

# Risk Factors of Fat Embolism Syndrome After Trauma



## A Nested Case-Control Study With the Use of a Nationwide Trauma Registry in Japan

Takako Kainoh, MD; Hiroki Iriyama, MD; Akira Komori, MD; Daizoh Saitoh, MD, PhD; Toshio Naito, MD, PhD; and Toshikazu Abe, MD, PhD

**BACKGROUND:** Fat embolism syndrome (FES) is a rare syndrome resulting from a fat embolism, which is defined by the presence of fat globules in the pulmonary microcirculation; it is associated with a wide range of symptoms.

**RESEARCH QUESTION:** What are the specific unknown risk factors for FES after we have controlled for basic characteristics and patient's severity?

**STUDY DESIGN AND METHODS:** This was a nested case-control study that used the Japan Trauma Data Bank database from 2004 and 2017. We included patients with FES and identified patients without FES as control subjects using a propensity score matching. The primary outcome was the presence of FES during a hospital stay.

**RESULTS:** There were 209 (0.1%) patients with FES after trauma; they were compared with 2,090 matched patients from 168,835 candidates for this study. Patients with FES had long bone and open fractures in their extremities more frequently than those without FES. Regarding treatments, patients with FES received bone reduction and fixation more than those without FES. Among patients who received bone reduction and fixation, time to operation was not different between the groups ( $P = .63$ ). The overall in-hospital mortality rate was 5.8% in patients with FES and 3.4% in those without FES ( $P = .11$ ). Conditional logistic regression models to identify risk factors associated with FES shows long bone and open fractures in extremities injury were associated with FES. Primary bone reduction and fixation was not associated independently with FES (OR, 1.80; 95% CI, 0.92-3.54), but delay time to the operation was associated with FES (OR, 2.21; 95% CI, 1.16-4.23).

**INTERPRETATION:** Long bone and open fractures in injuries to the extremities were associated with FES. Although bone reduction and fixation were not associated with FES, delay time to the operation was associated with FES. CHEST 2021; 159(3):1064-1071

**KEY WORDS:** extremities; fat embolism syndrome; trauma

**ABBREVIATIONS:** AIS = abbreviated injury scale; FES = fat embolism syndrome; ISS = injury severity score; JTDB = Japan Trauma Data Bank

**AFFILIATIONS:** From the Department of General Medicine (T. Kainoh, H. Iriyama, A. Komori, and T. Naito), Juntendo University Faculty of Medicine, Tokyo, Japan; Department of Traumatology and Emergency Medicine (D. Saitoh), National Defense Medical College, Tokorozawa, Japan; Department of Health Services Research, Faculty of Medicine, and the Health Services Research and Development Center (T. Abe), University of Tsukuba, and the Department of

Emergency and Critical Care Medicine, Tsukuba Memorial Hospital, Tsukuba, Japan.

**FUNDING/SUPPORT:** The authors have reported to CHEST that no funding was received for this study.

**CORRESPONDENCE TO:** Toshikazu Abe, MD, PhD; e-mail: [abetoshi11@gmail.com](mailto:abetoshi11@gmail.com)

Copyright © 2020 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

**DOI:** <https://doi.org/10.1016/j.chest.2020.09.268>

The pathophysiologic mechanisms of fat embolism syndrome (FES) arising from fat embolism, which is defined by the presence of fat globules in the pulmonary microcirculation, regardless of their clinical significance, have not yet been elucidated completely.<sup>1</sup> Additionally, the clinical characteristics, patterns, and outcomes of FES remain unknown due to a wide range of symptoms that are associated with this rare syndrome. Most cases of FES appear to be related to the fractures of long bones and pelvis containing high-fat bone

marrow.<sup>2-4</sup> However, some cases of FES are associated with trauma in the absence of orthopedic fractures; other FES cases are not related to trauma. Furthermore, because severe cases are associated with respiratory failure, neurologic deficits, and death, FES remains a challenge for clinicians, and early recognition is important for the prompt initiation of supportive therapy. Therefore, we aimed to investigate specific unknown risk factors for acute FES in trauma patients with the use of a nationwide trauma registry in Japan.

