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Utility of Measurement of Serum Lactate in Diagnosis of Coagulopathy Associated with Peripheral Circulatory Insufficiency: Retrospective Evaluation Using Thromboelastometry from a Single Center in Japan

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Recently, serum lactate level rather than systolic blood pressure (sBP) has been widely used to diagnose peripheral circulatory insufficiency, which often leads to coagulopathy with systemic inflammation. However, most of the reported disorders were examined by plasma samples. The aim of this study was to evaluate the utility of serum lactate for detecting coagulopathy with circulatory failure by using thromboelastometry as well as standard coagulation test. 192 adult patients transported to our hospital between January 2013 and September 2014 were enrolled in this retrospective study. The sBP, serum lactate and thromboelastometry (ROTEM®) were measured in these patients in the emergency department. All patients were divided into three groups based on serum lactate levels: (1) the severe group (≥4 mmol/L, n=41); (2) the mild group (<4 mmol/L and ≥2 mmol/L, n=59); and (3) the normal group (<2 mmol/L, n=92). Patients in the severe group were of a significantly younger age but had lower pH and poor outcome. SBP was significantly lower and heart rates were higher in the severe group than in the other groups. Prolonged PT-INR and APTT were statistically confirmed in the severe group. ROTEM findings in the severe group revealed significantly lower alpha angle, shortened Lysis Onset Time and significantly more cases exhibited hyperfibrinolysis. The same analysis with the cut-off level of sBP at 90 mmHg showed no significant difference in ROTEM findings between the two groups. Abnormal serum lactate levels (≥4.0 mmol/L) properly reflected peripheral circulatory insufficiency and were more closely associated with coagulopathy such as hyperfibrinolysis and hypocoagulability than sBP.
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Key words: systemic inflammation, thromboelastometry, lysis onset time, hyperfibrinolysis, prognosis

Introduction

A systolic blood pressure [SBP] of less than 90 mmHg has long been used as a marker for peripheral circulatory insufficiency[1–3]. However, blood pressure shows no decrease in some patients with hemorrhagic shock, despite a loss of circulatory blood volume as great as 30%, because of vascular contraction and increased pulse rates and is insufficient as an early marker for detecting shock[1,4].

Lactate levels have been widely used to detect the early phase of peripheral circulatory insufficiency and to evaluate therapeutic efficacy[5,6]. The relation of lactate levels to clinical outcome has been increasingly emphasized, especially in patients who are critically ill[7,8]. Systemic inflammation characterized by vascular endothelial damage activates the extrinsic coagulation pathway in patients who have peripheral circulatory insufficiency with lactic acidosis[9–11]. This hypercoagulability often leads to disseminated intravascular coagulation with or without hyperfibrinolysis.

Whole blood viscoelastic tests are performed with rotational thromboelastometry (ROTEM®; Tem International

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GmbH, Munich, Germany) within 60 minutes after blood samples are obtained. The ROTEM is a point-of-care test using whole blood[12]. With this test coagulopathy can be diagnosed more pathophysiologically than with standard coagulation tests. In fact, the ROTEM is used for such treatments as cardiac surgery, organ transplantation, and the repair of trauma[12–14]. With ROTEM the following can be evaluated in a real-time manner by analyzing several variables: (1) clotting time, (2) speed of clot formation during the early stage, (3) clot firmness at each time point, and (4) degrees of fibrinolysis. In addition, ROTEM can be used to evaluate both the extrinsic and intrinsic clotting systems, the function of fibrinogen, effect of heparin, and presence or absence of hyperfibrinolysis by changing the combination of the coagulation accelerating agents. Although the severity of lactic acidosis might be related to coagulopathy, the lactic acidosis was evaluated in previous studies with standard coagulation tests, but not with ROTEM[15].

Lactic acidosis is a lethal triad that triggers trauma-induced coagulopathy[16–18]. However, the lactate level causing shock-induced coagulopathy and the presence of hyper/hypo coagulability, hyperfibrinolysis and their severity have appeared in few reports. In the present study, to evaluate the effectiveness that serum lactate level is a feasible predictor of shock-induced coagulopathy, we measured serum lactate levels with ROTEM and the standard coagulation test.

