | 0 (0–0) | 0 (0–0) | .024 | −0.156 | 0 (0–0) | 0 (0–0) | .812 | 0.045 |
| Fresh frozen plasma (U) | 0 (0–0) | 0 (0–0) | .004 | −0.246 | 0 (0–0) | 0 (0–0) | .626 | 0.022 |
| Platelet concentrate (U) | 0 (0–0) | 0 (0–0) | .953 | 0.011 | 0 (0–0) | 0 (0–0) | .984 | 0.105 |
| Fibrinogen (g) | 0 (0–0) | 0 (0–0) | .104 | −0.181 | 0 (0–0) | 0 (0–0) | .645 | 0.108 |

Values are presented as median with the 25th to 75th interquartile range or number (percentage). DIC = disseminated intravascular coagulation, ED = emergency department, ISS = Injury Severity Score, SMD = standardized mean difference, TXA = tranexamic acid.
3. Results

3.1. Classifications of the patients

The JAAM FORECAST TRAUMA–registered 276 patients were classified into 2 groups based on the presence or absence of tranexamic administration. After propensity score matching, 36 patients each in the TXA and non-TXA groups were included (Fig. 1).

3.2. Effects of TXA

The patient demographics after propensity score matching in TXA and non-TXA groups are shown in Table 1. Table 2 shows the patients’ outcomes after propensity score matching, indicating no marked differences in the 24-hour transfusion volume or SOFA scores between TXA and non-TXA groups. TXA was administered to the patients within 3 hours (median, 64 minutes) after injury (Table 1).

Both the TXA and non-TXA groups showed consistently higher levels of soluble fibrin and lower levels of antiplasmin from time points 0 to 3 than healthy controls. The plasmin and antiplasmin complex levels were decreased in both groups at time point 3 (P < .05), but only the TXA groups showed significant decreases in FDP (P < .01) and D-dimer (P < .01) levels from time points 0 to 3. The PAI-1 levels equally increased in the TXA (P < .001) and non-TXA groups (P < .001) from time points 0 to 3, remaining significantly higher than those in healthy controls. These results are shown in Figures 2 and 3.

4. Discussion

The key finding of this propensity score–matched study is the significant reduction in fibrin(o)genolysis observed as decreased levels of FDP and D-dimer in patients administered TXA within 3 hours after injury. However, no marked differences in the 24-hour transfusion volume were noted between the groups. In addition, marked soluble fibrin and PAI-1 increases were confirmed in both the TXA and non-TXA groups.

Although these results did not indicate a causal relationship, this study suggested for the first time that inhibition of fibrin(o)genolysis might be a mechanism by which TXA reduces bleeding death in severely injured trauma patients. Reduced levels of plasmin as evaluated by the plasmin and antiplasmin complex were decreased in both groups; however, reductions in the FDP and D-dimer levels were only observed in the TXA group. The plasmin and antiplasmin complex actually measures inactive plasmin complexed with antiplasmin, and antiplasmin decreases due to consumption, as observed in this study. Therefore, the results indicate that TXA-blocked active plasmin escaped from antiplasmin complexing, leading to reductions in both FDP and D-dimer levels, which support the effects of TXA on plasmin(o)gen.

Inhibition of fibrinolysis by PAI-1 complexing tPA may play a role in the reductions of FDP and D-dimer levels. This hypothesis may be denied, however, because of the same levels of increases in PAI-1 in both the TXA and non-TXA groups at time point 3. In addition, TXA blocks the final processes of plasmin action on fibrin(o)gen, so irrespective of PAI-1 levels, TXA-bound plasmin(o)gen can neither bind to fibrin(o)gen nor degrade fibrin(o)gen, resulting in reduced FDP and D-dimer levels.

Table 2

|                      | Non-TXA (n = 36) | TXA (n = 36) | P value |
|----------------------|-----------------|-------------|---------|
| 24-h intravenous fluids and transfusion |                 |             |         |
| Packed red blood cells (U) | 5 (0–15)       | 3 (0–12)    | .547    |
| Fresh frozen plasma (U) | 0 (0–15)       | 4 (0–15)    | .598    |
| Platelet concentrate (U) | 0 (0–0)        | 0 (0–0)     | .445    |
| Fibrinogen (g)        | 0 (0–0)        | 0 (0–0)     | .307    |
| Crystalloids (mL)     | 4296            | 4530        | .532    |
| Colloids (mL)         | (2007–5580)     | (3017–6650) |         |
| SOFA score at 24 h after admission | 6 (4–8)        | 4 (3–7)     | .145    |
| Hospital death, n (%) | 1 (2.8)         | 3 (8.3)     | .303    |

Values are presented as median with the 25th to 75th interquartile range or number (percentage). SOFA = sequential organ failure assessment, TXA = tranexamic acid.
for transfusion requirement after TXA administration. The need for emergency operation and time period from admission to surgery was adjusted by the propensity score; however, the requirement of a transfusion during each operation was not determined in the present study, which may explain the equal transfusion volumes between the 2 groups.

In contrast to tPA-mediated fibrinolysis, the action of urokinase-type plasminogen activator (uPA) on plasminogen can be promoted by TXA, thereby accelerating plasmin generation.\(^{[11,12]}\) This possibility was confirmed in a traumatic brain injury model and in vitro study.\(^{[11,14]}\) The mouse study showed that intracerebral hemorrhage was increased when TXA was administered at 8 hours after head injury, the timing of peak uPA and low tPA levels.\(^{[11]}\) Longstaff and Locke\(^{[14]}\) confirmed that this phenomenon was likely to occur due to the loss of the benefits of TXA caused by increased uPA levels. TXA in the present study was administered based on the CRASH-2 protocol: 1 g administration followed by 1 g infusion over 8 hours.\(^{[1]}\) The lack of differences in 24-hour transfusion volume between the groups despite the reduction of fibrin(ogen)olysis in the TXA might be due to the influence of uPA on the effects of TXA.