## Methods

### Study Design, Setting, and Data Source

This nested case-control study used a nationwide trauma registry, the Japan Trauma Data Bank (JTDB) database from 2004 and 2017. The JTDB is a nationwide trauma registry that was established in 2003 by the Japanese Association for the Surgery of Trauma and the Japanese Association for Acute Medicine to improve and ensure the quality of trauma care in Japan.<sup>5</sup> A total of 264 hospitals, including 95% of all tertiary emergency medical centers in Japan, participated in the JTDB in 2017.

### Study Participants

We included patients who had blunt or penetrating trauma, with injury severity scores  $\geq 9$  and those who were admitted to ICU or a general ward. Only patients who survived for more than 2 days after hospital admission were included to exclude the impact of early deaths. We also excluded patients who were pregnant (Fig 1).

### Data Collection

The JTDB includes data related to patient and hospital information such as patient demographics, Abbreviated Injury Scale (AIS) scores, injury severity scores, prehospital and in-hospital procedures, complications, and clinical outcomes. Data collection was performed as part of routine clinical patient treatment.

### Data Definitions

The primary outcome was the occurrence of FES during the hospital stay of each patient. FES was diagnosed clinically by the physician in charge. Definitions of other complications were also as per the JTDB.<sup>6</sup> Fractures were categorized as open, closed, or unclassified with the use of AIS90 Update 98 and AIS 2005 Update 2008: 752604.3 (humerus fracture), 752804.3 (radius fracture), 753204.3 (ulna fracture), 853422.3 (tibia fracture), and 852604.3 (pelvic fracture) in AIS 90 Update 98 were included in the open fractures. Although these codes include several different kinds of fractures, almost all of these were open fractures. Time to bone reduction and fixation was divided into two groups: operation performed at  $<24$  hours or  $\geq 24$  hours.

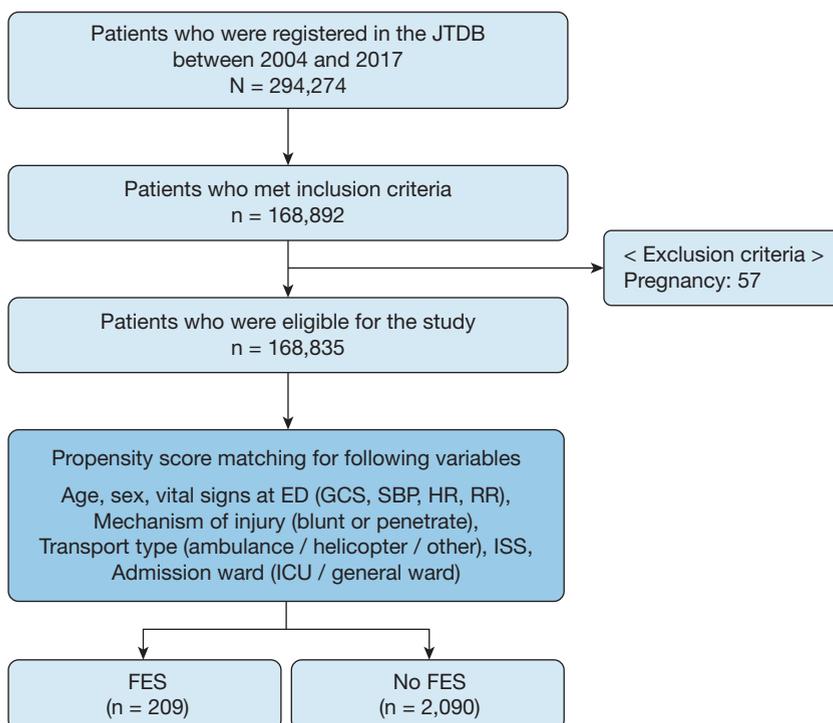


Figure 1 – Study patient selection. FES = fat embolism syndrome; GCS = Glasgow come scale; HR = heart rate; ISS = injury severity score; JTDB = Japan Trauma Data Bank; RR = respiratory rate; SBP = systolic BP.

## Statistical Analysis

To identify risk factors of FES, patients without FES from the JTDB database were selected as control subjects. We used a propensity score that matched sample control subjects to ensure that patients and control subjects were balanced equally with respect to baseline characteristics and severity of trauma. The following variables that are associated with the probability of trauma were included in the propensity model: age, sex, vital signs at ED (Glasgow Coma Scale, systolic BP, heart rate, respiratory rate), mechanism of injury (blunt or penetrate), transport type (ambulance without physician, ambulance and helicopter with physician, other), injury severity score, and admission ward (ICU or general ward). The variables were selected based on clinical relevance. Nearest neighbor propensity matching was used in a 1:10 manner based on an averaged propensity score with a caliper of 0.01. We used the standardized mean difference of variables was used to evaluate the match balance after PS matching. We generally considered that a standardized mean difference of  $>0.1$  was evaluated as a meaningful imbalance.