Materials and Methods

This retrospective study has been approved by the Institutional Review Board (Protocol Identification Number: 20150606). After obtaining institutional review board approval, 192 adult patients (mean age, 66.9 years; males accounted for 52%) transported to the Saga University Hospital from January 2013 through September 2014 were enrolled in this retrospective study. The SBP, serum lactate level, and ROTEM were measured in the emergency department. The patients with cardiopulmonary arrest were excluded. Blood samples were taken within 15 minutes after admission to our emergency department. All patients were divided into three groups based on the severity of the serum lactate level; severe group (≥4 mmol/L, 41 cases), mild group (<4 mmol/L and ≥2 mmol/L, 59 cases), and normal group (<2 mmol/L, 92 cases). Clinical demographics, vital signs, laboratory data and ROTEM findings were retrospectively analyzed in each group. In addition, on the basis of sBP, the subjects were divided into the hypotension group (<90 mmHg, 31 cases) and normotension group (≥90 mmHg, 161 cases) for the same analysis and the results were compared with those based on serum lactate levels.

We performed extrinsically activated thromboelastometric test (EXTEM) reflecting the extrinsic coagulation pathway on the ROTEM system and in vitro inhibition with aprotinin (APTEM) to evaluate the presence of hyperfibrinolysis. Variables analyzed in the EXTEM include the clotting time, the amplitude at 10 minutes (A10) and 20 minutes (A20) after the clotting time, maximum clot firmness, clot formation time (CFT), the alpha angle (α angle), the presence of hyperfibrinolysis, and the lysis onset time. A 15% or more of maximum lysis in EXTEM test and a 20% or more improvement of maximum lysis in APTEM test compared with that in EXTEM were defined as hyperfibrinolysis. The ROTEM was run more than 60 minutes at 37℃.

Continuous variables were expressed in medians (the first quartile [Q1], the third quartile [Q3]). For statistical analysis, Kruskal-Wallis, the Mann-Whitney U test, and Fisher's exact test were used and a p value less than 0.05 was considered statistically significant. Bonferroni correction was performed for multiple comparisons. IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) was performed for statistical analyses.

Results

The results of univariate analysis in each group are shown in **Table 1, 2**. The severe group was significantly younger than the normal group (P=0.023). There was no significant difference in the proportion of sex and past medical history in each group. With regard to the diagnosis, there were less number of patients with sepsis in the normal group but no other remarkable tendency was observed (**Fig. 1**). As for vital signs, respiratory rates were significantly higher in the mild and severe group than in the normal group (P=0.001). Additionally, sBP was significantly lower and heart rates were significantly higher in the severe group than in the other groups (P< 0.001). Shock index (HR/sBP) in the severe group was significantly higher than the other groups (P<0.001) (**Fig. 2**). There was no significant difference in body temperature.

Arterial blood gas analysis showed significantly lower pH and base excess, suggesting peripheral circulatory insufficiency, in the severe group than in the other groups (P<0.001). Significantly prolonged prothrombin time-international normalized ratio (PT-INR) (P<0.001) and activated partial thromboplastin time (APTT) (P=0.001)

Table 1 Background, past medical history, vital signs, arterial blood gas, and outcome in each group based on the serum lactate levels

	Severe group (n=41)	Mild group (n=59)	Normal group (n=92)	P value
Age (year)	66.0† [53, 74]	70.0 [60, 78]	73.0 [61, 82]	0.023*
Male (%)	43.9	55.9	53.3	0.472
Liver cirrhosis (%)	5.1	5.2	2.3	0.591
catecholamines (%)	7.7	3.5	3.4	0.514
anti-platelet agents (%)	7.7	14.0	11.4	0.631
warfarin (%)	5.1	1.8	8.0	0.273
other anti-coagulants (%)	7.7	0.0	8.0	0.093
RR (/min)	25.0† [19, 30]	21.0† [18, 25]	19.0 [16, 22]	0.001*
sBP (mmHg)	98.0†‡ [81, 126]	127† [93, 154]	139 [112, 164]	<0.001*
HR (/min)	106.0†‡ [94, 133]	90.0† [75, 116]	81.0 [69, 99]	<0.001*
BT (°C)	36.5 [36, 38]	36.6 [36, 38]	36.7 [36, 37]	0.954
shock index	1.00†‡ [0.8, 1.5]	0.73† [0.6, 1.0]	0.62 [0.4, 0.8]	<0.001*
pH	7.34†‡ [7.2, 7.4]	7.39 [7.4, 7.4]	7.41 [7.4, 7.4]	<0.001*
BE (mmol/L)	–7.4†‡ [–13, –4]	–0.8† [–3, 0]	0.0 [–2, 1]	<0.001*
Lac (mmol/L)	5.7†‡ [4, 9]	2.6† [2, 3]	1.4 [1, 2]	<0.001*
Mortality (%)	29.3	10.2	9.8	0.007*

