The fibrinogen levels on admission is a predictive marker of the contrast extravasation on enhanced computed tomography in sacral fracture

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Abstract
Sacral fracture is the most frequent posterior injury among unstable pelvic ring fractures and is prone to massive hemorrhage and hemodynamic instability. Contrast extravasation (CE) on computed tomography (CT) is widely used as an indicator of significant arterial bleeding. However, while CE is effective to detect significant arterial bleeding but negative result cannot completely rule out massive bleeding. Therefore, additional factors help to compensate CE for the prediction of early hemodynamically unstable condition.

We evaluated the risk factors that predict CE on enhanced computed CT in patients with sacral fractures. Patients were classified into 2 groups: CE positive on enhanced CT of the pelvis [CE(+)] and CE negative [CE(−)]. We compared age, sex, injury severity score (ISS), systolic blood pressure (sBP), type of sacral fracture based on Denis classification, platelet (PLT), base excess, lactate, prothrombin time-international normalized ratio, hemoglobin (Hb), activated partial thromboplastin time, D-dimer, and fibrinogen between the 2 groups.

A total of 82 patients were treated for sacral fracture, of whom 69 patients were enrolled. There were 17 patients (10 men and 7 women) in CE(+) and 52 patients (28 men and 24 women) in CE(−). Age, ISS, and blood transfusion within 24 hours were significantly higher in the CE(+) group than in the CE(−) group (P < .023, P < .001, P < .001). sBP, Hb, PLT, fibrinogen were significantly lower in the CE(+) group than in the CE(−) group (P < .001, P < .001, P < .001, P < .001). D-dimer and lactate were higher in the CE(+) group than in the CE(−) group (P = .038, P < .001) with significant differences. On multivariate analysis, the level of fibrinogen was an independent predictor of CE(+). The area under the curve value for fibrinogen was 0.88, and the optimal cut-off value for prediction was 199 mg/dL.

The fibrinogen levels on admission can predict contrast extravasation on enhanced CT in patients with sacral fractures. The optimal cut-off value of fibrinogen for CE(+) prediction in sacral fracture was 199 mg/dL. The use of fibrinogen to predict CE(+) could lead to prompt and effective treatment of active arterial hemorrhage in sacral fracture.

Abbreviations: APTT = activated partial thromboplastin time, BE = base excess, CE = contrast extravasation, CPA = cardio pulmonary arrest, CT = computed tomography, ED = emergency departments, Hb = hemoglobin, ISS = injury severity score, PLT = platelet, PT-INR = prothrombin time-international normalized ratio, RR = respiratory rate, sBP = systolic blood pressure, TAE = transcatheter arterial embolization, TIC = trauma-induced coagulopathy.

Keywords: contrast extravasation, fibrinogen, sacral fracture
1. Introduction
Sacral fracture is the most frequent posterior injury among unstable pelvic ring fractures, and about half of the patients with pelvic ring fractures have a sacral fracture.\textsuperscript{11–13} Sacral fractures with pelvic ring fractures are often caused by high-energy trauma and are prone to massive hemorrhage and hemodynamic instability. Mortality rates in hemodynamically unstable patients with a pelvic fracture range from 18% to 40%. Death within the first 24 hours of injury commonly results from blood loss.\textsuperscript{4,5} There are 3 major sources of bleeding in sacral fractures: the veins, arteries, and cancellous bone. Most hemorrhage can be controlled conservatively; however, active arterial hemorrhage may require a hemostatic procedure.\textsuperscript{6}

In most emergency departments (ED), polytrauma patients are initially evaluated by enhanced computed tomography (CT). Contrast extravasation (CE) on enhanced CT is widely used as an indicator of significant arterial bleeding. CE is often used to make decisions regarding invasive interventions including pelvic angiography\textsuperscript{7} and transcatheter arterial embolization (TAE).\textsuperscript{8,9} However, while CE is effective to detect significant arterial bleeding but negative result cannot completely rule out massive bleeding.\textsuperscript{6} Therefore, additional factors help to compensate CE for the prediction of early hemodynamically unstable condition.

Previous reports indicated that other parameters such as unstable hemodynamics, high blood glucose levels, and coagulation biomarkers are useful to predict the need for TAE.\textsuperscript{10} The aim of the present study was to evaluate risk factors on admission that can predict CE on enhanced CT in sacral fracture.

