


## Original Article

## Novel screening criteria for post-traumatic venous thromboembolism by using D-dimer

Keita Iyama,<sup>1</sup>  Takamitsu Inokuma,<sup>1</sup> Shuntaro Sato,<sup>2</sup> Shuhei Yamano,<sup>1</sup> Goro Tajima,<sup>1</sup> Tomohito Hirao,<sup>1</sup> and Osamu Tasaki<sup>1</sup><sup>1</sup>Acute and Critical Care Center, and <sup>2</sup>Clinical Research Center, Nagasaki University Hospital, Nagasaki, Japan

**Aim:** Because severe trauma patients frequently manifest coagulopathy, it is extremely important to detect venous thromboembolism (VTE) in the acute phase. However, no reference value for D-dimer in post-traumatic VTE has been reported given the substantial increase in its levels after injury. Therefore, this study evaluates the ability of our screening criteria using D-dimer to detect VTE in severe trauma patients.

**Methods:** Trauma patients ( $n = 455$ ) who were admitted to our emergency medical center during October 2011–June 2015 were included in this study. To prevent VTE, intermittent pneumatic compression was carried out in most patients. Our screening criteria included the following: (i)  $\geq 5$  days of hospital stay, (ii) increasing D-dimer levels across 3 measuring days, (iii) D-dimer levels  $\geq 15 \mu\text{g/mL}$ . Patients who met these screening criteria underwent contrast-enhanced computed tomography (CE-CT) to detect VTE.

**Results:** During the study period, 108 cases satisfied the screening criteria; 73 of these underwent CE-CT, 34 of whom were diagnosed with VTE (positive predictive value, 46.6%). The median hospital stay on satisfying the screening criteria and before undergoing CE-CT was 7 and 10 days, respectively. No patient had VTE symptoms at the time of diagnosis. Also, none of the remaining 347 patients who did not satisfy the screening criteria had VTE symptoms.

**Conclusion:** The screening criteria using D-dimer presented herein can be used as reference for efficiently detecting VTE in severe trauma patients.

**Key words:** Contrast-enhanced computed tomography, D-dimer, trauma, venous thromboembolism

## INTRODUCTION

NAGASAKI UNIVERSITY HOSPITAL Acute and Critical Care Center (Nagasaki, Japan) is the only tertiary medical institution in the medical area with a population of approximately 540,000 that has been actively accepting serious cases. Among such cases, especially in severe trauma patients, the risk of developing venous thromboembolism (VTE), including pulmonary thromboembolism

**Corresponding:** Keita Iyama, MD, PhD, Acute and Critical Care Center, Nagasaki University Hospital, 852-8102, 1-7-1, Sakamoto, Nagasaki-City, Nagasaki, Japan. E-mail: k-iyama@nagasaki-u.ac.jp.

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(PTE) and deep vein thrombosis (DVT), has been quite high despite standard venous thrombotic prophylaxis.

The incidence of VTE after general surgery has been found to reach 30% without any prevention, and the fatality rate among these cases has been considered to be 1%.<sup>1</sup> Additionally, 25% of trauma patients developed coagulopathy at the time of visit, and the mortality rate in such cases was reportedly five times higher than that in cases without coagulopathy.<sup>2</sup> Therefore, early recognition of VTE onset is extremely important for improving patient prognosis and for shortening hospital stay.

D-dimer levels determined through blood testing have been generally known as a marker for predicting venous thrombosis. However, because D-dimer levels show a sharp increase immediately after severe traumatic injuries, a clear cut-off value for predicting VTE has yet to be established.

We have herein established novel screening criteria using D-dimer for the early-phase detection and prevention of lethal VTE in trauma cases.

## METHODS

OVERALL, 455 TRAUMA patients who were admitted to our center between October 2011 and June 2015 were included. The protocol for this research project was approved by a suitably constituted Ethics Committee of Nagasaki University Hospital (approval no. 15122113), and it conforms to the provisions of the Declaration of Helsinki.

To prevent VTE, intermittent pneumatic compression was carried out whenever possible following hospitalization in all cases, except for those with unattachable limbs, such as in external fixation. No new anticoagulants had been given for the purpose of preventing VTE. Those who required regular anticoagulant or antiplatelet treatment because of underlying diseases were prevented from receiving medications until no risk for bleeding was present.