Median [Q1, Q3], *p<0.05, †vs. the normal, ‡vs. the mild group
RR; respiratory rate, sBP; systolic blood pressure, HR; heart rate; BT; body temperature, BE; base excess, Lac; lactate, Q; quartile.

Table 2 Results of standard coagulation tests and ROTEM findings based on the serum lactate levels

	Severe group (n=41)	Mild group (n=59)	Normal group (n=92)	P value
Platelet (/mm)	17.6 [13, 24]	18.4 [13, 24]	19.0 [14, 24]	0.808
PT-INR	1.19†‡ [1.1, 1.5]	1.06 [1.0, 1.2]	1.02 [1.0, 1.1]	<0.001*
APTT (s)	34.8†‡ [30, 50]	30.7 [27, 35]	31.1 [28, 35]	0.001*
Fibrinogen (mg/dL)	310.5 [216, 432]	310.5 [224, 437]	334.5 [269, 438]	0.378
FDP (μg/mL)	32.2†‡ [16, 235]	12.4 [4, 102]	7.7 [4, 21]	0.001*
DD (μg/mL)	14.4†‡ [4, 87]	4.2 [1, 20]	3.2 [1, 10]	0.002*
CT (s)	61.0 [47, 76]	52.0 [46, 62]	51.5 [45, 67]	0.161
A10 (mm)	54.0 [43, 66]	58.0 [51, 65]	60.0 [53, 65]	0.126
A20 (mm)	60.0 [51, 71]	64.0 [58, 69]	65.0 [60, 70]	0.202
MCF (mm)	62.0 [53, 71]	64.0 [59, 70]	65.0 [60, 70]	0.284
CFT (s)	96.0 [58, 129]	86.0 [59, 107]	75.0 [61, 100]	0.136
α angle (°)	72.5† [65, 79]	75.0 [70, 78]	76.0 [72, 79]	0.040*
HF (%)	15.4	5.1	3.5	0.040*
LOT (s)	3,274†‡ [1,956, 4,524]	4,803 [4,357, 5,074]	4,542 [4,075, 4,976]	0.024*

Median [Q1, Q3], *p<0.05, †vs. the normal group, ‡vs. the mild group
PT-INR; prothrombin time-international normalized ratio, APTT; activated partial thromboplastin time, FDP; fibrinogen and fibrin degradation products, DD; D-dimer, CT; clotting time, MCF; maximum clot firmness, CFT; clot formation time, HF; hyperfibrinolysis, LOT; lysis onset time, Q; quartile.

were found in the standard coagulation tests, as well as fibrinogen and fibrin degradation products (P=0.001), and D-dimer (P=0.002).

Although EXTEM findings showed no significant difference in the clotting time and clot firmness at each time point, the α angle was significantly decreased in the severe group (P=0.040) (**Fig. 2**). In addition, the number of patients with hyperfibrinolysis (P=0.040) and shorter lysis onset time (P=0.024) (**Fig. 2**) was increased indicating the initiation of hyperfibrinolysis was markedly greater in the severe group than in the other groups. Clinical outcome was significantly poorer in the severe group (P=