The activation of neutrophils with elevated neutrophil elastase levels has been repeatedly confirmed in cases of severe trauma.\(^{[15,16]}\) Neutrophil elastase as well as plasmin-mediated fibrinolysis play an important role in severe trauma, contributing to a poor outcome in such patients. Fibrin degradation products produced by neutrophil elastase that are distinguished from plasmin-mediated fibrin degradation products have been shown to be markedly elevated in parallel with increases in the neutrophil elastase level in DIC after severe trauma.\(^{[16]}\) This study confirmed that these patients required a greater transfusion volume than non-DIC patients. Although propensity score adjustment was applied for DIC and the DIC score, the involvement of neutrophil elastase–mediated fibrinolysis might explain the lack of any differences in transfusion volume between the 2 groups in the present study.

Figure 3. Box plots show the levels of FDP, D-dimer, antiplasmin, and PAI-1 in healthy controls (white boxes) and non-TXA (hatched boxes) and TXA (dark boxes) groups. Both the FDP and D-dimer levels were significantly decreased only in the TXA group from time points 0 to 3. Both the TXA and non-TXA groups showed marked elevations in PAI-1 levels at time point 3. The normal upper limit of FDP is 10 mg/L. Horizontal bars in the box indicate the median (middle) and interquartile ranges (upper, 25%; lower, 75%). Black squares are the mean values. 0, time point 0; 3, time point 3. FDP = fibrin/fibrinogen degradation product, PAI-1 = plasminogen activator inhibitor-1, TXA = tranexamic acid. †† P < .01, ††† P ≤ .001 versus time point 0 of each group.
The modulation of inflammatory responses by TXA needs to be discussed. DIC and systemic inflammation are determinants of posttrauma organ dysfunction due to bidirectional interplay between coagulation and inflammation. In a rodent model of hemorrhagic shock, TXA decreased inflammation associated with amelioration of multiple organ damage. These studies suggest that the anti-inflammatory effects of TXA may reduce the progression of organ dysfunction, thereby improving the prognosis of trauma. While the present study adjusted for the DIC diagnosis, namely via adjusting for the coagulation status, the organ dysfunction (as evaluated by the SOFA scores) showed no difference between the 2 groups, which may weaken the hypothesis that the anti-inflammatory effects of the TXA played a role in the present findings.

Plasmin accelerates complement pathways resulting in increased coagulation and inflammation. Activated thrombin-activatable fibrinolysis inhibitor (TAFIa) is the only molecule to inhibit coagulation and inflammation through C3a and C5a in the complement pathways. The inhibition of fibrinolysis and inflammation by TAFIa was not evaluated in the present study. However, TAFIa is a molecule to consider when the effects of TXA on inflammation and fibrinolysis are studied in patients with trauma.

One important clinical implication of this study is that both groups showed persistently high levels of thrombin generation (soluble fibrin) from time points 0 to 3 and significant increases in PAI-1 levels at time point 3. The early administration of TXA within 3 hours was more effective than its later use after trauma, which was reconfirmed in a systematic review and meta-analysis, as well as in a randomized clinical trial. A subgroup of the patients with shock benefited particularly from the administration of TXA, however, shock-induced hypoperfusion and hypoxia are the potent stimulators of thrombin generation. Delayed TXA administration at several hours after injury overlaps with the period of increased thrombin and PAI-1 levels, which may worsen the risk of thromboembolic events, although a systematic review denied the increased risk of thromboembolic events with tranexamic administration. The consensus seems to agree with the prehospital administration of the TXA. The next topic for discussion is whether the drug should be administered nonselectively or selectively to shock patients.

4.1. Limitations
Several limitations associated with the present study warrant mention. Propensity score matching generated nonsignificant P values for all demographics and confounders; however, the standard mean differences of a few confounders may bias the equality of the matched groups. Although nonsignificant, the low SOFA and high mortality rate in the TRX group may suggest the existence of potential confounders that affected patient outcomes and which were not controlled by propensity score matching. In addition, the retrospective nature and moderately small number of patients may be a limitation. The study being conducted in a single country may limit the generalizability of the obtained results. The results concerning TXA do not prove causal relationship, so multicenter prospective validation will be needed to clarify the mechanisms underlying the TXA-induced reduction in bleeding death among trauma patients.

5. Conclusions
TXA significantly reduced fibrin(ogen)olysis based on the FDP and D-dimer levels, which may partially explain the mechanism underlying TXA-induced blocking of plasmin(ogen) binding to fibrin(ogen) in severely injured trauma patients. Whether or not these effects result in a reduced need for transfusion and decrease in bleeding death among trauma patients will require further validation. Both patients with and without administered TXA were associated with excessive fibrinogen generation and markedly high PAI-1 levels at time point 3. Therefore, the delayed administration of tranexamic should be performed with caution due to both increased coagulation and the inhibition of fibrinolysis.

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Author contributions
S. Gando analyzed the data, interpreted the results, drafted the figures and tables and wrote the manuscript. A. Shiraishi checked the statistics, interpreted the results, and critically inspected the manuscript. T. Wada and K. Yamakawa gave advice on the analytical methods, interpreted the results and critically inspected the manuscript. A. Gando, A. Shiraishi, H. Ogura, D. Saitoh, S. Fujishima, T. Mayumi, S. Kushimoto and T. Abe designed the study and organized the data collection and critically inspected the manuscript. The other authors contributed to the design of the study, organization of data collection, drafting of database charts and scientific discussion of all of the processes of the study as well as reviewed the manuscript and registered the patients. All authors approved the final version of the manuscript.

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