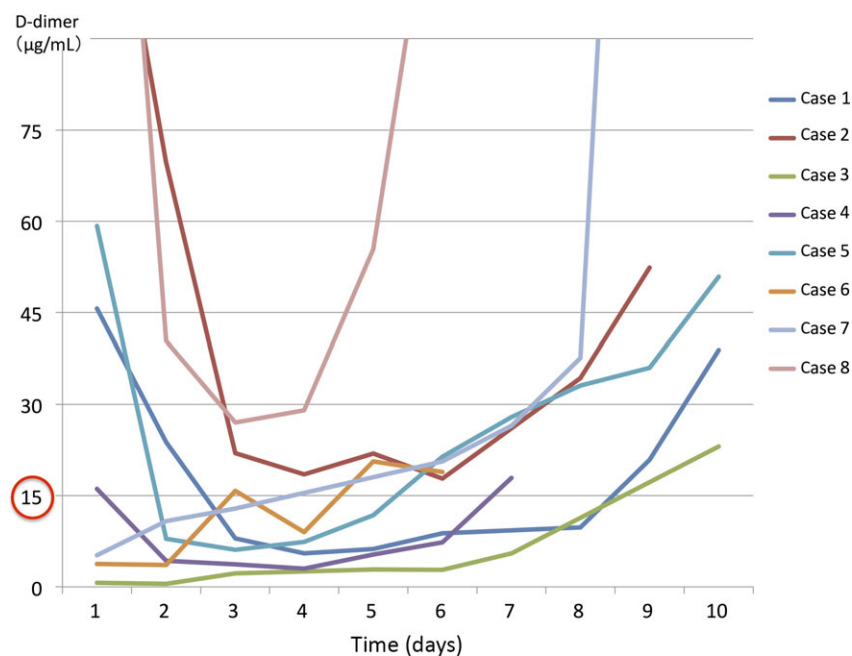
Blood tests were undertaken every day during the acute period, and D-dimer levels were measured at the in-hospital central examination department. Nanopia D-dimer (reference value,  $<1.0 \mu\text{g/mL}$ ) (Sekisui Medical Co., Tokyo, Japan) was used to measure D-dimer levels in our hospital.

Before starting the present study, and given our experience with fatal VTE after trauma requiring emergency thoracotomy, post-traumatic VTE cases that developed at our center were retrospectively analyzed. Accordingly, eight

cases of VTE had occurred within 7 months; the D-dimer level transitions of these cases are shown in Figure 1. High D-dimer levels immediately following trauma tended to decrease once, after which they increased continuously for  $\geq 3$  days in seven cases (except case 6) and reached  $\geq 15 \mu\text{g/mL}$  after 5 hospital days in all eight cases. Case 6 also showed an increasing trend, though not continuous. Consequently, our screening criteria were established based on the aforementioned results and references,<sup>3</sup> recognizing 10–15  $\mu\text{g/mL}$  as the screening cut-off value for D-dimer.

Our criteria for screening post-traumatic VTE in trauma patients comprised: (i)  $\geq 5$  days of hospital stay, (ii) increasing D-dimer levels across 3 measuring days, (iii) D-dimer levels  $\geq 15 \mu\text{g/mL}$  (Table 1). Contrast-enhanced computed tomography (CE-CT) was carried out for cases satisfying all the screening criteria. The exclusion criteria for CE-CT included the following: renal dysfunction, history of contrast agent allergy, refusal of resuscitation treatment in the treatment policy, or non-necessity of CE-CT as determined by the physician in charge.

Dual tube CT (SOMATOM Definition; Siemens Co., Munich, Germany) was used from the beginning of the research until March 2014, after which the SOMATOM Definition Flash (Siemens) was used. Iohexol (iodine content, 300 mg/mL) was used as the contrast medium. After



**Fig. 1.** Serial changes in D-dimer in eight cases of post-traumatic venous thromboembolism. In all cases, the D-dimer levels reached 15  $\mu\text{g/mL}$  on or after day 5. The D-dimer levels increased continuously for  $\geq 3$  days in seven patients; however, it did not increase continuously in case 6 but followed a trend in the increase.

