Injury, Int. J. Care Injured 47 (2016) 1702–1706

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Prediction of extravasation in pelvic fracture using coagulation biomarkers

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ARTICLE INFO

Article history:
Received 25 February 2016
Received in revised form 2 May 2016
Accepted 9 May 2016

Keywords:
Fibrinogen
Fibrin degradation products (FDP)
D-dimer (DD)
Pelvic fracture
Extravasation

ABSTRACT

Purpose: To evaluate the usefulness of coagulation biomarkers, which are easy and quick to analyze in emergency settings, for prediction of arterial extravasation due to pelvic fracture.
Patients and methods: The medical records of pelvic fracture patients transferred to the emergency department of Gunma University Hospital between December 2009 and May 2015 were reviewed. Patients were divided into two groups, those with (Extra(+)) and without (Extra(−)) arterial extravasation on enhanced CT or angiography. Levels of fibrin degradation products (FDP), D-dimer, fibrinogen, the ratio of FDP to fibrinogen, the ratio of D-dimer to fibrinogen, systolic blood pressure, heart rate, the Glasgow Coma Scale, pH, base excess, hemoglobin and lactate levels, the pattern of pelvic injury, and injury severity score were measured at hospital admission, and compared between the two groups. Parameters with a significant difference between the two groups were used to construct receiver operating characteristic (ROC) curves.
Results: The study included 29 patients with pelvic fracture. FDP, D-dimer, the ratio of FDP to fibrinogen and the ratio of D-dimer to fibrinogen were the most useful parameters for predicting arterial extravasation due to pelvic fracture. FDP, D-dimer, the ratio of FDP to fibrinogen, the ratio of D-dimer to fibrinogen, and hemoglobin and lactate levels were significantly higher in the Extra(+) group than in the Extra(−) group (FDP, 354.8 μg/mL [median] versus 96.6 μg/mL; D-dimer, 122.3 μg/mL versus 42.1 μg/mL; the ratio of FDP to fibrinogen, 3.39 versus 0.42; the ratio of D-dimer to fibrinogen, 1.14 versus 0.18; hemoglobin, 10.5 g/dL versus 13.5 g/dL; lactate, 3.5 mmol/L versus 1.7 mmol/L). The area under the ROC curves for FDP, D-dimer, the ratio of FDP to fibrinogen, the ratio of D-dimer to fibrinogen, hemoglobin and lactate levels were 0.900, 0.882, 0.918, 0.900, 0.815 and 0.765, respectively.
Conclusion: Coagulation biomarkers, and hemoglobin and lactate levels could be useful to predict the existence of arterial extravasation due to pelvic fracture. The ratio of FDP to fibrinogen and the ratio of D-dimer to fibrinogen were the most accurate markers. Coagulation biomarkers may enable more rapid and specific treatment for pelvic fracture.

Introduction

Pelvic fracture has been shown to be an independent risk factor for death after blunt trauma. It is associated with increased mortality in the blunt trauma population, with rates ranging from 4.4% to 30% [1–3]. In pelvic fracture, the presence of retroperitoneal bleeding may induce hemodynamic instability, and 5% to 20% of retroperitoneal bleeding events are reported to be of pelvic arterial origin [4]. Thus, the identification of active arterial hemorrhage is important to determine the appropriate treatment strategy. Enhanced computed tomography (CT) is the standard procedure for detection of arterial extravasation [5]; however, angiographic embolization is sometimes required in cases without arterial extravasation on enhanced CT [6,7]. One study reported that approximately 20% of patients without arterial extravasation on enhanced CT eventually underwent transcatheter arterial embolization (TAE) [8]. In the report, the need for TAE should be under consideration if the pelvic injury patient had hemodynamic

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http://dx.doi.org/10.1016/j.injury.2016.05.012

deterioration without arterial extravasation on enhanced-CT [8]. Thus, therapeutic decision-making for pelvic fracture should not be based on enhanced CT alone. Some investigations indicate that other parameters, including unstable hemodynamics, the type of pelvic fracture and higher blood glucose levels, are useful to predict the need for embolization [6–9]. However, the relationship between laboratory data and prediction of arterial extravasation using enhanced CT and/or angiography has not been evaluated.

