Observational Study

Medicine®

OPEN

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

Naoki Notani, MD, PhD[a], Masashi Miyazaki, MD, PhD[a,*], Shozo Kanezaki, MD, PhD[a], Toshibobu Ishihara, MD, PhD[a], Tomonori Sakamoto, MD[a], Tetsutaro Abe, MD[a], Masashi Kataoka, MD, PhD[b], Hiroshi Tsumura, MD, PhD[a]

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 ($P = .036$, $P < .001$) 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

Editor: Mehmet Sonmez.

This study was not funded.

This study was approved by the Oita University Hospital Institutional Review Board (No: 1089) on October 17, 2016. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Orthopaedic Surgery, Faculty of Medicine, [b] Physical Therapy Course of Study, Faculty of Welfare and Health Sciences, Oita University, Oita, Japan.

[*] Correspondence: Masashi Miyazaki, Department of Orthopaedic Surgery, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasama-machi, Yufu-shi, Oita 879-5593, Japan (e-mail: masashim@med.oita-u.ac.jp).

How to cite this article: Notani N, Miyazaki M, Kanezaki S, Ishihara T, Sakamoto T, Abe T, Kataoka M, Tsumura H. The fibrinogen levels on admission is a predictive marker of the contrast extravasation on enhanced computed tomography in sacral fracture. Medicine 2021;100:10(e25056).

Received: 1 November 2020 / Received in final form: 18 January 2021 / Accepted: 12 February 2021

http://dx.doi.org/10.1097/MD.0000000000025056

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.[1–3] 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.[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.[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[7] and transcatheter arterial embolization (TAE).[8,9] However, while CE is effective to detect significant arterial bleeding but negative result cannot completely rule out massive bleeding.[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.[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 (Fig. 1). Patients were classified into 2 groups: those with CE positive on enhanced CT in the pelvis [CE(+)] and those with CE negative [CE(−)]. CE positive were evaluated by 2 of the present study authors (TS and NN) using enhanced CT in the pelvis at the time of arrival at the ED. Injury severity score (ISS) was also evaluated 2 of the present study authors (KS and NN). We compared age, sex, ISS, systolic blood pressure (sBP), type of sacral fracture based on Denis classification, hemoglobin (Hb), platelet (PLT), base excess (BE), lactate, prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), D-dimer, and fibrinogen between the 2 groups. Blood samples were collected on admission to the ED and before resuscitation.

2.2. Blood samples

Blood samples were collected at the time of arrival at the ED and before the administration of fluids. Whole blood was collected, with sodium citrate as an anticoagulant, in a conventional blood collection tube (NIPRO, Osaka, Japan). Hemostatic markers were measured within an hour of collection. PT-INR was measured using Thromborel S (Sysmex, Japan) (clotting time method). APTT were measured using Coagpia APTT-N (Sekisui Medical Co, Ltd) (clotting times method). Fibrinogen was measured using Coagpia Fbg (Sekisui Medical Co, Ltd) (thrombin time assay). D-dimer was measured using Factor Auto D-dimer (Q-may Laboratory Co, Ltd) (latex agglutination assay). All parameters were analyzed on automated coagulation analyzer Coapresta 2000 (Sekisui Medical Co, Ltd).

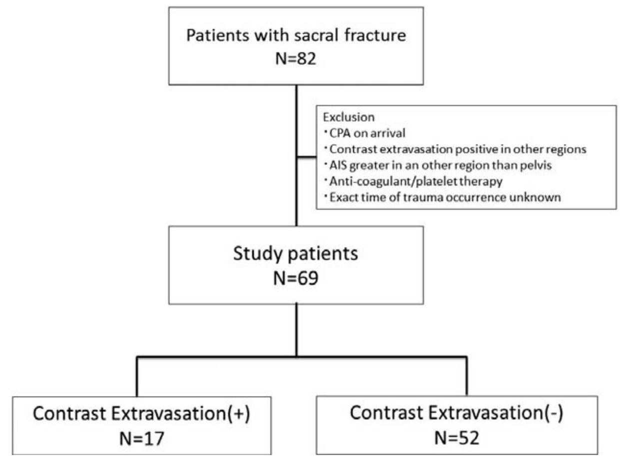

Figure 1. Study design. A total of 82 patients were treated for sacral fracture at our institution. Exclusion criteria were as follows: patients with CPA on arrival, CE positive in other regions, AIS greater in other regions than in the pelvis, anticoagulant or antiplatelet therapy, and exact time of 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.