**Table 1.** Screening criteria using D-dimer to detect venous thromboembolism in patients with severe trauma

Screening criteria	
(i)	≥5 days of hospital stay
(ii)	Increasing D-dimer levels across 3 measuring days
(iii)	D-dimer levels ≥15 µg/mL
Patients who met (i)–(iii) underwent contrast-enhanced computed tomography	

single imaging of the chest, 60 mL contrast medium was injected through the upper limb vein at 4 mL/s followed by chest imaging 17 and 40 s later in principle. Thereafter, 90 mL contrast medium was injected at 2 mL/s followed by liver to lower limb imaging 240 s later. The slice thickness of the two tubes was 2.0–2.0 mm for the chest and 3.0–2.4 mm for the liver to lower limbs.

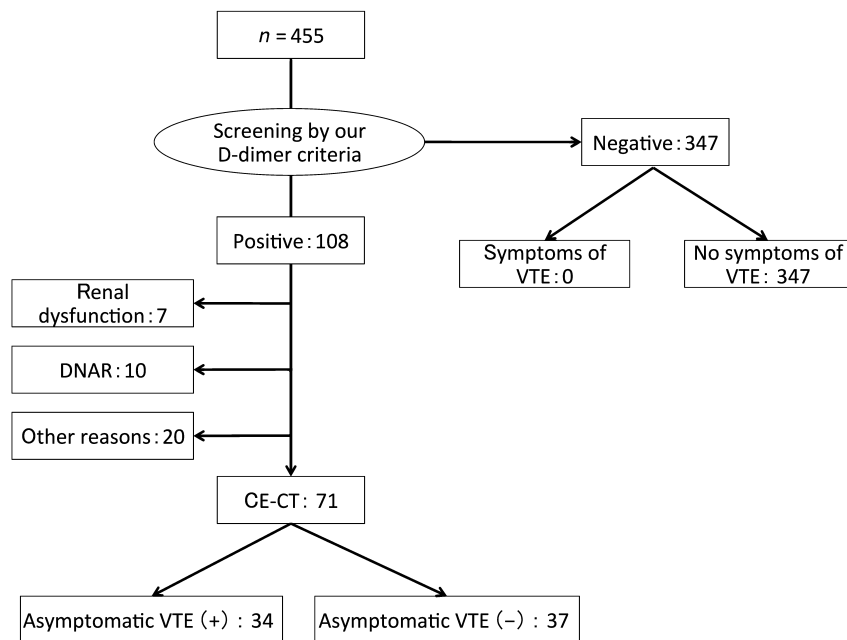
Patients unable to undergo CE-CT were alternatively subjected to lower limb venous ultrasound examination or simple CT. However, cases without CE-CT were excluded from analysis. Additionally, the evaluation of the presence or absence of VTE through CE-CT was carried out under the interpretation of a radiology specialist. Then, cases wherein a diagnosis of VTE had been reached were referred to a cardiologist to determine the appropriate treatment for each case.

Patient background, type of injury, Injury Severity Score (ISS),<sup>4,5</sup> Abbreviated Injury Scale (AIS), and Probability of Survival (PS)<sup>6</sup> were among the items evaluated. The risk assessment profile (RAP) score<sup>7</sup> was calculated on hospitalization. The Wells score for DVT<sup>8</sup> was calculated on the day the screening criteria were satisfied. The aforementioned items were compared between patients with and without VTE.

The continuous data are presented as medians (interquartile ranges), and the categorical data are presented as percentages. Wilcoxon's rank-sum test and Fisher's exact test were used for association analysis. The relationships between VTE and ISS, age, sex, mechanism of injury, and RAP score were also examined using logistic regression analysis. JMP Pro 11 (SAS Institute, Cary, NC, USA) was used for all statistical analyses, with statistical significance set at 5%.

## RESULTS

**D**URING THE OBSERVATION period, 108/455 patients satisfied the screening criteria, among whom 37 did not undergo CE-CT due to the exclusion criteria. Seventy-one CE-CT images were taken, with 34 cases diagnosed as VTE (Fig. 2). None of the cases required periodic intake of anticoagulants due to underlying diseases before trauma. Furthermore, 3/34 VTE (+) cases and 1/37 VTE (–)



**Fig. 2.** Patient flowchart showing the use D-dimer criteria to identify severe trauma patients at risk of venous thromboembolism (VTE). One hundred eight patients met the criteria, 71 of which underwent contrast-enhanced computed tomography (CE-CT). None of the patients excluded by the screening criteria had symptoms of VTE. (+), present; (–), absent; DNAR, do not attempt resuscitation.