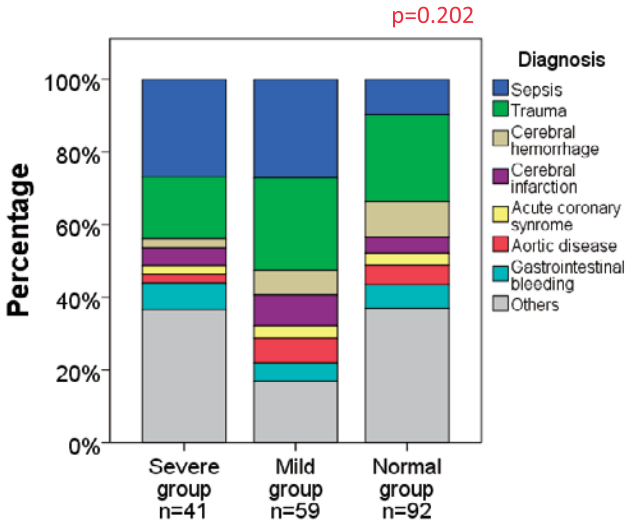

Fig. 1 Distribution of diagnosis in each group
Sepsis tended to be less frequently observed in the normal group, but there was no other remarkable tendency.

0.007).

Next, the results of univariate analysis based on sBP are shown in **Table 3**. Standard coagulation tests showed that PT-INR and APTT were significantly prolonged in the hypotension group, but there was no significant difference in fibrin degradation products or D-dimer. ROTEM findings showed that there were no notable findings in clotting time, clot firmness, speed of thrombus formation, or the marker for fibrinolysis.

Discussion

This study demonstrated that an elevation of serum lactate levels, in particular, 4.0 mmol/L or greater reflected coagulopathy associated with peripheral circulatory insufficiency more accurately than sBP.

The relationship between peripheral circulatory insufficiency and lactate levels has been increasingly reported recently[8,19–27]. Generally, patients with critical illness are considered to have normal lactate levels at concentrations of less than 2 mmol/L[19,20]. Furthermore, hyperlactatemia is well defined as 4 mmol/L which indicates hypoperfusion and poor clinical outcome[20–22]. The systematic review of 33 papers by Kruse et al. showed that lactate levels of 2.5 mmol/L or greater on emergency admission indicates a poor prognosis[23]. Similarly, in the cohort study of 830 cases with severe sepsis, elevated lactate levels correlated with clinical outcome in the presence or absence of organ failure and shock[24]. Other recent reports gave emphasis to the clearance of lactate[7,25,27–29]. Better lactate clearance six hours after the time of arrival at the hospital in patients with severe sepsis and septic shock is reported to improve clinical outcome[27]. The cohort study of 4,742 cases with trauma showed that lactate levels 4.0 mg/dL or more upon arrival at the hospital resulted in significantly poorer outcome, and mortality was significantly higher in cases with poor clearance of lactate six hours after the onset of trauma[25]. Our results also demonstrated a strong association between lactate level and systemic tissue perfusions. Importantly, abnormal lactate level of 4 mmol/L or greater was correlated with severe condition and poor outcome.

In this study, we utilized ROTEM as well as the standard coagulation test in order to examine the coagulation status of the patients. One of the characteristics of ROTEM is to use whole blood, unlike standard coagulation tests such as PT, where plasma is used. Although plasma derived coagulation test eliminates component of blood cells such as activated platelets, which play a vital role in the coagulation cascade, ROTEM involves these interactions. Therefore it is considered a more physiological test than conventional methodology[30]. Another study by Brummel et al. indicated that measurement of clotting time is only the initiation phase of blood coagulation, which represents only the first 4% of thrombin production[31]. Furthermore, ROTEM yields more abundant information since its parameters are evaluable at a variety of phases of coagulation and fibrinolysis. PT is normally measured at the center laboratory and requires a longer time to get the results whereas ROTEM provides measurements in a real-time manner[32]. In our hospital, each and all physicians measure the ROTEM on their own to check the presence of the coagulation abnormalities in critically ill patients. It is useful to assess the indication of massive transfusion and anti-fibrinolytic agent in the early phase of severe injury.