Recent studies have demonstrated that coagulation biomarkers are useful tools for predicting the severity of trauma, including our previous study [10–12]. Coagulation biomarkers are advantageous for assessing trauma because data can be rapidly obtained at the clinical site without the need for highly specialized staff.

The purpose of this study was to evaluate the usefulness of coagulation biomarkers and other clinical parameters (systolic blood pressure, heart rate, the Glasgow Coma Scale, pH, base excess, hemoglobin and lactate levels, and the pattern of pelvic injury) for the prediction of arterial extravasation in pelvic fracture.

Patients and methods

The study protocol was approved by the institutional review board. The medical records of pelvic fracture patients transferred to the emergency department of Gunma University Hospital between December 2009 and May 2015 were reviewed. Patients who received prehospital treatment comprising only crystalloids and/or packed red blood cell infusions were included, whereas patients who underwent treatment to arrest bleeding due to pelvic fracture were excluded. The Abbreviated Injury Scale (AIS) score and the Injury Severity Score (ISS) were calculated. The dominant region of injury was defined as that with the highest AIS score. Key exclusion criteria were: 1) an AIS score in another region that was higher than the pelvis AIS score, and 2) arterial extravasation in regions other than the pelvis. Patients were divided into two groups, Extra(+) and Extra(−), according to the presence and absence of arterial extravasation on enhanced CT or angiography, respectively. Enhanced CT was performed in the arterial phase and the portal venous phase. Monitoring scanning was initiated 10 s after the start of the contrast media. Breath-hold dual-phase diagnostic scanning was performed 10 s (the arterial phase) and 110 s (the portal venous phase) after the aortic enhancement in the monitoring images reached bolus-tracking threshold attenuation (220 HU). Arterial extravasation was defined as extravascular high-attenuating regions with attenuation similar to or greater than that of the aorta on arterial phase images. Arterial extravasation on enhanced CT was analyzed by at least one radiologist. Angiography was performed in patients with unstable hemodynamics and/or progressive retroperitoneal hematoma, without obvious arterial extravasation on enhanced CT. After TAE, the majority of patients underwent damage control orthopedics. If necessary in the acute phase, external pelvic fixation was performed in our hospital using only a pelvic belt (SAM Pelvic Sling II, SAM Medical Products, Wilsonville, USA). The following parameters were obtained at hospital arrival: levels of fibrin degradation products (FDP), D-dimer and fibrinogen, systolic blood pressure, heart rate, the Glasgow Coma Scale, pH, base excess, hemoglobin and lactate levels, the pattern of pelvic injury, and the injury severity score. Ratios of FDP to fibrinogen (FDP/fibrinogen) and D-dimer to fibrinogen (D-dimer/fibrinogen) were also calculated. All these parameters were compared between the two groups. In addition, the quantity of packed red blood cells transfused within 24 h of the time of injury was compared between the two groups. (In Japan, 1 U of packed red blood cells is approximately 140 mL). FDP and D-dimer were measured using an immunoturbidimetric method using the Cs-2000i and Cs-5100 systems (Sysmex Corporation., Hyogo, Japan).

Statistical analysis

Data are expressed as the mean ± standard deviation (SD). Comparisons of each parameter between the Extra(+) and Extra(−) group were performed using the Mann-Whitney *U* test and Chi-squared test. The efficacy of predicting arterial extravasation was evaluated using the area under the receiver operating characteristic (ROC) curves, with low, medium and high accuracy defined as <0.7, $\geqq 0.7$ to <0.9, and $\geqq 0.9$, respectively [13]. The optimal cut-off point was defined by the maximum of the sum of sensitivity and specificity using the Youden index approach. Statistical analysis was performed with IBM SPSS Statistics version 22.0 (Armonk, NY, USA) A p-value < 0.05 was considered to denote statistical significance.

