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Original Article

Fat embolism syndrome in blunt trauma patients with extremity fractures

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ABSTRACT

Objective: This study sought to provide a national, descriptive analysis to determine fat embolism syndrome (FES) risk factors, hypothesizing that femur fractures and multiple fractures are associated with an increased risk.
Methods: The Trauma Quality Improvement Program was queried (2010–2016) for patients with extremity fractures. A multivariable logistic regression analysis model was used.
Results: From 324,165 patients, 116 patients (0.04%) were diagnosed with FES. An age ≤30, closed femur fracture, and multiple long bone fractures were associated with an increased risk of FES.
Conclusion: Future research to validate these findings and develop a clinical risk stratification tool appears warranted.

1. Introduction

Fat embolism syndrome (FES) is a rare complication of long bone fractures with an incidence ranging from 0.9 to 11%[1,4,5,12] in trauma patients and can develop within hours to days post-injury.[6,24] FES occurs when adipose tissue passes into the circulation, typically from a fracture, which then migrates and obstructs a vessel, often collecting in the pulmonary or cerebral vasculature.[7] While rare, it can lead to acute respiratory distress syndrome (ARDS), respiratory failure, and even brain death secondary to hypoxia and/or massive cerebral fat emboli leading to cerebral edema.[2,27] Mechanical ventilation is required in as many as 50% of patients with FES,[8] and patients that develop FES have a mortality rate of 5–15%.[3,16]

The classic triad of respiratory insufficiency, central nervous system dysfunction, and petechial rash is quite rare in patients with FES, but up to 80% of patients have neurologic symptoms and up to 50% have a petechial rash.[3,9,10] Diagnosis of FES can be challenging due to the fact that only non-specific clinical and laboratory studies exist,[11] such as the presence of fat globules in the blood and urine, or bronchial lavage producing >30% lipid-inclusion-filled alveolar macrophages.[3,12,13] Furthermore, these studies are not routinely performed and the laboratory processing may be quite time-consuming. Several different diagnostic criteria for FES have been proposed, including the criteria from Gurd and Wilson. These criteria require one major feature (respiratory insufficiency, cerebral involvement [e.g. altered mentality, confusion, stupor, coma, depression disproportionate to hypoxemia], or petechial rash) and four minor features (pyrexia, tachycardia, jaundice, retinal changes, renal changes, thrombocytopenia, anemia, and elevated erythrocyte sedimentation rate), together with fat macroglobulinemia.[14] Therapy for FES is largely supportive consisting of supplemental oxygen and/or mechanical ventilation to offset hypoxia, as well as fluid and/or vasopressor support for circulatory collapse. It is therefore crucial for clinicians to be aware of the greatest risk factors for the development of FES in order to facilitate early diagnosis and prompt supportive care as this may reduce the complications (e.g. hypoxia leading to tissue damage) and mortality associated with FES.[15,17]

The majority of the published studies regarding FES have been single-center case reports or case series,[6,8,11,17,29] which have demonstrated an association of femur fractures and multiple fractures with FES.[18,19] In addition, pelvic fractures and closed fractures have also been demonstrated to be associated with a higher rate of FES.[21] We sought to provide a nationwide, descriptive analysis on FES in blunt trauma patients, hypothesizing femur fractures and multiple fractures to be associated with an increased risk of FES. In addition, we aimed to evaluate

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other previously proposed risk factors for FES as well as elucidate additional novel risk factors.

2. Methods

The Trauma Quality Improvement Program (TQIP)[22] was queried from 2010 to 2016 for patients ≥18 years-old who suffered blunt trauma resulting in fractures of the humerus, femur, tibia, and patella. These were identified by the appropriate international classification of diseases (ICD) version-9 diagnosis codes. No patients that met the inclusion criteria were excluded from the study. The TQIP database is a large trauma database that collects data from over 800 trauma centers across the United States.[22] The primary outcome studied was the rate of FES. The patients were divided into two cohorts: those with and those without FES. Secondary outcomes studied included total hospital length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, and mortality. Additional information collected included the presence of multiple fractures, and complications including acute kidney injury, ARDS, cardiac arrest with cardiopulmonary resuscitation, central line associated bloodstream infection, extremity compartment syndrome, cerebrovascular accident (CVA), unplanned ICU admission, unplanned intubation, pneumonia, deep vein thrombosis, and pulmonary embolism (PE).