2.3. 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(+). 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(+). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, 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.[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

Table 1

Patient demographics and clinical characteristics.

Variables	Normal range	CE(+) (n=17)	CE(−) (n=52)	P value
Age (years)		69.7±14.1	57.8±20.8	.023
Sex (male: female)		10:7	28:24	n.s
ISS		29.9±10.2	16.5±7.1	<.001
sBP, mm Hg	<120	106.8±24.1	129.3±25.9	<.001
Hb, mg/dL	13.7–16.8	9.7±2.7	12.2±2.7	<.001
PLT (×10^4)	158–348	130.1±69.9	201.9±67.8	<.001
PT-INR	0.85–1.15	1.19±0.22	1.10±0.13	n.s
APTT	0.85–1.15	45.7±36.7	32.8±8.4	n.s
D-dimer	<0.5	104.4±84.3	58.0±37.2	.036
Fbg, mg/dL	200–400	148.4±55.8	267±75.2	<.001
BE, mmol/L	male −3.2 to 1.8 female: −2.3 to 2.7	−6.3±6.2	−1.7±4.1	n.s
Lactate, mmol/L	0.56–1.39	4.6±3.5	2.3±1.9	<.001
Transfusion within 24 h				
PRBC, U		16.2±11.1	2.7±8.5	<0.001
Denis classification				
Type 1		10	42	n.s
2		7	10	n.s
3		0	0	n.s

APTT=activated partial thromboplastin time, BE=base excess, BT=body temperature, Fbg=fibrinogen, Hb=hemoglobin, ISS=injury severity score, n.s=not significant, PLT=platelet, PT-INR=prothrombin time-international normalized ratio, sBP=systolic blood pressure.

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).

Table 2

Results of multivariate logistic regression analysis for predicting CE.

Variables	P value	Odds ratio	95% CI
Fibrinogen, mg/dL	.000365	0.977	0.965–0.990

CI=confidence interval.

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

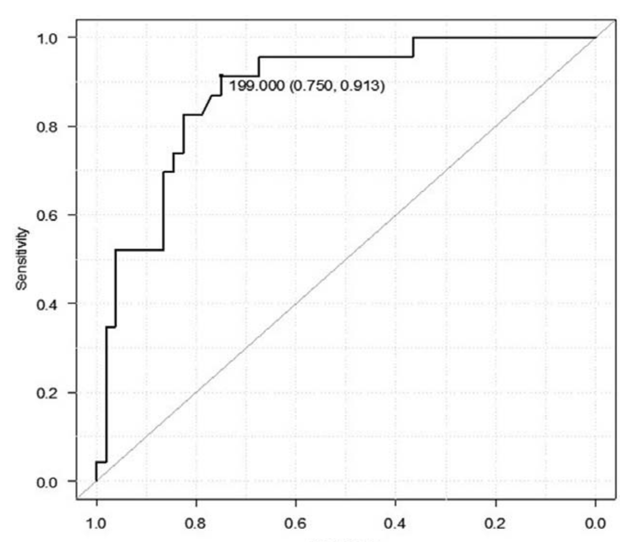

Figure 2. Receiver operating characteristic curves for predicting massive contrast extravasation based on fibrinogen level in sacral fracture. The area under the curve value for fibrinogen was 0.88, and the optimal cut-off value was 199 mg/dL.

Table 3

Receiver operating characteristic curve analysis.

Variables	AUC	95% CI	Sensitivity	Specificity
Age	0.637	0.507–0.767	73.9	64.2
sBP	0.737	0.611–0.862	69.6	73.6
Hb	0.751	0.633–0.869	47.8	90.6
PLT	0.782	0.658–0.906	65.2	84.9
Fibrinogen	0.88	0.80–0.96	91.3	75.0
D-dimer	0.687	0.56–0.815	87.0	44.2
Lactate	0.75	0.628–0.873	90.9	58.3

AUC=area under the curve, CI=confidence interval, Fbg=fibrinogen, Hb=hemoglobin, PLT=platelet, sBP=systolic blood pressure.

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 hemorrhage, 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 hyper-fibrinolysis. 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 100 mg/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 (150 mg/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 190 mg/dL.[15] 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 193 mg/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 199.0 mg/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 199 mg/dL. The use of fibrinogen to predict CE(+) could lead to prompt and effective treatment of active arterial hemorrhage in sacral fracture.