cases had taken antiplatelet drugs before the injury. None of the cases required hemodiafiltration or percutaneous cardiopulmonary assistance devices, nor new anticoagulants or antiplatelet drugs for other reasons, during the hospitalization. Additionally, 2/71 patients satisfied the criteria twice during the observation period, both of whom underwent CE-CT at each instance. Although VTE was not confirmed during the first CE-CT, the second one was able to confirm the diagnosis of VTE. Therefore, statistical analysis related to CE-CT was carried out with the assumption that 73 cases satisfied the criteria.

Among the 71 cases, 39 were men and 32 were women, aged 67 (57–78) years (median, 25%–75%) (Table 2). The injury mechanisms included traffic

accidents ( $n = 43$ ), falling off ( $n = 24$ ), falling down ( $n = 1$ ), burns ( $n = 2$ ), and compression ( $n = 1$ ). An ISS of 29 (19–38), RAP score of 12 (9–17), and Wells score of 2 (2–2) were obtained. The screening criteria were satisfied on day 7 (6–10), and CE-CT was carried out on day 10 (7–14) (Table 2).

Among the 73 patients who underwent CE-CT, 34 were diagnosed with VTE through imaging (positivity rate, 46.6%). Although women tended to develop VTE more easily, no statistically significant difference was found ( $P = 0.098$ ). Age was significantly higher in VTE (+) than in VTE (–) cases ( $P = 0.032$ ). Regarding the type and severity of trauma, no significant differences in ISS, AIS, or PS were observed between the two groups (Table 2).

**Table 2.** Characteristics of severe trauma patients assessed for their risk of developing venous thromboembolism (VTE)

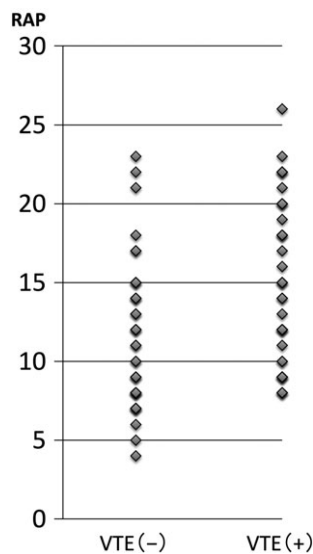
	Total	VTE (+)	VTE (–)	<i>P</i> -value
<i>n</i>	71	34	37	
Sex				
Male, <i>n</i>	39	15	24	0.098
Female, <i>n</i>	32	19	13	
Age, median (IQR)	67 (57–78)	70.5 (59.75–78.25)	64 (41–76.5)	0.032
Antiplatelet therapy before injury, <i>n</i>	4	3	1	0.264
Mechanism of injury, <i>n</i>				
Traffic accident	43	23	20	0.242
Falling off	24	10	14	0.453
Falling down	1	0	1	0.334
Burn	2	0	2	0.169
Compression	1	1	0	0.293
ISS, median (IQR)	29 (19–38)	26.5 (21.75–36)	29 (15.5–42)	0.931
RAP score, median (IQR)	12 (9–17)	15 (10.75–20)	11 (8–14.5)	0.003
Wells score, <i>n</i> (%)				
1	23 (32.4%)	8 (23.5%)	15 (40.5%)	0.109
2	45 (63.4%)	24 (70.6%)	21 (56.8%)	
3	3 (4.2%)	2 (5.9%)	1 (2.7%)	
Max AIS (head), median (IQR)	1 (0–4)	0 (0–3)	3 (0–4)	0.383
Max AIS (face), median (IQR)	0 (0–2)	0 (0–1.25)	0 (0–2)	0.979
Max AIS (neck), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.179
Max AIS (chest), median (IQR)	3 (0–4)	3 (0–4)	2 (0–3.5)	0.272
Max AIS (abdomen), median (IQR)	0 (0–2)	0 (0–2.25)	0 (0–2)	0.858
Max AIS (spine), median (IQR)	0 (0–2)	0 (0–3)	0 (0–2)	0.463
Max AIS (arms), median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0.839
Max AIS (lower), median (IQR)	3 (0–3)	3 (0.75–3)	3 (0–3)	0.966
Max AIS (surface), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.262
PS (%), median (IQR)	82.4 (63.6–93.4)	78.7 (48.3–89.5)	88.7 (65.0–95.2)	0.105
Criteria met (day), median (IQR)	7(6–10)	7(6–10.25)	7(6–10)	0.955
	( <i>n</i> = 73)	( <i>n</i> = 34)	( <i>n</i> = 39)	
CE-CT carried out (day), median (IQR)	10(7–14)	9.5(7–14)	10(7–13)	0.811
	( <i>n</i> = 73)	( <i>n</i> = 34)	( <i>n</i> = 39)	