We analyzed patients' demographics and injury profiles, including mechanism of injury and injury severity score (ISS). Additional information including hypotension on admission, concomitant injuries, fracture classification including open or closed, and pre-hospital comorbidities including diabetes, hypertension, congestive heart failure, chronic obstructive pulmonary disease, and cirrhosis was collected. Information regarding fracture treatment was also obtained, however this data is limited by the terminology utilized within the TQIP database (e.g. internal/external fixation, open/closed reduction), which was not designed as an orthopedic surgery database and lacks pertinent details regarding the specific management.

Descriptive statistics were performed for all variables. To compare continuous variables, we used a Mann-Whitney-U test, and these data were reported as means with standard deviation or as medians with interquartile ranges. To study the association between categorical variables, we used a chi-square test, and these data were reported as percentages. A multivariable logistic regression analysis was used to measure the strength of the association between predictor variables and mortality. A hierarchical multivariable logistic regression analysis was used to control for covariates using an odds ratio and associated 95% confidence interval. In the multivariable analysis, the covariates controlled for were multiple fractures, open and closed femur fractures, open and closed humerus fractures, open and closed tibia fractures, pelvic fractures, age ≤30, and non-operative fractures. In addition, we performed a multivariable analysis evaluating serious body region injuries using an Abbreviated Injury Scale (grade >2) for head, spine, abdomen, chest, lower extremity, and upper extremity for risk of development of FES. A p-value <0.05 was considered statistically significant and all p-values were two-sided. The statistical software used was IBM SPSS Statistics for Windows, Version 24 (Armonk, 96 NY: IBM Corp). This study adhered to all pertinent recommendations and standards as outlined in the Strengthening the Reporting of Observational studies in Epidemiology guidelines. Institutional Review Board approval was obtained and informed consent was not possible as the TQIP holds a deidentified dataset. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

3. Results

3.1. Patient demographics

Out of 324,165 patients in total, 116 (0.04%) suffered from FES. Of FES patients, 101 patients (87.1%) had femur fractures, 42 patients (36.2%) had tibia fractures, and 14 patients (12.1%) had humerus fractures. The FES cohort had a median age of 29 years-old, compared to 59 years-old in the non-FES cohort ($p < 0.001$). The FES cohort was 70.7% male in comparison to 50.9% male in the non-FES group ($p < 0.001$). The two cohorts had similar rates of comorbidities including smoking and obesity ($p > 0.05$). However, the rates of hypertension (13.8% vs. 40.1%, $p < 0.001$) and dementia (0.9% vs. 5.9%, $p = 0.02$) were lower in the FES cohort (Table 1). The FES cohort had increased rates of pelvic (20.7% vs. 11.8%, $p = 0.003$) and rib fractures (26.7% vs. 16.6%, $p = 0.004$). The FES cohort had higher rates of high speed mechanisms including motor vehicle collisions (39.7% vs. 22.5%, $p < 0.001$) and motorcycle collisions (22.4% vs. 8.2%, $p < 0.001$) (Table 2).