The standard coagulation tests revealed statistically prolonged PT/APTT only in severe hyperlactatemia. ROTEM findings also showed that an increase in lactate levels (≥4.0 mmol/L) correlated with a decreased speed of thrombus formation and increased fibrinolysis, in addition to abnormal results of standard coagulation tests. Alpha angle primarily reflect the rate of clot formation and polymerization. And reversible impairment of alpha angle was confirmed by lactic acidosis in healthy samples[33]. The possible mechanisms of lower alpha angle include an early deficiency or loss of coagulation factors such as platelet, fibrinogen and some coagulation factors[34]. Our hematological analyses using plasma samples showed that higher lactate levels were significantly re-

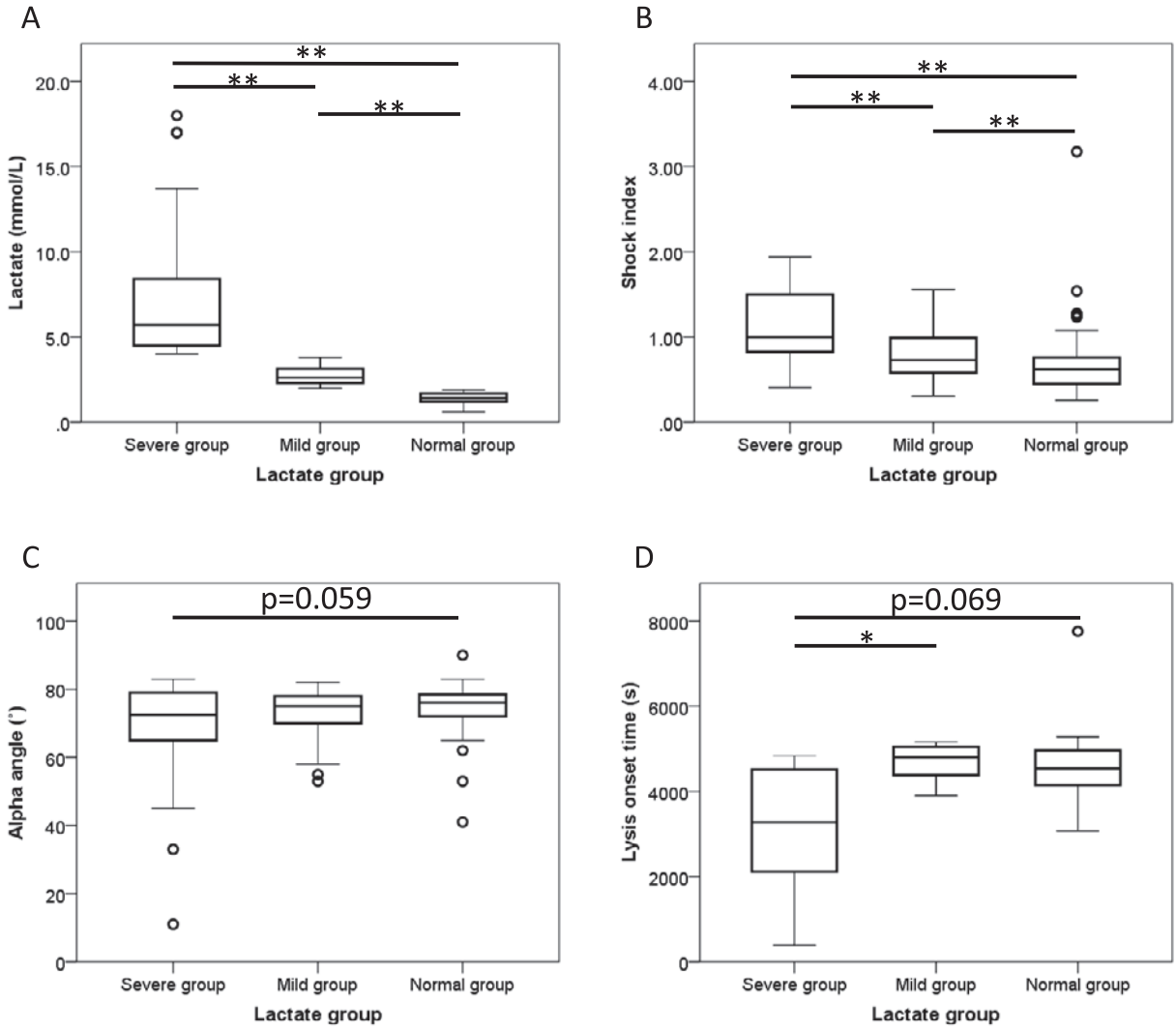

Fig. 2 Lactate (A), Shock index (B), Alpha angle (C) and Lysis onset time (D) in each group.
Kruskal-Wallis test after Bonferroni adjustment showed that shock index (HR/sBP) in severe group was significantly higher than that of the other groups (P<0.001). Although significant differences were observed according to alpha angle (p=0.040) by Kruskal-Wallis test, Bonferroni correction didn't show statistical differences between alpha angle in severe group and normal group. Lysis onset time (p=0.024) in severe group was significantly faster than that in mild group. *, p<0.05; **, p<0.01.