(+), present; (–), absent; AIS, Abbreviated Injury Scale; CE-CT, contrast-enhanced computed tomography; IQR, interquartile range; ISS, Injury Severity Score; Max, maximum; PS, Probability of Survival; RAP, Risk Assessment Profile.

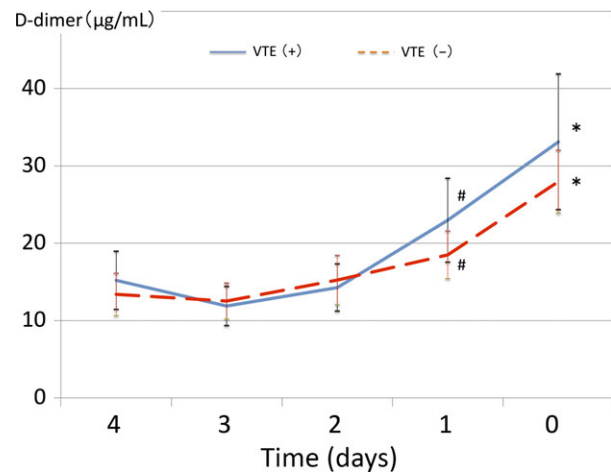
Among the 71 patients who underwent CE-CT, 70 had a RAP score  $\geq 5$  on the day of visit (Fig. 3). Although RAP scores were significantly higher in VTE (+) than in VTE (–) cases ( $P = 0.003$ ), no substantial difference was found to establish a clear cut-off value. To assess the risk of DVT, including predisposition to thrombotic tendencies, we evaluated the Wells score on the day the screening criteria were satisfied. However, no significant difference was observed between the two groups ( $P = 0.109$ ). Moreover, multivariate analysis found a significant association between the presence of VTE and RAP score ( $P = 0.010$ ).

Figure 4 shows the D-dimer transition over the previous 5 days until the screening criteria were satisfied. No significant difference between VTE (+) and VTE (–) cases was observed for D-dimer transition. Intragroup comparisons within VTE (+) and VTE (–) cases showed significantly higher D-dimer levels on day 0 (upon satisfying the criteria) than on day 1. Moreover, D-dimer levels on day 1 were significantly higher than that on day 2. No significant difference was observed between the two groups from the day of injury until the screening criteria were satisfied (Table 2). Figure 5 shows the days on which the screening criteria were satisfied and CE-CT was carried out, as well as the number of days between criteria satisfaction and actual CE-CT enforcement. In 39 cases (53.4%), CE-CT had been mostly undertaken on the same day the screening criteria were satisfied; most