2. Materials and methods
2.1. Participants
This is a single-center, retrospective observational study. A total of 82 patients were treated for sacral fracture at our institution between October 2012 and September 2018. Of 82 sacral fracture cases, 74 patients (90.2%) had pelvic ring fractures. We excluded patients with Cardiopulmonary Arrest on arrival, CE positive in other regions, Abbreviated Injury Scale greater in regions other than the pelvis, received anticoagulant or antiplatelet therapy, and exact time of trauma occurrence unknown. Finally, 69 patients with pelvic fractures were enrolled. There were 17 and 53 patients in the CE(+) and CE(−) group, respectively. AIS = abbreviated Injury scale, CE = contrast extravasation, CPA = cardio pulmonary arrest.

2.2. Blood samples
Blood samples were collected at the time of arrival at the ED and before resuscitation.

2.3. Statistical analysis
The variables measured in the study are expressed as mean ± standard deviation. Comparisons between 2 groups were made using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables. To identify the risk factors for CE, we performed univariate and multiple logistic regression modeling. Age, sex, ISS, sBP are categorical variables. Hb, PLT, BE, lactate, PT-INR, APTT, D-dimer, and fibrinogen are continuous variables. Receiver operating characteristic (ROC) curves of variables with statistical significance in the logistic regression analysis were constructed to predict CE(+) and CE(−). The cut-off values were defined based on the Youden Index. The optimal cut-off values are defined as the point that results in both the highest sensitivity and specificity on the ROC curve to predict CE(+) and CE(−). All statistical analyses were performed with EZR (Saitama Medical Co, Ltd) (logistic regression analysis, factor Auto D-dimer (Q-may Laboratory Co, Ltd) (statistical significance in the logistic regression analysis was constructed to predict CE(+) and CE(−)), and fibrinogen are continuous variables. Receiver operating characteristic (ROC) curves of variables with statistical significance in the logistic regression analysis were constructed to predict CE(+) and CE(−). The cut-off values were defined based on the Youden Index. The optimal cut-off values are defined as the point that results in both the highest sensitivity and specificity on the ROC curve to predict CE(+) and CE(−). All statistical analyses were performed with EZR (Saitama Medical Center, Chiba, Japan) which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R commander designed to add statistical functions frequently used in biostatistics.\textsuperscript{11} A P value <.05 was considered statistically significant.

3. Results
3.1. Patient characteristics
The patient characteristics and outcomes are shown in Table 1. There were 17 patients (10 men and 7 women) in CE(+) and
52 patients (28 men and 24 women) in CE(−). Age, ISS, and blood transfusion within 24 hours were significantly higher in the CE(+) group than in the CE(−) group (P = .023, P < .001, P < .001). sBP, Hb, PLT, fibrinogen were significantly lower in the CE(+) group than in the CE(−) group (P < .001, P < .001, P < .001, P < .001). D-dimer and lactate were higher in the CE(+) group than in the CE(−) group (P = .036, P < .001) with significant differences. Sex, fracture type, PT-INR, APTT, and BE had no significant difference between the 2 groups.

### 3.2. Multivariate logistic regression analysis

On univariate analysis, there were significant differences in age, sBP, Hb, PLT, fibrinogen, D-dimer, and lactate. We entered these variables into the multiple logistic regression model. On multivariate analysis, the level of fibrinogen was an independent predictor of extravasation (odds ratio 0.977, 95% confidence interval (CI) 0.965–0.989; Table 2).

### 3.3. Receiver operating curve (ROC) analysis

Figure 2 shows the ROC curves for the prediction of CE based on fibrinogen levels. The area under the curve value for fibrinogen was 0.88, 95% CI 0.80–0.96 and the optimal cut-off value was 199 mg/dL. The sensitivity and specificity were 91.3% and 75.0%, respectively (Table 3).

### 4. Discussion

In the present study, we found that the fibrinogen level on admission was an independent predictor of CE on enhanced CT in patients with sacral fractures. According to recent guidelines, CE is an indicator of arterial hemorrhage and suggests that a patient will require TAE to achieve hemostasis.[12] However, the absence of CE does not exclude the possibility of active arterial hemorrhage due to the interference of vasospasm, the quality of CT images, or even the
scanning protocol.\(^{[13]}\) Therefore, an additional factor is needed to compensate for CE for the detection of early arterial bleeding.