Then, we compared patients with FES and those without FES. We performed comparisons of categoric variables using the chi-square test and of continuous variables using the Wilcoxon signed-rank test or *t*-test.

After the baseline characteristics had been compared, conditional logistic regression models were used to identify risk factors for FES. Explanatory variables for which  $\leq 10$  patients in the groups were not included in the conditional logistic regression models. Variance inflation factor of the variables was calculated to evaluate multicollinearity. Variance inflation factor of  $>5$  was evaluated as meaningful multicollinearity. Additionally, there was no interaction

among the variables we selected, although we carefully examined clinically plausible interactions for multicollinearity. The candidates for risk factors in the conditional logistic regression model 1 were AIS  $\geq 3$  in the head, thorax, upper extremity, and lower extremity; those in the conditional logistic regression model 2 were AIS  $\geq 3$  in the head, thorax, and the presence of long-bone fracture in the upper and lower extremity. Conditional logistic regression model 3 candidates had AIS  $\geq 3$  in the head, thorax, and open fracture in upper and lower extremity injury. To identify any influence from having undergone an operation, the covariates in conditional logistic regression model 4 were the same as those in the conditional logistic regression model 3 in addition to having received primary bone reduction and fixation or not.

## Subgroup Analysis

We conducted a subgroup analysis by focusing on patients who had undergone primary bone reduction and fixation to evaluate its influence on early total care. The covariates were the same as those for the conditional logistic regression model 4.

All probability values were two-sided, and a  $P < .05$  was considered statistically significant. All statistical analyses were performed using R software (version 3.6.3; The R Foundation for Statistical Computing).

## Ethics Approval

The Ethics Committee of the Juntendo University, which did not require consent from patients in observational studies using anonymous data, approved this study. The JTDB administrators also provided permission to use the data from their database. This study was conducted in accordance with the amended Declaration of Helsinki.

## Results

Among 294,274 trauma patients who were registered in the JTDB between 2004 and 2017, 168,835 patients were eligible for this study (Fig 1). There were 209 (0.1%) patients who experienced FES after trauma, and they were compared with 2,090 matched patients. The baseline characteristics were well balanced between patients with and without FES (Table 1). Patients with FES had extremities and pelvic injury more frequently than those without FES. In details, patients with FES had long bone and open fracture in upper and lower extremities more frequently than those without FES. There were no significant differences with respect to comorbidities between patients with and without FES. Individual concomitant complications did not show a consistent pattern between the groups (e-Table 1).

Regarding treatments, patients with FES received more blood transfusion, bone reduction and fixation, and transcatheter arterial embolization than those without FES (Table 2). Among patients who received bone reduction and fixation, time to operation was not different between the groups ( $\leq 24$  h: 23.6% vs 26.2%;  $P = .63$ ).

The overall in-hospital mortality rate was 5.8% in patients with FES and 3.4% in those without FES ( $P = .11$ ) (Table 3). Patients with FES more likely transferred to other facilities than those without FES (75.8% vs 57.6%;  $P < .001$ ). Patients with FES stayed in the hospital longer than those without FES (30 [interquartile range, 20-53] days vs 23 [interquartile range, 12-37] days;  $P < .001$ ).

Table 4 shows conditional logistic regression models to identify risk factors that are associated with FES. Head and thoracic injuries were not associated with FES in any models. Conversely, injury to the extremities, especially long bone and open fractures, was associated consistently with FES. Primary bone reduction and fixation did not independently associate with FES (OR, 1.80; 95% CI, 0.92-3.54), but delay time to the operation was associated with FES (OR, 2.21; 95% CI, 1.16-4.23).