Author contributions

Conceptualization: Masashi Miyazaki, Toshinobu Ishihara, Tomonori Sakamoto, Hiroshi Tsumura.
Data curation: Shozo Kanezaki.
Investigation: Tetsutaro Abe.
Supervision: Masashi Kataoka, Hiroshi Tsumura.
Writing – original draft: Naoki Notani.

References

[1] Bonnin JG. Sacral fractures and injuries to the cauda equina. J Bone Joint Surg 1945;27:113–27.
[2] Yahata T, Suzuki T, Shindo M. Treatment of sacral fractures in pelvic ring injuries. J Jpn Assoc Surg Trauma 2015;29:36–42.
[3] Denis F, Davis S, Comfort T. Sacral fractures: an important problem. Retrospective analysis of 236 cases. Clin Orthop Relat Res 1988;227:67–81.
[4] Davis JW, Moore FA, McIntyre RCJr, et al. Western trauma association critical decisions in trauma: management of pelvic fracture with hemodynamic instability. J Trauma 2008;65:1012–5.
[5] Smith W, Williams A, Agudelo J, et al. Early predictors of mortality in hemodynamically unstable pelvis fractures. J Orthop Trauma 2007;21:31–7.
[6] Kuo LW, Yang SJ, Fu CY, et al. Relative hypotension increases the probability of the need for angioembolisation in pelvic fracture patients without contrast extravasation on computed tomography scan. Injury 2016;47:37–42.
[7] Juern JS, Milia D, Codner P, et al. Clinical significance of computed tomography contrast extravasation in blunt trauma patients with a pelvic fracture. J Trauma Acute Care Surg 2017;82:138–40.
[8] Agolini SF, Shah K, Jaffe J, et al. Arterial embolization is a rapid and effective technique for controlling pelvic fracture hemorrhage. J Trauma 1997;43:395–9.

[9] Mucha PJr, Welch TJ. Hemorrhage in major pelvic fractures. Surg Clin North Am 1988;68:757–73.
[10] Aoki M, Hagiwara S, Tokue H, et al. Prediction of extravasation in pelvic fracture using coagulation biomarkers. Injury 2016;47:1702–6.
[11] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.
[12] Cullinane DC, Schiller HJ, Zielinski MD, et al. Eastern Association for the Surgery of Trauma practice management guidelines for hemorrhage in pelvic fracture—update and systematic review. J Trauma 2011; 71:1850–68.
[13] Provenzale JM, Nelson RC, Vinson EN. Duke Radiology Review: Imaging, Differential Diagnosis, and Discussion. 2nd ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2012; x 636 pp.
[14] Hayakawa M, Sawamura A, Gando S, et al. Disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase. Surgery 2011;149:221–30.
[15] Sawamura A, Hayakawa M, Gando S, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. Thromb Res 2009;124:608–13.
[16] Gando S, Kameue T, Matsuda N, et al. Combined activation of coagulation and inflammation has an important role in multiple organ dysfunction and poor outcome after severe trauma. Thromb Haemost 2002;88:943–9.
[17] Mauffrey C, Cuellar DO3rd, Pieracci F, et al. Strategies for the management of haemorrhage following pelvic fractures and associated trauma-induced coagulopathy. Bone Joint J 2014;96-B: 1143–54.
[18] Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81:360–5.
[19] Hiippala S. Replacement of massive blood loss. Vox Sang 1998;74(Suppl 2):399–407.
[20] Schochl H, Cotton B, Inaba K, et al. FIBTEM provides early prediction of massive transfusion in trauma. Crit Care 2011;15:R265.
[21] Chambers LA, Chow SJ, Shaffer LE. Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol. Am J Clin Pathol 2011;136: 364–70.
[22] Inaba K, Karamanos E, Lustenberger T, et al. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. J Am Coll Surg 2013;216:290–7.
[23] Hayakawa M, Gando S, Ono Y, et al. Fibrinogen level deteriorates before other routine coagulation parameters and massive transfusion in the early phase of severe trauma: a retrospective observational study. Semin Thromb Hemost 2015;41:35–42.
[24] Notani N, Miyazaki M, Kanezaki S, et al. Fibrinogen level on admission is a predictive marker of the need for massive blood transfusion after pelvic fracture. Am J Emerg Med 2020;38:789–93.