Recently, there were reports that coagulation parameters can be predictive markers of massive bleeding and transfusion in blunt trauma. Severe trauma and subsequent hemorrhagic shock cause coagulopathy which is called trauma-induced coagulopathy (TIC). In TIC, the consumption of PLT and coagulation factors and hyper-fibrinolysis induce bleeding that leads to hemmorhage, and this requires hemostasis operation.\(^{[14–16]}\) We often use PT, APTT, PLT counts, and fibrinogen, as routine coagulation parameters in blood sample tests. However, PT, APTT, and platelets do not directly reflect the state of coagulation, and thus, they cannot be used as markers for early diagnosis of bleeding.\(^{[17]}\) On the other hand, some authors stated that the level of fibrinogen decreases more rapidly than that of other coagulation factors in active bleeding.\(^{[18,19]}\) Therefore, fibrinogen can be used as an early predictor of bleeding, even in sacral fracture.

Fibrinogen is one of the coagulation factors and the final substrate of the coagulation factor cascade.\(^{[19]}\) No factor can compensate for fibrinogen, and blood clots will not form and hemostasis cannot be obtained without sufficient fibrinogen. In addition, fibrinogen is an essential protein for platelets to function in aggregation and adhesion. Thus, fibrinogen plays an important role in forming and maintaining clots and in hemostasis.

Fibrinogen is substantially diminished as a result of hyperfibrinolysis. Therefore, low fibrinogen levels are associated with hemostatic impairment and induction of massive bleeding.\(^{[20–22]}\)

Previous studies have indicated fibrinogen deficiency develops before other hemostatic abnormalities. Hiippala et al reported that the fibrinogen level reached 100mg/dL when there was a 42% blood loss in animal models.\(^{[18,19]}\) Hayakawa et al reported that the fibrinogen level reached a critical level (150mg/dL) before any other coagulation parameters in severe trauma patients.\(^{[23]}\) Sawamura et al reported that the optimal cut-off value of fibrinogen to predict massive bleeding and death was 190mg/dL.\(^{[13]}\) Our previous report indicated that the fibrinogen level on admission was an independent predictor of massive transfusion after pelvic fracture and that the optimal cut-off value for prediction of massive transfusion was 193mg/dL.\(^{[24]}\) In the present study, the optimal cut-off value of fibrinogen for the prediction of CE(+) on enhanced CT in sacral fracture was 199.0mg/dL. This value is similar to that reported in previous studies. Enhanced CT is associated with complications such as contrast agent allergy and kidney function disorder. On the other hand, the advantage of a blood sample test is that there are no contraindications, and tests can be performed quickly and easily at the clinical site. However, the fibrinogen level may not have adequate sensitivity and specificity for the prediction of CE(+) as a single parameter.\(^{[12]}\) Kuo et al\(^{[6]}\) reported that relative hypotension increases the probability of the need for TAE in pelvic fracture patients without CE on enhanced CT. By checking these parameters before enhanced CT, we can anticipate arterial bleeding in patients with sacral fractures and be prepared to deal with it.

The present study has several limitations. First, the major limitation is the small sample size; therefore, the present study is an initial study with preliminary data. Second, the design of this study is a single-center and retrospective study. Therefore, multicenter prospective study with large sample size is necessary to confirm these results. Third, we defined the exclusion criteria to exclude the effects of regions other than pelvis. However, the effects of other trauma regions could not be completely removed. Fourth, we did not consider the volume of prehospital infusion and transport time to our hospital. The prehospital infusion might potentially induce hemodilution which leads to coagulopathy. Therefore, further studies are required to address these limitations.

5. Conclusion

The results of this study indicated that fibrinogen levels on admission could be useful in the prediction of CE(+) on enhanced CT in patients with sacral fractures. The optimal cut-off value of fibrinogen for CE(+) prediction in sacral fracture was 199mg/dL. The use of fibrinogen to predict CE(+) could lead to prompt and effective treatment of active arterial hemorrhage in sacral fracture.

**Author contributions**

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