## Discussion

### Summary

The prevalence of FES was very low among patients with trauma. Extremities and pelvic injury, especially long bone and open fractures, were associated with the

**TABLE 1 ] Demographics and Characteristics That Compare Trauma Patients With and Without Fat Embolism Syndrome**

Characteristics	Fat Embolism Syndrome (n = 209)	No Fat Embolism Syndrome (n = 2,090)	Standardized Mean Difference	P Value
Age, <sup>a</sup> median (interquartile range), y	73 (43-85)	71 (49-83)	0.002	...
Sex <sup>a</sup> : male, median (interquartile range), No.	80 (38.3)	816 (39.0)	0.016	...
Mechanism of injury <sup>a</sup> : blunt, No. (%)	209 (100)	2,090 (100)	<0.001	...
Transport type, <sup>a</sup> No. (%)			.03	
Ambulance w/o physician	193 (92.3)	1,944 (93.0)	...	...
Ambulance/helicopter with physician	15 (7.2)	136 (6.5)	...	...
Other	1 (0.5)	10 (0.5)	...	...
Vital signs at ED, <sup>a</sup> median (interquartile range), No.				
Glasgow Coma Scale	15 (14-15)	15 (14-15)	0.02	...
Systolic BP	137 (114-156)	132 (113-155)	0.02	...
Heart rate	84 (75-100)	84.50 (73.25-97)	0.02	...
Respiratory rate	20 (17-25)	20 (18-24)	0.03	...
Admission ward <sup>a</sup> : general ward/ICU, No. (%)	114/95 (54.5/45.5)	1,152/938 (55.1/424.9)	0.01	...
Injury severity score, <sup>a</sup> median (interquartile range)	9 (9-19)	10 (9-18)	0.006	...
Abbreviated Injury Scale $\geq$ 3, No. (%)				
Head	28 (13.4)	601 (28.8)	...	<.001
Face	1 (0.5)	12 (0.6)	...	1.00
Neck	2 (1.0)	2 (0.1)	...	.05
Thorax	34 (16.3)	474 (22.7)	...	.04
Abdomen / pelvis	8 (3.8)	122 (5.8)	...	.30
Spine	10 (4.8)	227 (10.9)	...	.01
Upper extremity	23 (11.0)	102 (4.9)	...	<.001
Lower extremity	182 (87.1)	945 (45.2)	...	<.001
Others	0 (0)	0 (0)	...	NA
Upper extremity (detail)				
Long bone fracture (all)	24 (11.5)	102 (4.9)	...	<.001
Open	23 (11.0)	89 (4.3)	...	<.001
Closed	3 (1.4)	14 (0.7)	...	.42
Unclassified	0 (0)	2 (0.1)	...	1.00
Lower extremity (detail)				
Long bone & pelvic fracture (all)	176 (84.2)	932 (44.6)	...	<.001
Open	66 (31.6)	125 (6.0)	...	<.001
Closed	17 (8.1)	77 (3.7)	...	.004
Unclassified	122 (58.4)	712 (34.1)	...	<.001
Comorbidities				
Ischemic heart diseases	16 (7.7)	87 (4.2)	...	.03
Heart failure	5 (2.4)	61 (2.9)	...	.83
Hypertension	67 (32.1)	619 (29.6)	...	.51
Other cardiac diseases	8 (3.8)	131 (6.3)	...	.21
Asthma	8 (3.8)	71 (3.4)	...	.90
COPD	1 (0.5)	17 (0.8)	...	.91
Other chronic lung diseases	2 (1.0)	14 (0.7)	...	.97

(Continued)

**TABLE 1 ] (Continued)**

Characteristics	Fat Embolism Syndrome (n = 209)	No Fat Embolism Syndrome (n = 2,090)	Standardized Mean Difference	P Value
Liver cirrhosis	0 (0)	14 (0.7)	...	.47
Chronic hepatitis	3 (1.4)	30 (1.4)	...	1.00
Peptic ulcer	8 (3.8)	28 (1.3)	...	.01
Inflammatory bowel diseases	3 (1.4)	11 (0.5)	...	.25
Other GI diseases	3 (1.4)	78 (3.7)	...	.13
Diabetes mellitus	30 (14.4)	256 (12.2)	...	.44
Obesity	2 (1.0)	3 (0.1)	...	.10
Other metabolic diseases	6 (2.9)	81 (3.9)	...	.59
Stroke	24 (11.5)	111 (5.3)	...	.001
Psychiatric disease	10 (4.8)	139 (6.7)	...	.37
Dementia	28 (13.4)	185 (8.9)	...	.04
Other neurologic diseases	4 (1.9)	69 (3.3)	...	.38
HIV	0 (0)	0 (0)	...	NA
Malignancies	2 (1.0)	54 (2.6)	...	.22
Hematologic diseases	0 (0)	8 (0.4)	...	.78
Steroid use	0 (0)	13 (0.6)	...	.51
Immunosuppressant use	1 (0.5)	3 (0.1)	...	.81
Anticoagulant use	1 (0.5)	49 (2.3)	...	.13
Hemodialysis	2 (1.0)	34 (1.6)	...	.65
Others	3 (1.4)	94 (4.5)	...	.06

Missing data (due to missing data of each outcome measures): None. NA = not available.