The FES cohort had increased rates of closed femur fractures (81.9% vs. 67.6%, $p = 0.001$). The FES cohort also had increased rates of femur fractures receiving external fixation (12.1% vs. 2.4%, $p < 0.001$), open reduction and internal fixation (39.7% vs. 28.5%, $p = 0.01$), and open femur fracture debridement (6.0% vs. 2.8%, $p = 0.04$). However, the FES cohort had lower rates of non-operative femur fractures (13.9% vs. 32.9%, $p < 0.001$). The FES cohort had higher rates of open tibia fractures (16.4% vs. 10.6%, $p = 0.04$) and tibia fractures treated with open reduction and internal fixation (21.6% vs. 14.0%, $p = 0.02$), compared to the non-FES cohort. The two cohorts had similar rates of closed humerus fractures (9.5% vs. 11.1% in the non-FES group, $p > 0.05$) and operative humerus fractures (7.8% vs. 7.0% in the non-FES group, $p > 0.05$). There was a higher rate of multiple fractures in the FES group (44.0% vs. 19.3%, $p < 0.001$) (Table 3).

3.2. Risk of fat embolism syndrome

On multivariable logistic regression, multiple fractures (OR 2.18, CI 1.08–4.42, $p = 0.03$), closed femur fractures (OR 4.11, CI 2.18–7.76, $p < 0.001$), and age ≤30 years-old (OR 5.30, CI 3.62–7.75, $p < 0.001$) were all associated with an increased risk for FES. There was no

Table 1
Demographics of blunt trauma patients with long-bone extremity fractures.

Characteristic	Without embolism (n = 324,049)	Fat embolism (n = 116)	p-value
Age, year, median (IQR)	59.0 (37, 76)	29.0 (23, 51)	<0.001
Male, n (%)	164,802 (50.9%)	82 (70.7%)	<0.001
ISS, median (IQR)	9.0 (11, 16)	12.0 (11, 21)	<0.001
Hypotension on admission, n (%)	12,711 (4.2%)	9 (8.5%)	0.03
Comorbidities, n (%)			
Congestive heart failure	17,470 (5.4%)	6 (5.2%)	0.92
Smoker	54,047 (16.7%)	19 (16.4%)	0.93
Chronic renal failure	5960 (1.8%)	1 (0.9%)	0.43
Diabetes	48,929 (15.1%)	14 (12.1%)	0.36
Hypertension	129,889 (40.1%)	16 (13.8%)	<0.001
Chronic obstructive pulmonary disease	31,501 (9.7%)	8 (6.9%)	0.31
Cerebrovascular accident	10,310 (3.2%)	5 (4.3%)	0.49
Cancer, disseminated	2956 (0.9%)	0	0.30
Dementia	19,149 (5.9%)	1 (0.9%)	0.02
History of myocardial infarction	5075 (1.6%)	1 (0.9%)	0.54
Peripheral vascular disease	2478 (0.8%)	0	0.34
Psychiatric illness	24,189 (7.5%)	6 (5.2%)	0.35
Obesity	17,763 (5.5%)	8 (6.9%)	0.50
Steroid use	3174 (1.0%)	2 (1.7%)	0.42
Cirrhosis	2395 (0.7%)	2 (1.7%)	0.22
Alcohol use, n (%)	35,515 (12.1%)	10 (9.9%)	0.49
Drug use, n (%)	38,794 (13.8%)	23 (24.5%)	0.003
Race, n (%)			
African-American	32,939 (11.5%)	12 (12.8%)	0.71
Caucasian	252,773 (78%)	82 (71%)	0.06
Asian	4886 (1.9%)	2 (2.4%)	0.75
Hispanic	23,653 (8.6%)	12 (12.2%)	0.20
Teaching university, n (%)	170,174 (52.5%)	70 (60.3%)	0.09
Glasgow coma scale, mean	14.08	13.79	0.99

IQR = interquartile range, ISS = injury severity score

Table 2
Mechanisms and injuries of blunt trauma patients with extremity fractures.