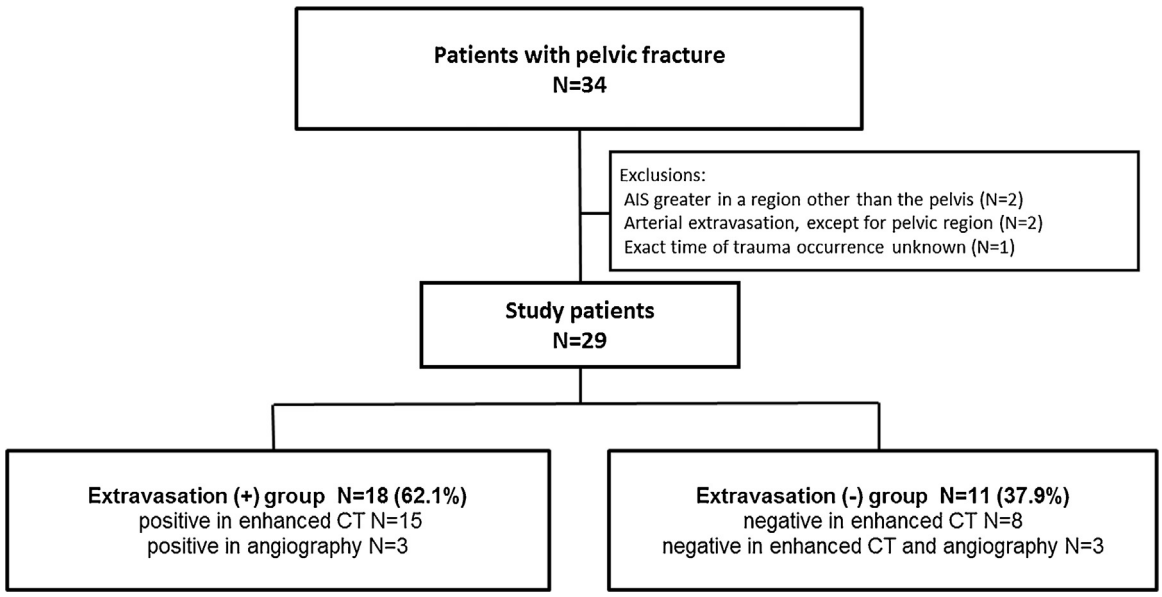

Fig. 1. Study flow chart.

AIS:abbreviated injury scale

Table 1
Clinical characteristics of the Extra(+) and Extra(−) group.

	Extra(+) (n = 18)	Extra(−) (n = 11)	*P*-value
Injury severity score[a]	30.5 ± 8.7	12.3 ± 7.1	<0.001
Age, y[a]	76.4 ± 12.0	56.7 ± 16.6	0.002
Systolic blood pressure, mmHg[a]	123.7 ± 33.9	138.4 ± 34.0	0.412
Heart rate, beats per minute[a]	90.2 ± 16.2	79.1 ± 20.4	0.092
Glasgow Coma Scale[a]	13.2 ± 2.9	14.1 ± 2.4	0.188
Hemoglobin level, g/dL[a]	10.5 ± 2.8	13.5 ± 1.3	0.007
pH[a]	7.35 ± 0.83	7.40 ± 0.58	0.131
Base excess, mmol/L[a]	−3.6 ± 4.2	−2.2 ± 4.1	0.403
Lactate level, mmol/L[a]	3.5 ± 2.3	1.7 ± 1.0	0.047
Fibrin degradation product, μg/mL[a]	354.8 ± 211.5	96.6 ± 82.2	<0.001
D-dimer, μg/mL[a]	122.3 ± 83.9	42.1 ± 31.7	<0.001
Fibrinogen, μg/mL[a]	197.9 ± 93.0	233.1 ± 54.6	0.332
Ratio of FDP to fibrinogen[a]	3.39 ± 4.55	0.42 ± 0.27	<0.001
Ratio of D-dimer to fibrinogen[a]	1.14 ± 1.44	0.18 ± 0.10	<0.001
Packed red blood cells, U[a]	9.0 ± 9.7	2.7 ± 8.4	0.002
AO classification Type A(n)[†]	0	7	<0.001
Type B(n)[†]	13	3	0.018
Type C(n)[†]	5	1	0.228