<sup>a</sup>Variables for the propensity score matching.

development of FES. Although bone reduction and fixation were not associated with FES, delay time to the operation was associated with FES. Early total care may reduce the development of FES.

The prevalence of FES was 0.1% among patients registered in the JTDB. Similarly, the prevalence of FES was fairly low (0.004%; 41,000/928,324,000) in an analysis of the National Hospital Discharge Survey data from 1979 to 2005.<sup>3</sup> FES generally is associated with trauma, particularly trauma associated with long bone or pelvic fractures. The prevalence of FES after long bone fractures and orthopedic injuries was 0.12% to 11% based on several studies.<sup>3,7,8</sup> The target populations among these studies and challenges in the diagnosis of FES might be related to these variations. The current study included not only all patients with any fracture type but also those with any type of trauma with an AIS  $\geq 9$  and therefore revealed the frequency of FES encountered during general trauma care.

Our analyses validated that the risk factors of FES were long bone and pelvic fractures, as reported in previous studies.<sup>1-3,9</sup> In the upper and lower long bone and pelvic

fractures in the details, open fractures were more associated with FES development in our study. The evidence is not clear, although it is classically said that FES is more common in closed fractures than in open fractures. The most frequent primary surgery in patients with FES was bone reduction and fixation. Although surgical trauma during orthopedic procedures such as bone marrow manipulation might have resulted in FES in the previous reports,<sup>10,11</sup> bone reduction and fixation itself was not related to FES development in our study. We also found delay time to the operation was associated with FES. Early surgical correction might prevent or reduce the development of FES compared with temporary conservative management. Early total care would be better than damage control orthopedics surgery in terms of complications with FES.

The mortality rate for FES, which was 10% to 20% in the 1970s,<sup>9,12</sup> has dropped to 7% to 10% since 1990.<sup>1,7,9</sup> The in-hospital mortality rate of 5.8% in the current study was relatively low compared with other studies on FES.<sup>3,13</sup> This distinction might be related to the generalized use of early internal skeletal fixation, which contributes to the prevention of fat embolism, and the

**TABLE 2 ]** Treatments That Compared Trauma Patients With and Without Fat Embolism Syndrome

Characteristics	Fat Embolism Syndrome (n = 209), No. (%)	No Fat Embolism Syndrome (n = 2,090) No. (%)	P Value
Blood transfusion	56 (27.3)	310 (15.1)	<.001
Primary surgeries			
Craniotomy	2 (1.0)	55 (2.6)	.21
Craterization	0 (0.0)	33 (1.6)	.13
Thoracotomy	1 (0.5)	8 (0.4)	1.00
Celiotomy	3 (1.4)	40 (1.9)	.83
Bone reduction and fixation	168 (80.4)	886 (42.4)	<.001
Revascularization	0 (0)	3 (0.1)	1.00
Transcatheter arterial embolization	20 (9.6)	84 (4.0)	<.001
Endoscopic surgery	0 (0)	4 (0.2)	1.00
Replantation of limbs and digits	0 (0)	1 (0.0)	1.00
Hemostasis	1 (0.5)	17 (0.8)	.91
Others	10 (4.8)	54 (2.6)	.10
Time to bone reduction and fixation			.63
≤24 h	30 (23.6)	146 (26.2)	...
>24 h	97 (76.4)	412 (73.8)	...