Characteristic	Without embolism (n = 324,049)	Fat embolism (n = 116)	p-value
Mechanism, n (%)			
Bicycle accident	6363 (2.0%)	0	0.13
Motorcycle collision	26,506 (8.2%)	26 (22.4%)	<0.001
Pedestrian struck	22,924 (7.1%)	7 (6.0%)	0.66
Fall	179,512 (55.4%)	26 (22.4%)	<0.001
Motor vehicle collision	72,774 (22.5%)	46 (39.7%)	<0.001
Injury, n (%)			
Traumatic brain injury	57,532 (17.8%)	25 (21.6%)	0.29
Face or neck	23,696 (7.3%)	9 (7.8%)	0.85
Spine	49, 277 (15.2%)	24 (20.7%)	0.10
Rib	53,909 (16.6%)	31 (26.7%)	0.004
Sternum	8671 (2.7%)	6 (5.2%)	0.10
Pelvic fracture	38,113 (11.8%)	24 (20.7%)	0.003
Upper extremity	82,914 (25.6%)	39 (33.6%)	0.047
Lower extremity	297,345 (91.8%)	114 (98.3%)	0.01
Esophagus	51 (0.02%)	0	0.89
Lung	46,486 (14.3%)	35 (30.2%)	<0.001
Heart	1743 (0.5%)	4 (3.4%)	<0.001
Stomach	239 (0.1%)	0	0.77
Small intestine	2223 (0.7%)	2 (1.7%)	0.18
Colorectal	2385 (0.7%)	2 (1.7%)	0.21
Pancreas	41 (0.01%)	0	0.90
Liver	11,793 (3.6%)	9 (7.8%)	0.02
Spleen	11,960 (3.7%)	10 (8.6%)	0.01
Kidney	5527 (1.7%)	4 (3.4%)	0.15
Other genitourinary	2614 (0.8%)	0	0.33
Crush	913 (0.3%)	1 (0.9%)	0.24
Burn	757 (0.2%)	0	0.60

associated risk of FES with humerus, tibia, or pelvic fractures (Table 4).

In blunt trauma patients with femur fractures, age ≤30 (OR 5.13, CI 3.41–7.71, $p < 0.001$) and multiple fractures (OR 2.14, CI 1.43–3.20, $p < 0.001$) were both independently associated with increased risk of FES. Fractures amenable to non-surgical management were associated with a decreased risk of FES (OR 0.44, CI 0.25–0.77, $p = 0.004$) (Table 5).

There was no association with FES for non-operative treatment as compared to operative treatment in tibia or humerus fractures ($p > 0.05$). Multiple fractures (OR 16.30, CI 2.13–124.6, $p = 0.01$) as well as age ≤30 years-old (OR 8.20, CI 2.53–26.56, $p < 0.001$) were associated with an increased risk of FES in patients with humerus fractures. In patients with tibia fractures, multiple fractures (OR 6.71, CI 3.10–14.53, $p < 0.001$) and age ≤30 (OR 3.76, CI 2.03–6.97, $p < 0.001$) were associated with an increased risk of FES (Tables 6 and 7).

In blunt trauma patients with extremity fractures and other serious regional body injuries, defined as a grade >2 for abbreviated injury scale (AIS), lower extremity injuries (OR 7.59, CI 2.73–21.06, $p < 0.001$) and thoracic injuries (OR 2.76, CI 1.76–4.32, $p < 0.001$) were associated with an increased risk of FES. There was no associated risk of FES for patients with serious head, abdominal, spinal, or upper extremity injuries ($p > 0.05$) (Table 8).

3.3. Hospital outcomes

Compared to blunt trauma patients without FES, the FES patients had an increased mortality rate (11.2% vs. 4.1%, $p < 0.001$). The FES group also had an increased median hospital LOS (12 vs. 6 days, $p < 0.001$), ICU LOS (6 vs. 4, $p = 0.02$), and complications of ARDS (22.4% vs. 1.2%, $p < 0.001$), extremity compartment syndrome (2.6% vs. 0.5%, $p = 0.002$), CVA (5.2% vs. 0.4%, $p < 0.001$), unplanned intubations (10.3% vs. 1.2%, $p < 0.001$), PE (7.8% vs. 0.9%, $p < 0.001$), and pneumonia (18.1% vs. 3.3%, $p < 0.001$) (Table 9).