All values are expressed as the mean ± SD.
[W]Chi-squared test. AO, Arbeitsgemeinschaftfur Osteosynthesefragen/Orthopedic Trauma Association classification.
[a] Mann-Whitney *U* test.

Results

Between December 2009 and May 2015, 34 patients were admitted to hospital with pelvic fracture. Two patients with an AIS score greater in another region than the pelvis AIS score, two patients with arterial extravasation in a non-pelvic region, and one patient with an unknown time of trauma occurrence were excluded, resulting in a study population of 29 patients (Fig. 1). The Extra(+) group included 18 patients, 15 with contrast extravasation on enhanced CT, and 3 with contrast extravasation only found on angiography. In the Extra(−) group comprising 11 patients, none had contrast extravasation on enhanced CT, and 3 underwent angiography without evidence of contrast extravasation.

The sources of trauma were traffic accident (17 patients), fall (11 patients), and natural disaster (1 patient). The male/female ratio was 19/10, and the mean (SD) age was 69.0 (16.8) years (range, 32–87 years). Among the 29 patients, 23 were discharged from hospital and 6 died, corresponding to a hospital mortality rate of 21% (6/29). The cause of death was intractable coagulopathy and/or multisystem organ failure in the acute phase in 2 patients, and multisystem organ failure in the late phase in the other 4 patients.

As shown in Table 1, age, lactate, FDP, D-dimer, FDP/fibrinogen, D-dimer/fibrinogen and the quantity of packed red blood cell transfused within 24 h of the time of injury were significantly higher in the Extra(+) than the Extra(−) group. The pattern of pelvic injury was more severe and the hemoglobin level was lower in the Extra(+) group than the Extra (−) group.

ROC curves for FDP, D-dimer, FDP/fibrinogen and D-dimer/fibrinogen are shown in Fig. 2, and the area under the ROC curves for FDP, D-dimer, FDP/fibrinogen, D-dimer/fibrinogen, hemoglobin and lactate levels are presented in Table 2. The results suggest that coagulation biomarkers, hemoglobin and lactate were useful for predicting arterial extravasations due to pelvic fracture. The area under the ROC curves for FDP, D-dimer, the ratio of FDP to fibrinogen, the ratio of D-dimer to fibrinogen, hemoglobin and lactate levels were 0.900, 0.882, 0.918, 0.900, 0.815 and 0.765, respectively. The sensitivity and specificity of FDP was almost the same as that of D-dimer. FDP/fibrinogen and D-dimer/fibrinogen were stronger predictors of extravasation than FDP, D-dimer, hemoglobin and lactate levels.