No. of missing data: Blood transfusion, 40; time to bone reduction and fixation, 369.

development of intensive care techniques.<sup>1,3,9</sup>

Alternatively, the true mortality rate for FES might be lower because of improvements in diagnostic methods.<sup>14</sup>

FES is very rare. The personal experience of physicians and the reported cases of FES are limited. The diagnosis of FES is only a clinical suspicion that is based on symptoms in high-risk patients presenting with respiratory failure, neurologic abnormalities, and petechial rash that occur 24 to 72 hours after trauma. Clinical reports that we have accumulated may be indicative of these limitations and the rarity of the disease. The cause of trauma-related death involves not only the initial impact but also the complications after admission. Although outcomes have improved due to

advances in early trauma care,<sup>15</sup> it is critical to understand the characteristics of complications to develop preventative measures in the future. Moreover, successful resolution of complications is important because “failure to rescue” is an indicator for the quality of care after injury.<sup>6,16,17</sup>

### Limitations

The current study has several important limitations that warrant discussion. First, there were no data on the time at which FES and other complications occurred due to the retrospective study. However, certain sequences might be predicted based on the complication type. Second, the diagnosis of FES was based on the reports of the physician in charge, and potential misclassification

**TABLE 3 ]** Outcomes of Trauma Patients With and Without Fat Embolism Syndrome

Outcomes	Fat Embolism Syndrome (n = 209)	No Fat Embolism Syndrome (n = 2,090)	P Value
In-hospital deaths, No. (%)	12 (5.8)	70 (3.4)	.11
Place after discharge, No. (%)			<.001
Home	47 (24.2)	808 (40.4)	...
Other facilities	147 (75.8)	1150 (57.6)	...
Other	0 (0)	40 (2.0)	...
Length of hospital stay, median (interquartile range), d	30 (20-53)	23 (1-37)	<.001

Missing data (due to missing data of each outcome measures): in-hospital deaths, 21; place after discharge, 107.

**TABLE 4 ]** Conditional Logistic Regression Models for Identify Risk Factors Associated With Fat Embolism Syndrome

Variable	Model, OR (95% CI)				Subgroup OR (95% CI)
	1	2	3	4	
Head: Abbreviated Injury Scale $\geq 3$	1.36 (0.70-2.65)	1.10 (0.58-2.09)	1.02 (0.53-1.97)	1.20 (0.60-2.38)	1.09 (0.42-2.87)
Thorax: Abbreviated Injury Scale $\geq 3$	1.20 (0.65-2.20)	0.99 (0.55-1.78)	0.87 (0.47-1.61)	0.94 (0.51-1.77)	0.92 (0.35-2.38)
<b>Upper extremity</b>					
Abbreviated Injury Scale $\geq 3$	3.75 (1.86-7.59)	...	...	...	...
Long bone fracture (all)	...	2.96 (1.55-5.63)	...	...	...
Open	...	...	2.96 (1.50-5.83)	2.58 (1.30-5.12)	3.23 (1.46-7.15)
Closed	...	...	... <sup>a</sup>	... <sup>a</sup>	... <sup>a</sup>
Unclassified	...	...	... <sup>a</sup>	... <sup>a</sup>	... <sup>a</sup>
<b>Lower extremity</b>					
Abbreviated Injury Scale $\geq 3$	5.14 (2.69-9.79)	...	...	...	...
Long bone & pelvic fracture (all)	...	3.56 (2.04-6.24)	...	...	...
Open	...	...	3.16 (1.99-5.04)	2.90 (1.80-4.66)	4.25 (2.22-8.13)
Closed	...	...	1.39 (0.73-2.65)	1.38 (0.72-2.64)	0.60 (0.21-1.69)
Unclassified	...	...	1.66 (1.09-2.55)	1.45 (0.92-2.28)	1.27 (0.74-2.20)
Primary bone reduction & fixation	...	...	...	1.80 (0.92-3.54)	...
Time to operation (bone reduction & fixation)	...	...	...	...	...
<24 h	...	...	...	...	Reference
$\geq 24$ h	...	...	...	...	2.21 (1.16-4.23)

<sup>a</sup>Cases <10 variance inflation factor of the models <5.

or underestimation could not be ruled out. Mild cases might have been missed. Furthermore, standard criteria for the diagnosis of FES were not available; therefore, clinical diagnoses of FES might not have been accurate. However, currently, there are no standardized, validated diagnostic criteria for FES.<sup>1</sup> Thus, the diagnosis of FES was established clinically. FES remains a diagnostic challenge and potentially is underdiagnosed. The major differential diagnoses of FES are other embolization syndromes such as pulmonary embolism. There may have been some duplications. The definitive diagnosis may have been difficult to achieve in some cases with respiratory failure because pulmonary embolism may present with the same symptoms and at the same time as FES. Third, we excluded patients who did not survive for

>48 hours to exclude the impact of early deaths due to lethal trauma. However, some patients with FES might have been lost from this study because the typical time window to diagnose FES is 24 to 72 hours. Fourth, no data were found on the treatment of complications, and it remains unclear whether the deaths in patients with FES were due to the complications or the primary injury.