4. Discussion

FES is a relatively rare although potentially fatal complication following long bone fractures in high energy trauma. To our knowledge, this is the first study in the United States to analyze and evaluate outcomes in FES patients using the TQIP large, national database. In our analysis spanning seven years, the rate of FES in blunt trauma patients

Table 3
Classifications of extremity fractures in blunt trauma patients.

Characteristic	Without embolism (n = 324,049)	Fat embolism (n = 116)	p-value
Humerus fracture, n (%)			
Closed	35, 954 (11.1%)	11 (9.5%)	0.58
Open	8153 (2.5%)	3 (2.6%)	0.96
External fixation	935 (0.3%)	1 (0.9%)	0.25
Internal fixation without reduction	279 (0.1%)	0	0.75
Closed reduction without external fixation	3818 (1.2%)	2 (1.7%)	0.59
Closed reduction with external fixation	871 (0.3%)	0	0.58
Open reduction without fixation	426 (0.1%)	0	0.70
Open reduction and internal fixation	18,571 (5.7%)	8 (6.9%)	0.59
Debridement	4882 (1.5%)	3 (2.6%)	0.34
All operative	22,582 (7.0%)	9 (7.8%)	0.74
Non-operative	21,537 (49.5%)	5 (35.7%)	0.30
Femur fracture, n (%)			
Closed	219,136 (67.6%)	95 (81.9%)	0.001
Open	14,686 (4.5%)	9 (7.8%)	0.10
External fixation	7724 (2.4%)	14 (12.1%)	<0.001
Internal fixation without reduction	12,544 (3.9%)	12 (10.3%)	<0.001
Closed reduction without external fixation	8486 (2.6%)	14 (12.1%)	<0.001
Closed reduction with external fixation	49,539 (15.3%)	30 (25.9%)	0.002
Open reduction without fixation	1447 (0.4%)	0	0.47
Open reduction and internal fixation	92,261 (28.5%)	46 (39.7%)	0.01
Debridement	9141 (2.8%)	7 (6.0%)	0.04
All operative	156,523 (48.3%)	87 (75.0%)	<0.001
Non-operative	76,055 (32.9%)	14 (13.9%)	<0.001
Patella fracture, n (%)			
Patella closed	5951 (1.8%)	6 (5.2%)	0.01
Patella open	2736 (0.8%)	2 (1.7%)	0.30
Tibia fracture, n (%)			
Closed	56,397 (17.4%)	26 (22.4%)	0.16
Open	34,303 (10.6%)	19 (16.4%)	0.04
External fixation	18,498 (5.7%)	14 (12.1%)	0.003
Internal fixation without reduction	3843 (1.2%)	2 (1.7%)	0.59
Closed reduction without external fixation	1772 (0.5%)	0	0.43
Closed reduction with external fixation	10,265 (3.2%)	6 (5.2%)	0.22
Open reduction without fixation	2047 (0.6%)	1 (0.9%)	0.75
Open reduction and internal fixation	45,266 (14.0%)	25 (21.6%)	0.02
Debridement	25,552 (7.9%)	15 (12.9%)	0.04
All operative	65,230 (20.1%)	39 (33.6%)	<0.001
Non-operative	26,330 (31.3%)	10 (23.8%)	0.31
Multiple fractures, n (%)	62,631 (19.3%)	51 (44.0%)	<0.001

Note: all procedures performed in the operating room.

Table 4
Multivariable analysis for risk of fat embolism in blunt trauma patients with extremity fractures.