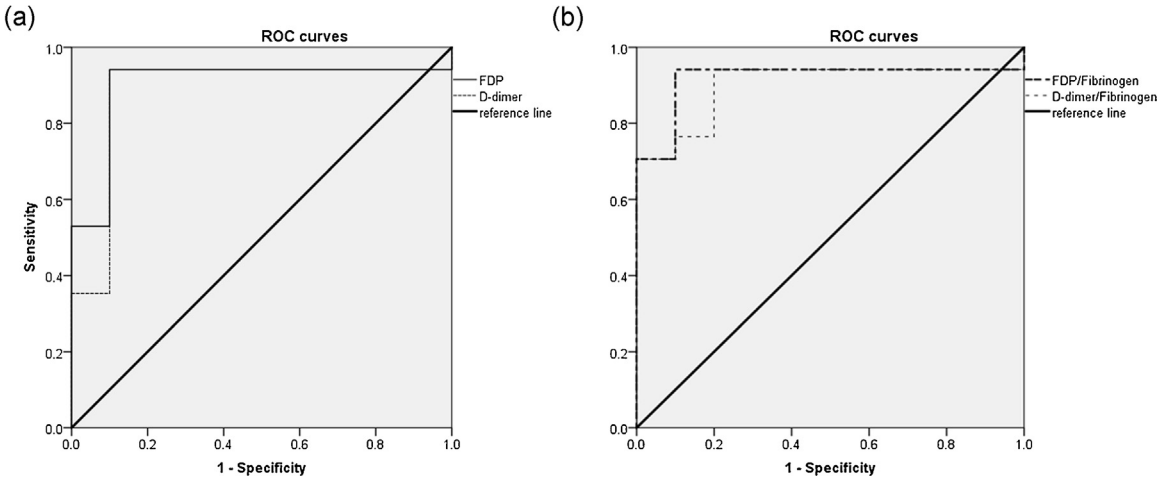

Fig. 2. (a) Receiver operating characteristic (ROC) curves for FDP and D-dimer for the ability of parameters to predict arterial extravasation in patients with pelvic fracture. FDP, fibrin degradation products. (b) Receiver operating characteristic (ROC) curves for the ratio of FDP to fibrinogen and the ratio of D-dimer to fibrinogen for the ability of parameters to predict arterial extravasation in patients with pelvic fracture. FDP, fibrin degradation products.

Table 2
Area under the receiver operating characteristic curves (AUC) and cut-off points of parameters to predict arterial extravasation in pelvic fracture patients.

	FDP	D-dimer	Ratio of FDP to fibrinogen	Ratio of D-dimer to fibrinogen	Hemoglobin level	Lactate level
AUC (95%CI)	0.900 (0.765–1.000)	0.882 (0.728–1.000)	0.918 (0.797–1.000)	0.900 (0.773–1.000)	0.815 (0.656–0.974)	0.765 (0.563–0.967)
Cut-off point	126.8 μg/mL	46.0 μg/mL	0.656	0.215	11.0 g/dL	2.75 mmol/L
Sensitivity, %	94.1	94.1	94.1	94.1	61.1	58.8
Specificity, %	90.0	90.0	90.0	80.0	0.0	85.7

CI, confidence interval; FDP, fibrin degradation product.

Discussion

Early diagnosis of arterial hemorrhage is vital for the management of pelvic fracture [6,7]. Extravasation of contrast material in the pelvis on enhanced CT is considered to be an accurate indicator of active arterial hemorrhage, and the findings of contrast extravasation are commonly used to decide on the requirement for TAE in patients with pelvic fracture [5,14]. However, a lack of contrast extravasation is not preclusive of active arterial hemorrhage and the requirement for TAE [8,15]. The quality of CT images may be related to the scanning protocol or affected by interference caused by vasospasm [15–17]. In addition, there is the relatively rare problem of contrast media allergy. Thus, alternative methods for evaluating the existence of arterial extravasation are needed [18].

Recent studies have demonstrated that coagulation biomarkers are useful tools for predicting the severity of trauma [10–12]. The advantages of coagulation biomarkers for evaluation of trauma include rapid and easy collection of data at the clinical site. As described above, our previous research demonstrated that FDP and D-dimer are related to the severity of trauma. Furthermore, pelvic fractures are known to be an independent risk factor for death after blunt trauma [1]. Thus, this study was focused on the usefulness of coagulation biomarkers to predict the existence of contrast extravasation in pelvic fracture patients. To the best of the authors' knowledge, this is the first report that examines the cut-off points between contrast extravasation and blood samples (coagulation biomarkers).