lated to higher PT-INR and longer APTT. On the other hand, previously reported mechanisms of hyperfibrinolysis induced by peripheral hypoperfusion are associated with endothelial damage of peripheral blood vessels and stimulation of the secretion of t-PA from endothelial cells[35]. Another mechanism is mediated through the activation of thrombomodulin[36]. Reports on the relationship between lactate acidosis and coagulopathy have been increasingly observed. Lesperance et al. who developed a swine model of lactate acidosis, confirmed prolonged PT-INR, CFT and a decreased α angle by EXTEM[37]. In vitro study with blood samples from healthy volunteers by Engstrom et al. showed that there was a decrease in α angles and prolonged CFT, while lactate levels were increased[33]. These results were consistent with our present data. However, there was no description about the presence of hyperfibrinolysis in the previous reports. Importantly, ROTEM in this study indicated the presence of hyperfibrinolysis as well as hypocoagulability in patients with peripheral circulatory insufficiency and severe hyperlactatemia.

Patients with sBP of 90 mmHg or lower showed significantly longer PT/APTT, however, hyperfibrinolysis and inhibition of the early phase of blood coagulation detected by ROTEM were undistinguishable. Although sBP has broad utility in a clinical setting, recent studies

Table 3 Comparison of the two groups based on systolic blood pressure (90 mm Hg)

	sBP<90 (n=31)	sBP ≥ 90 (n=161)	P value
PT-INR	1.16 [1.1, 1.4]	1.03 [1.0, 1.2]	0.001*
APTT (s)	35.0 [31, 42]	30.9 [28, 35]	0.002*
FDP (μg/mL)	23.5 [7, 70]	11.8 [4, 46]	0.153
DD (μg/mL)	9.5 [3, 27]	4.0 [1, 18]	0.068
CT (s)	61.0 [50, 71]	52.0 [45, 64]	0.090
A10 (mm)	61.0 [44, 68]	58.0 [51, 64]	0.846
A20 (mm)	66.0 [52, 72]	64.0 [57, 69]	0.823
MCF (mm)	67.0 [56, 72]	64.0 [59, 70]	0.881
CFT (s)	64.5 [55, 112]	78.0 [64, 107]	0.341
α angle (°)	77.5 [68, 79]	75.0 [69, 78]	0.428
HF (%)	12.9	5.3	0.124
LOT (s)	3,906 [1,797, 4,611]	4,544 [4,273, 4,975]	0.065

Median [Q1, Q3], *p<0.05

sBP; systolic blood pressure, PT-INR; prothrombin time-international normalized ratio, APTT; activated partial thromboplastin time, FDP; fibrinogen and fibrin degradation products, DD; D dimer, CT; clotting time, MCF; maximum clot firmness, CFT; clot formation time, HF; hyperfibrinolysis, LOT; lysis onset time, Q; quartile.

have reported the effectiveness of the prehospital and in-hospital measurement of lactate levels as a Point-of-care testing[5,38]. Early recognition of the presence of coagulopathy, especially with hyperfibrinolysis, detected by serum lactate level in the early phase of critically ill patients leads to early initiation of anti-fibrinolytic therapy recommended by the CRASH-II study[39].

There are some drawbacks to be improved in this study such as small sample size that may represent a possible selection bias. Pathophysiology of coagulation and fibrinolytic system in acute phase of severely ill/trauma patients changes drastically with time[40]. It is difficult to adjust the clinical backgrounds and severity to one particular population in this study. We evaluated all patients to grasp the overview of coagulation and fibrinolytic disorders only by adjusting the timing of every testing, on admission to the ED. Advanced analyses using severity-matched population with one particular cause is warranted near future.

In conclusion, abnormal serum lactate levels (≥4 mmol/L) properly reflected peripheral circulatory insufficiency and were more closely associated with coagulopathy such as hypocoagulability and hyperfibrinolysis than sBP.

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