Risk factor	OR	CI	p-value
Multiple fractures	2.18	1.08–4.42	0.03
Open femur fracture	1.54	0.73–3.24	0.26
Closed femur fracture	4.11	2.18–7.76	<0.001
Open humerus fracture	1.23	0.37–4.08	0.73
Closed humerus fracture	1.00	0.48–2.08	1.00
Open tibia fracture	1.76	0.95–3.26	0.07
Closed tibia fracture	1.26	0.70–2.26	0.44
Age ≤30 years	5.30	3.62–7.75	<0.001
Pelvic fracture	0.76	0.40–1.46	0.41

Table 5
Multivariable analysis for risk of fat embolism in blunt trauma patients with femur fractures.

Risk factor	OR	CI	p-value
Age ≤30 years	5.13	3.41–7.71	<0.001
Non-operative	0.44	0.25–0.77	0.004
Multiple fractures	2.14	1.43–3.20	<0.001

Table 6
Multivariable analysis for risk of fat embolism in blunt trauma patients with humerus fractures.

Risk factor	OR	CI	p-value
Age ≤30 years	8.20	2.53–26.56	<0.001
Non-operative	0.83	0.28–2.52	0.75
Multiple fractures	16.30	2.13–124.6	0.01

Table 7
Multivariable analysis for risk of fat embolism in blunt trauma patients with tibia fractures.

Risk factor	OR	CI	p-value
Age ≤30 years	3.76	2.03–6.97	<0.001
Non-operative	0.58	0.28–1.18	0.13
Multiple fractures	6.71	3.10–14.53	<0.001

Table 8
Multivariable analysis for risk of fat embolism from serious body region injuries (abbreviated injury scale grade >2) in blunt trauma patients.

Risk factor	OR	CI	p-value
Head	1.13	0.66–1.96	0.65
Thorax	2.76	1.76–4.32	<0.001
Abdomen	1.30	0.68–2.49	0.43
Spine	0.93	0.37–2.32	0.87
Lower extremity	7.59	2.73–21.06	<0.001
Upper extremity	1.32	0.65–2.67	0.45

with long-bone extremity fractures was less than 0.1%. Age ≤30 years-old, closed femur fractures, and multiple long bone fractures were all associated with an increased risk of FES. In patients with femur fractures, fractures amenable to non-surgical management were associated with a decreased risk of FES. There was no association for operative versus non-operative treatment in humerus fractures or tibia fractures. There was no increased risk of FES in patients with pelvic fractures.

Patients with serious thoracic injuries or serious lower extremity injuries (AIS grade >2) had an increased associated risk of developing FES. Future evaluation of this finding with serious thoracic trauma is needed to determine if this is merely an association or there may be causation with fat embolism from chest wall fractures.

Fractures have long been known to be associated with FES in trauma patients. Bulger et al. conducted a retrospective 10-year review at a single Level I trauma center to determine the demographics, injury severity and pattern, diagnostic criteria, and management of all patients diagnosed with FES. They reported that during this time, 27 blunt trauma patients were diagnosed with FES, resulting in an incidence of almost 1% of all patients with long-bone fractures. There were a total of 40 long-bone fractures in the patients, 22 (55%) of which were femur fractures and 10 (37%) of the patients had associated pelvic fractures.[25] Robert et al. over a 25-year study period found a 0.26% (20 patients) incidence of FES in trauma patients with 70% of patients suffering from femur fractures, 80% from tibia fractures, and 15% with pelvic fractures.[35] In support of the high rate of FES after a femur fracture, we specifically found that closed femur fractures were associated with an over four-times increased risk of FES when compared to open femur

Table 9
Outcomes of blunt trauma patients with extremity fractures.