### Conclusions

Our results show that FES was associated most frequently with open fractures, particularly those that resulted from injury to the upper and lower extremities. Although bone reduction and fixation are not associated with FES development, delay time to operation is associated with FES development.

## Acknowledgments

**Author contributions:** T. A. is the guarantor of the paper. T. K., H. I., A. K., D. S., and T. A. conceived the study. T. K., H. I., and T. A. performed analyses for the study. T. K. and T. A. wrote the first draft of the manuscript. All authors provided critical input into manuscript drafting and revisions.

**Financial/nonfinancial disclosures:** None declared.

**Other contributions:** The authors would like to thank Enago ([www.enago.jp](http://www.enago.jp)) for the English language review.

**Additional information:** The e-Table can be found in the [Supplemental Materials](#) section of the online article.

## References

1. Kosova E, Bergmark B, Piazza G. Fat embolism syndrome. *Circulation*. 2015;131(3):317-320.
2. Mellor A, Soni N. Fat embolism. *Anaesthesia*. 2001;56(2):145-154.
3. Stein PD, Yaekoub AY, Matta F, Kleerekoper M. Fat embolism syndrome. *Am J Med Sci*. 2008;336(6):472-477.
4. Eriksson EA, Pellegrini DC, Vanderkolk WE, Minshall CT, Fakhry SM, Cohle SD. Incidence of pulmonary fat embolism at autopsy: an undiagnosed epidemic. *J Trauma*. 2011;71(2):312-315.
5. Abe T, Aoki M, Deshpande G, et al. Is whole-body CT associated with reduced in-hospital mortality in children with trauma? A nationwide study. *Pediatr Crit Care Med*. 2019;20(6):e245-e250.
6. Abe T, Komori A, Shiraishi A, et al. Trauma complications and in-hospital mortality: failure-to-rescue. *Crit Care*. 2020;24(1):223.
7. Fabian TC, Hoots AV, Stanford DS, Patterson CR, Mangiante EC. Fat embolism syndrome: prospective evaluation in 92 fracture patients. *Crit Care Med*. 1990;18(1):42-46.
8. Robert JH, Hoffmeyer P, Broquet PE, Cerutti P, Vasey H. Fat embolism syndrome. *Orthop Rev*. 1993;22(5):567-571.
9. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome: a 10-year review. *Arch Surg*. 1997;132(4):435-439.
10. Ahmadzai H, Campbell S, Archis C, Clark WA. Fat embolism syndrome following percutaneous vertebroplasty: a case report. *Spine J*. 2014;14(4):e1-e5.
11. Al-Shaer DS, Ayoub O, Ahamed NA, Al-Hibshi AM, Baeesa SS. Cerebral fat embolism syndrome following total knee replacement causing a devastating neurocognitive sequelae. *Neurosciences (Riyadh)*. 2016;21(3):271-274.
12. Talbot M, Schemitsch EH. Fat embolism syndrome: history, definition, epidemiology. *Injury*. 2006;37(suppl4):S3-S7.
13. Sethi D, Kaval S, Saxena A. Neuroimaging findings in a case of cerebral fat embolism syndrome with delayed recovery. *Indian J Crit Care Med*. 2015;19(11):674-677.
14. Fulde GW, Harrison P. Fat embolism: a review. *Arch Emerg Med*. 1991;8(4):233-239.
15. Nagata I, Abe T, Uchida M, Saitoh D, Tamiya N. Ten-year in-hospital mortality trends for patients with trauma in Japan: a multicentre observational study. *BMJ Open*. 2018;8(2):e018635.
16. Glance LG, Dick AW, Meredith JW, Mukamel DB. Variation in hospital complication rates and failure-to-rescue for trauma patients. *Ann Surg*. 2011;253(4):811-816.
17. Kuo LE, Kaufman E, Hoffman RL, et al. Failure-to-rescue after injury is associated with preventability: the results of mortality panel review of failure-to-rescue cases in trauma. *Surgery*. 2017;161(3):782-790.