There are no published data on predictive factors of arterial extravasation in pelvic fracture; however, some reports have emphasized the necessity for angiography in pelvic fracture [5,8,14,19,20]. As mentioned above, contrast extravasation is the standard indicator of angiography [5,14]. Verbeek et al. emphasized the importance of quantifying the volume of free fluid on CT to predict the need for abdominal hemorrhage control in major pelvic fracture [19]. Ruatti et al. reported that the pattern of pelvic ring fracture was associated with bleeding treated by angiography [20]. In addition, Kuo et al. suggested that relative hypotension indicated the necessity for TAE, despite the absence of contrast extravasation on enhanced CT [8].

In the real-life clinical scenario, the necessity for angiography and TAE is generally decided by contrast extravasation on enhanced CT. The prediction of extravasation from blood sample analyses could be very useful. In this study, lactate levels was significantly higher in the Extra(+) group than the Extra(−) group, while the initial hemoglobin level was significantly lower in the Extra(+) group than the Extra(−) group. Other trauma studies assessing the prediction of massive transfusion have incorporated similar variables, including vital signs, initial hemoglobin level, lactate levels, the pattern of pelvic fracture and fluid accumulation on CT or ultrasound scans [21–26]. This study also identified some of these variables as predictors of arterial extravasation due to pelvic fracture. In the Extra(+) group, 83.3% (15/18) of patients required a blood transfusion and 33.3% (6/18) required a massive transfusion.

The superiority of coagulation biomarkers for determining trauma severity was reported in our previous study. Levels of coagulation biomarkers displayed a rapid, marked elevation after trauma incidence and correlated even with relatively mild trauma [10]. This study included all pelvic fracture patients, irrespective of whether hemostasis was stable or unstable. Thus, other parameters that are used to predict arterial extravasation may have lower specificity and sensitivity than coagulation biomarkers.

The mean age of the Extra(+) group was significantly higher than that of the Extra(−) group. This is consistent with previous reports, in which 60 years of age or more was identified as an independent predictor of mortality or massive transfusion due to pelvic fracture [27–29]. The high risk of extravasation due to pelvic fracture in patients over 60 years old was accompanied by a high rate of mortality or massive transfusion. Of note, coagulation biomarkers are affected by age, and the results may be different in a cohort of younger age [30].

To calculate the area under the ROC curves for the relationship between arterial extravasation and the requirement for blood transfusion, coagulation markers were included, in particular, FDP/fibrinogen and D-dimer/fibrinogen ratios. The accuracy of fibrinogen for detection of acute traumatic coagulopathy was previously reported [31,32]. The area under the ROC curves for pelvic fracture with active arterial bleeding were calculated using a decrease in fibrinogen, FDP/fibrinogen and D-dimer/fibrinogen. The results demonstrated that FDP/fibrinogen and D-dimer/fibrinogen were more useful to predict arterial extravasation and the requirement for blood transfusion in pelvic fracture than FDP and D-dimer.

This study has several limitations. The retrospective design, and data from only a single center and small sample size could be viewed as weaknesses. Secondly, patients with multiple trauma were included. To exclude the effects of regions other than the pelvis, we defined the Key exclusion criteria 1; an AIS score in another region that was higher than the pelvis AIS score, however, the possible contribution of another trauma region was not entirely eliminated. Thirdly, coagulation biomarkers are affected by multiple confounding factors. In trauma patients, coagulation biomarkers vary according to age, gender, the time from injury to blood sampling, and prehospital therapies such as intravenous infusion and transfusion. Prospective, multicenter studies with larger sample sizes are needed to validate the accuracy of this study.

Conclusion

Coagulation biomarkers, hemoglobin and lactate levels may represent useful biomarkers to predict the existence of arterial extravasation due to pelvic fracture. In particular, FDP/fibrinogen and D-dimer/fibrinogen had the strongest predictive value. The use of coagulation biomarkers to predict arterial hemorrhage could lead to more prompt and precise treatment in pelvic fracture.

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