	Without embolism	Fat embolism	
Characteristic	(n = 324,049)	(n = 116)	p-value
LOS, days, median (IQR)	6.0 (6, 12)	12.0 (9, 22)	<0.001
ICU, days, median (IQR)	4.0 (4, 11)	6.0 (4, 13)	0.02
Ventilator, days, median (IQR)	4.0 (4, 12)	7.0 (5, 14)	0.30
Complications, n (%)			
Acute kidney injury	4417 (1.4%)	4 (3.4%)	0.05
ARDS	4013 (1.2%)	26 (22.4%)	<0.001
Cardiac arrest with CPR	3709 (1.1%)	5 (4.3%)	0.001
CAUTI	120 (0.04%)	0	0.84
CLASBI	15 (0.005%)	0	0.94
Decubitus	3505 (1.1%)	3 (2.6%)	0.12
Deep site infection	990 (0.3%)	0	0.55
Extremity compartment syndrome	1713 (0.5%)	3 (2.6%)	0.002
Myocardial infarction	1842 (0.6%)	0	0.42
Organ space infection	893 (0.3%)	0	0.57
Cerebrovascular accident	1389 (0.4%)	6 (5.2%)	<0.001
Superficial infection	1151 (0.4%)	1 (0.9%)	0.36
Unplanned ICU admission	3725 (1.1%)	5 (4.3%)	0.001
Unplanned intubation	3976 (1.2%)	12 (10.3%)	<0.001
Deep vein thrombosis	5617 (1.7%)	9 (7.8%)	<0.001
Pulmonary embolism	2901 (0.9%)	9 (7.8%)	<0.001
Pneumonia	10,767 (3.3%)	21 (18.1%)	<0.001
Osteomyelitis	208 (0.1%)	0	0.79
Severe sepsis	1840 (0.6%)	0	0.42
Urinary tract infection	8605 (2.7%)	5 (4.3%)	0.27
Ventilator associated pneumonia	148 (0.05%)	0	0.82
Mortality, n (%)	13,377 (4.1%)	13 (11.2%)	<0.001

IQR = interquartile range, LOS = length of stay, ICU = intensive care unit, ARDS = acute respiratory distress syndrome, CAUTI = catheter associated urinary tract infection, CLABSI = central line associated bloodstream infection, CPR = cardiopulmonary resuscitation.

fractures. On multivariable analysis, however, pelvic fractures and tibia fractures were not independent predictors for FES. This is in contrast to previous reports that pelvic fractures are associated with FES.[21,41] This may be because most of the marrow in the flat bones of the adult skeleton including the pelvic bones is comprised of red bone marrow which has a lower fat content compared to yellow bone marrow (which is more prominent in the long bones).[23] Although clinicians are unable to change a patient's risk factors for fat embolism, having the knowledge that closed femur fractures increase the risk of developing FES is of paramount importance so that a high index of clinical suspicion for these patients can be maintained, ultimately leading to earlier diagnosis and treatment.[26]

The occurrence of multiple fractures, each of which may put the patient at risk for FES, has previously been demonstrated to be associated with an increased rate of FES.[37,38] Stein et al. looked at the incidence of FES in over 900,000,000 patients getting discharged from short-stay hospitals in the United States. They reported that among patients with multiple fractures including the femur (excluding neck), over 1% of them had FES in comparison to less than 1% of patients with isolated femur fractures (excluding neck).[39] Tsai et al. performed a 12-year retrospective study on patients with long bone fractures in a tertiary referral center and found that the incidence of FES in patients with multiple fractures was over 2% versus less than 1% in an isolated femur fracture and 0.15% in an isolated tibia fracture. We add to this literature by demonstrating that when controlling for age and other significant covariates (e.g. fracture types), that multiple fractures was independently associated with an over two-fold increased risk of FES. Therefore, vigilance for FES should be maintained when treating patients with multiple fractures.

Interestingly, we found that age ≤30 to be the strongest predictor of FES with an over five-fold associated increased risk of FES. In support of this, Tsai et al. found that in their 13 patients who developed FES, all except one were less than 35 years-old.[9] Similarly, Stein et al. found that

the patients who developed FES were more often between the ages of 10 and 39 years-old.[39] One possible explanation for the more frequent occurrence of FES in younger patients is the fracture location within the long bone. In older patients, low-energy trauma often results in typical geriatric fracture patterns such as femoral neck and intertrochanteric fractures. These patterns occur in a location where there is no fat-containing medullary canal.[28] This results in a lower chance for the development of FES. Future research to better elucidate if age or fracture location is the true risk factor is needed. Additionally, incorporation of our findings into a risk-stratification tool may help identify the patients at most risk for FES and thereby lead to more prompt diagnosis and/or studies regarding targeted interventions within a high-risk population.