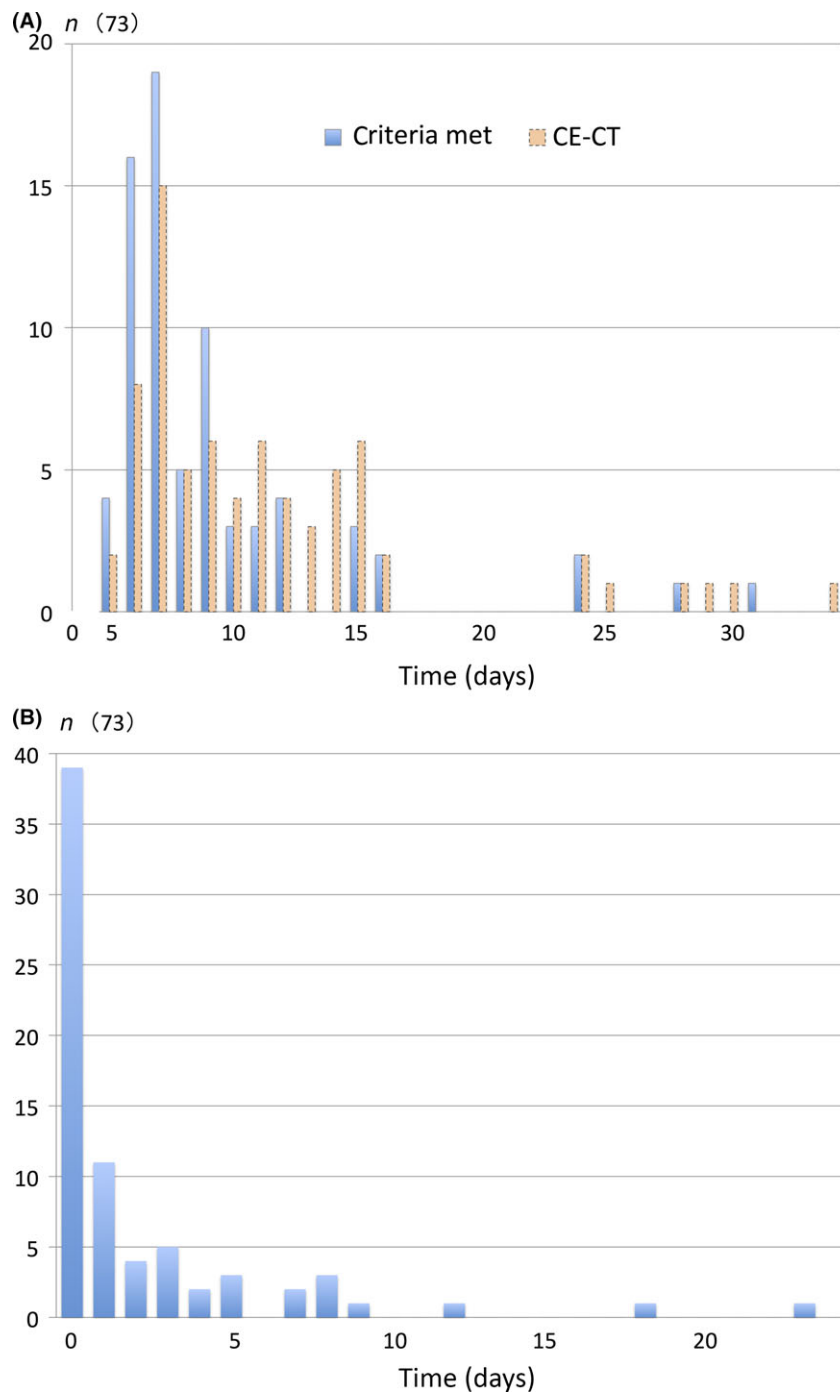
cases ( $n = 64$ , 87.7%) underwent CE-CT within 5 days of satisfying the criteria. Cases requiring  $>1$  week and  $<2$  weeks from criteria satisfaction until actual CE-CT examination were those in which CE-CT was delayed because it had just been carried out due to other reasons ( $n = 5$ ) and in which the respiratory condition had not been stabilized, thereby making immediate scanning impossible ( $n = 2$ ). In two cases, CT was carried out after  $>2$  weeks had elapsed. One case involved pronounced anterior mediastinal hematoma due to thoracoabdominal trauma. Because the high D-dimer level was caused by hematoma, CE-CT was not undertaken. However, considering that higher D-dimer levels were sustained, CE-CT was subsequently carried out. In the other case, because CE-CT was undertaken frequently due to severe head injury, we first performed ultrasonography of the lower limb vein following criteria satisfaction. However, no thrombus was observed, and follow-up observation was carried out. Accordingly, considering that high D-dimer levels were sustained, late CE-CT was performed. Subsequent treatment in VTE (+) cases included the following: inferior vena cava filter ( $n = 2$ ), treatment with heparin and warfarin ( $n = 24$ ), heparin only ( $n = 1$ ), fondaparinux and warfarin ( $n = 2$ ), and heparin and edoxaban ( $n = 2$ ). Follow-up observations without anticoagulant treatment were carried out in three patients with



**Fig. 3.** Dot-plot for the Risk Assessment Profile (RAP) score among severe trauma patients ( $n = 71$ ). A clear cut-off value could not be obtained for distinguishing between the absence (–) or presence (+) of venous thromboembolism (VTE).