There have been previously conflicting results regarding the association of FES with fracture surgery.[32,33,36] The majority of femoral shaft fractures are treated operatively with a medullary nail. In a prospective, consecutive, nonrandomized clinical trial, Kropfl et al. looked at 36 adult patients with femur fractures treated surgically with femoral nailing, separated into reamed and unreamed cohorts. They measured the intramedullary pressure during the operation and the bone marrow fat intravasation. The reamed nailing cohort had a significantly higher intramedullary pressure (396 ± 85 mmHg) and higher bone marrow fat intravasation (3.2 ± 0.4), compared to the unreamed nailing cohort, due to the fat release during the reaming process (intramedullary pressure 91 ± 26 mm Hg, fat intravasation 1.9 ± 0.2).[40] Increased intramedullary pressure, classically thought to arise from reaming and nail insertion during intramedullary nailing of fractures, can theoretically lead to an embolization of fat resulting in FES.[20,34] In addition to the method of fracture surgery, the timing of the procedure is another important consideration. Early stabilization of fractures may lead to a decreased rate of FES.[30,31] In our cohort, femur fractures amenable to non-operative treatment were associated with a decreased risk of FES, though this may be related to the effect of fracture pattern not captured by ICD-9 diagnosis. This was not the case for humerus fractures or tibia fractures, potentially because of the different fixation techniques used for the different long bones. Knowing that surgically treated femur fractures are associated with a higher risk of FES is important so clinicians can remain vigilant during these procedures and minimize increases in intramedullary pressure. In addition, future combined basic science and clinical research to better clarify what role operative technique has in the development of FES appears warranted.

There are several limitations to our study including the possibility of misclassification and missing data from the use of a large retrospective database. Also the TQIP database only includes trauma patients in trauma centers, and thus only includes patients who have significant mechanisms and/or injuries and thus does not incorporate all patients presenting to a hospital with extremity fractures. Additionally, the diagnosis for FES was not standardized in the dataset nor were the findings related to FES diagnosis and/or complications such as neurologic dysfunction, respiratory failure and petechial rash reported. In addition, missing pertinent data variables include the time from injury to diagnosis of FES, type and location of fracture(s) (e.g. proximal, distal, neck etc.), indication for operative fixation, details regarding exact operative techniques used for surgical stabilization of fractures (e.g. intramedullary instrumentation, nailing, plating etc.), the length of time from injury to operation, the timing of fracture stabilization, and the exact definitions of the TQIP terminology used for the procedures. Lastly, TQIP is limited to the index hospitalization, thus does not provide post-discharge information regarding complications, mortality, or long-term functional outcomes. Additionally, any post-discharge cases of FES would not have been captured. Despite these limitations our study is strengthened by its large nationwide sample and robust multivariable analysis controlling for known predictors of FES.

In summary, this retrospective national analysis found the incidence of FES in blunt trauma patients sustaining long bone extremity fractures to be less than 0.1%, however the mortality rate for FES was over 11%. In addition, we identified closed femur fractures, age ≤30 years-old, and multiple fractures to be associated with increased risk for FES. Future research is warranted to validate these results and use these findings to help develop a clinical risk stratification tool to identify patients at highest risk for FES with the hopes of reducing the significant associated morbidity and mortality.

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Declaration of competing interest

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Miriam Alpert, Dr. Areg Grigorian, and Dr. Jeffry Nahmias researched literature, conceived the study, and were involved in data analysis. Miriam Alpert wrote the first draft of the manuscript. All authors helped with the study design, data interpretation and reviewed and edited the manuscript.

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