**Fig. 4.** Transition of the D-dimer level in severe trauma patients until the screening criteria was met. There was no statistical significant difference between the two groups with absence (–) or presence (+) of venous thromboembolism (VTE). D-dimer levels on day 0 were significantly higher than those on other days in both VTE(+) and VTE(–) patients ( $*P < 0.01$ ). In addition, D-dimer levels on day –1 were significantly higher than those on days –2, –3, and –4 in both groups ( $\#P < 0.01$ ). Day 0, the day when screening criteria were met.



**Fig. 5.** A, Histogram of hospital days on which D-dimer screening criteria in severe trauma patients were met or contrast-enhanced computed tomography (CE-CT) was carried out. Most cases met the criteria and underwent CE-CT within 2 weeks. B, Histogram of the time when CE-CT was carried out after meeting the criteria. Most cases underwent CE-CT within 5 days ( $n = 64$ , 87.7%).

aortic injury and two cases with very small popliteal vein thrombus. None of the VTE (+) cases developed severe PTE, and all 34 patients survived and were discharged.

Conversely, symptomatic VTE was not observed among the 347 patients who did not satisfy the screening criteria during their hospital stay (Fig. 2).

## DISCUSSION

### Trauma and VTE

IN THE USA, 900,000 patients develop VTE annually with approximately 300,000 individuals dying as a result.<sup>9</sup> Venous thromboembolism can be life-threatening, especially considering that coagulation reactions increase after trauma.<sup>10–12</sup> Compared to the USA and Europe, Japanese individuals tend to have less PTE and DVT, with incidences in Japan being approximately 1/4 to 1/8 of that in the USA.<sup>13,14</sup> Accordingly, European and American populations have been reported to have gene mutations causing activated protein C resistance, which has been thought to affect VTE frequency.<sup>13</sup> However, this condition has not been found in the Japanese population. Westernized dietary habits in recent years, the aging population, and diagnostic advancements have thought to have led to an increase in VTE detection rates among Japanese individuals.<sup>13</sup> Because severe PTE could lead to sudden death, prevention and early detection are extremely important for trauma patients at high risk for VTE.

### Venous thromboembolism and D-dimer

D-dimer, the smallest unit of fibrin degradation products specific to secondary fibrinolysis, has been widely used for VTE screening. In addition to thrombus formation, D-dimer has been known to increase with trauma, surgical invasion, aneurysm, leukemia, and disseminated intravascular coagulation (DIC). Despite its low specificity, D-dimer reportedly has high sensitivity.<sup>13,15</sup> Therefore, although D-dimer examination is a relatively minimally invasive procedure (i.e., a blood test), VTE can be ruled out in patients who were originally under low suspicion of VTE and were negative after D-dimer screening. D-dimer measurements were undertaken every day throughout the acute period for VTE screening. Conversely, fibrin degradation product (FDP) has been frequently used as a marker for the same fibrinolytic system. Fibrin degradation product is a degradation product of fibrin and fibrinogen, reflecting both primary and secondary fibrinolysis. Therefore, D-dimer can be regarded as a part of FDP with many cases in which these two are correlated. In cases wherein D-dimer or FDP increase, differentiating VTE from DIC, mass thoracoabdominal fluid, or hematoma is imperative. In such cases, CE-CT according to our screening criteria allows for simultaneous VTE differentiation and identification. However, when discrepancies between FDP and D-dimer levels arise, it is necessary to suspect highly fibrinolytic DIC with advanced fibrinolytic activation.

A cut-off D-dimer level of approximately 10–15  $\mu\text{g/mL}$  is reportedly effective for VTE screening in patients

undergoing orthopedic surgery for lower limb or pelvic fractures.<sup>3</sup> However, there have been no reports showing an effective cut-off value for multiple injuries, including those involving the head, chest, and abdomen, which we actively accept at our center. After investigating previous VTE cases at our center, we found that all such cases had D-dimer levels  $>15 \mu\text{g/mL}$  at the time of diagnosis. Hence, our cut-off value had been set at 15  $\mu\text{g/mL}$ . However, because measurement values of D-dimer differ depending on the measurement kit, our cut-off value of 15  $\mu\text{g/mL}$  could differ from that established in hospitals using other measurement kits.<sup>16</sup>

### Lower limb venous ultrasonography and CE-CT

Herein, CE-CT had been considered the first examination option for patients who satisfied the screening criteria. Although the advantages of ultrasound examination include its noninvasive nature and ability to be performed at the bedside, its disadvantages include a specific posture, the requirement of a certain amount of time, and its dependence on the examiner's skill.<sup>13</sup> Considering the patients visiting our center, it was impossible to adequately screen for DVT using lower limb ultrasonography given the difficulty in securing the position needed for the procedure due to the high number of patients receiving external fixation and ventilator management. Therefore, CE-CT had been undertaken in all cases except those satisfying the exclusion criteria.

### Risk assessment profile score

The RAP score allows for determining the risk of developing VTE after injury in trauma patients.<sup>7,11,17</sup> Moreover, it focuses on patient background and age, the factor of iatrogenicity, and severity of trauma, and scoring can be done early after the injury. According to previous data in the USA, the risk of VTE is tripled with a RAP score  $\geq 5$ .<sup>17</sup> However, given that, compared to the USA and Europe, Japanese individuals are less likely to develop VTE, much consideration is necessary regarding its use in Japan. Although the present study observed statistically significant differences in RAP scores between patients with and without VTE, a clear cut-off value could not be established from the difference. Further research is necessary to predict the risk for post-traumatic VTE using RAP scores among Japanese individuals.

### Efficacy of screening criteria

With reference to our screening criteria, a positivity rate of 46.6% had been obtained as well as higher rates of VTE

detection. Moreover, considering that symptomatic VTE had not been observed among cases that did not satisfy our screening criteria, we believe that the screening criteria presented herein could be usable in daily clinical practice. Therefore, the possible early detection and treatment of asymptomatic VTE using this screening criteria could prevent the onset of symptomatic VTE.

### Limitations

Several problems are inherent to this research. First, although the establishment of our screening criteria and performance of CE-CT examinations were undertaken prospectively, the analysis had been conducted retrospectively. Accordingly, a prospective study design could have reduced the variation in the number of days between the criteria satisfaction and the CE-CT examination.

Second, CE-CT had been carried out in patients that satisfied the criteria and asymptomatic VTE was detected. However, the presence or absence of asymptomatic VTE in the 347 patients who did not satisfy the criteria had not been evaluated. Therefore, asymptomatic VTEs could have been present among the 347 cases. Moreover, the sensitivity or specificity of this screening criteria had been determined. However, based on actual clinical practice, it would be unrealistic to undertake CE-CT in all the cases. The final objective of this protocol was to prevent the onset of life-threatening VTE. Therefore, because symptomatic VTE had not been observed in cases that did not meet these screening criteria, we believe that further examination was unnecessary and that our criteria could be used in daily practice.

Third, >1 week had passed between the criteria satisfaction and the actual CE-CT examination in nine cases that had not been diagnosed at an early stage. In such cases, however, it was clinically impossible to immediately carry out CE-CT. Nevertheless, we believe it to be important to shorten the number of days between criteria satisfaction and CE-CT examination for the early detection of VTE.

Fourth, although the present study detected asymptomatic VTE in the early phase, it remained unclear whether all cases diagnosed as VTE (+) by this screening actually needed treatment. In fact, three cases did not receive treatment, although symptomatic VTE did not subsequently develop. Anticoagulation therapy had been provided for the remaining cases, considering the possibility of deterioration. However, future studies should consider whether anticoagulation therapy is necessary.

Finally, because this study was carried out in a single facility with a small number of cases, our results cannot be generalized. Therefore, future multicenter studies are imperative.

### CONCLUSION

**A** SYMPTOMATIC VTE AFTER trauma could be detected using the following screening criteria: (i)  $\geq 5$  days of hospital stay, (ii) increasing D-dimer levels across 3 measuring days, (iii) D-dimer levels  $\geq 15$   $\mu\text{g/mL}$ . Additionally, symptomatic VTE development had not been observed in all cases, including those that did not satisfy these screening criteria. Therefore, the criteria presented herein can serve as a reference for establishing routine practices that efficiently detect VTE after trauma.

### DISCLOSURE

Approval of the research protocol: This study was carried out with the approval of the ethics committee of Nagasaki University Hospital (No.15122113).

Informed consent: Not applicable.

Registry and the registration no. of the study/trial: Not applicable.

Animal studies: Not applicable.

Conflict of interest: None declared.

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