ORIGINAL RESEARCH

Fat Embolism Syndrome and in-Hospital Mortality Rates According to Patient Age: A Large Nationwide Retrospective Study

Sung Huang Laurent Tsai 🆔 [1–3], Chien-Hao Chen[1,2], Eric H Tischler[3,4], Shyam J Kurian[5], Tung-Yi Lin[1,2], Chun-Yi Su[1,2], Greg Michael Osgood[3,5], Amber Mehmood[6], Tsai-Sheng Fu[2,7]

[1]Department of Orthopedic Surgery, Chang Gung Memorial Hospital, Keelung branch, Keelung, 204, Taiwan; [2]School of medicine, Chang Gung University, Taoyuan, 333, Taiwan; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4]Department of Orthopaedic Surgery and Rehabilitation Medicine, State University of New York, Downstate Medical Center, Brooklyn, NY, USA; [5]Department of Orthopaedic Surgery, Johns Hopkins Hospital, Baltimore, MD, USA; [6]University of South Florida College of Public Health, Tampa, FL, USA; [7]Department of Orthopedic Surgery, Chang Gung Memorial Hospital, Linkou, Taiwan

Correspondence: Chien-Hao Chen, Department of Orthopedic Surgery, Chang Gung Memorial Hospital, Keelung branch, Taoyuan, 20401, Taiwan, Tel +886-2231131 (ext. 3016), Email john1982@adm.cgmh.org.tw

Introduction: Fat embolism syndrome (FES) is a rare life-threatening condition that can develop after traumatic orthopedic injuries. Controversy remains concerning the epidemiology in the elderly population. Therefore, this study aims to report FES related to in-hospital mortality stratified by age.

Methods: A retrospective trauma cohort study was conducted using data from the National Trauma Data Bank (NTDB) from 2007 to 2014. All FES cases were included in the study with the diagnosis of FES (ICD9 958.1). Death on arrival cases were excluded. Patients were stratified by age cohort: less than 40 (G1), 40–64 (G2), and greater than 65 (G3) years of age. The primary outcome evaluated was in-hospital mortality. Multivariable regression models were performed to adjust for potential confounders.

Results: Between 2007 and 2014, 451 people from a total of 5,836,499 trauma patients in the NTDB met the inclusion criteria. The incidence rate was 8 out of 100,000. The inpatient mortality rate was 11.8% for all subjects with the highest mortality rate of 17.6% in patients over 65. Multivariable analyses demonstrated that age greater than 65 years was an independent predictor of mortality (aOR 24.16, 95% CI 3.73, 156.59, p=0.001), despite higher incidence and injury severity of FES among patients less than 40. No significant association with length of hospital stay, length of intensive unit care, or length of ventilation use was found between the groups. Subgroup analysis of the elderly population also showed a higher mortality rate for FES in femoral neck fracture patients (18%) than other femoral fractures (14%).

Conclusion: In this retrospective cohort analysis, old age (≥ 65 years) was found to be an independent risk factor for in-hospital mortality among fat embolism syndrome patients. Elderly patients specifically with femoral neck fractures should be monitored for the development of FES.

Keywords: fat embolism, trauma, database, mortality, age

Introduction

Fat embolism syndrome (FES) is a rare life-threatening condition that can develop after sustaining a traumatic orthopedic injury.,[2] Historically, the incidence rate of FES in orthopedic trauma settings was initially reported to be as high as 30%; however, recent literature has claimed that the incidence is closer to 1%, which has decreased over time.[3–7] This significant decrease in incidence may be attributed to the advances in pre-hospital care, but also to increased administration of prophylactic medication use for FES such as corticosteroids, and increased practice of early surgical fixation within 24 hours of trauma.[8] There was also a difference in the incidence rate between retrospective and prospective studies. While prospective studies reported a higher incidence rate, retrospective studies reported a lower incidence rate.[9,10] The main reason remains unknown. Large datasets in retrospective studies might have reported a closer estimation of the real-world

data.[11] Also, a lack of standardized criteria in the past may have contributed to the cause of overdiagnosis previously.[12] Mechanical and biomechanical disruption to bone and intraosseous blood vessels can create negative venous pressure, allowing fat globules to enter circulation.[7,13,14] Once the fat embolizes to the lungs, the local release of lipase breaks fat down into free fatty acids and glycerol. Free fatty acids are toxic to endothelial cells which inflammatory response yielding vasogenic edema and hemorrhage.[2,7,13,14] FES remains a diagnosis of exclusion and is based on clinical criteria.[3] Typically, the more severe the injury, the greater the magnitude of physiological response. The classic clinical triad includes respiratory insufficiency, neurological impairment, and petechial rash, of whom 80% and 20–50% present with neurological and petechial rash, respectively.[5,6,15]

Damage control orthopedics (DCO) and early stabilization protocols have been developed to decrease rates of morbidity and mortality among polytrauma patients.[7] Patients with delayed care reported increased rates of complications including fat embolism, acute respiratory distress syndrome, pneumonia, as well as intensive-care unit (ICU) admissions, and length of stay (LOS) were all greater among the cohort with delayed treatment.[16] Overall, the mortality of FES is estimated to be 5–30%.[4,17–19] Despite critical care improvement, a mortality rate as high as 30% was reported in a recent meta-analysis.[18] The difference in incidence rates and mortality rates may be due to a difference in the age of the FES of the studies.

Additional patient parameters that have been reported to influence FES development are bilateral lower extremity fractures, multiple medical comorbidities, sex, and age. Bilateral femur fractures, male sex, young age, multiple fractures, closed fractures, and conservative therapy for long-bone fractures have been reported as risk factors for FES development.[7,17,20] Since these risk factors occur more often in a younger age group, the existing literature reported a bias towards this subgroup of patients.[21] The relation to mortality rates across age groups is less known and less reported. Current literature has reported that FES typically occurs between 10–40 years old.[7] Gurd et al reported an average age of 31 among patients that developed FES after sustaining a long bone fracture.[22] Furthermore, Stein et al reported no cases of FES among 1,178,000 children in their discharge database study.[23] Decreased rates of pediatric FES may be attributed to higher content of hematopoietic and lower fat cell content among pediatric patients. Although FES is commonly seen following blunt trauma among young patients, other etiologies include burns, liposuction, cardiopulmonary bypass surgery, diabetes mellitus, carbon tetrachloride poisoning, decompression sickness, and parenteral lipid infusion have been reported.[24–28] This may have a bearing on the elderly since pre-existing comorbidities are more prevalent among this population.

A paucity of FES literature exists with regards to age stratification and impact of comorbidities on FES outcome, as well as fracture type, time to surgery and final fixation method. Therefore, this study aims to identify patients diagnosed with fat embolism syndrome (FES) and report the epidemiology of associated fractures, hospital course, and in-hospital mortality stratified by patient age.

Methods

A retrospective cohort analysis of the United States National Trauma Data Bank (NTDB) was queried between 2007–2014 to identify patients diagnosed with Fat Embolism Syndrome (FES) (ICD 958.1) that sustained an orthopedic injury. FES has been a clinical diagnosis of different criteria in the past. These include the Gurd's criteria, the Schonfeld's criteria and the Lindeque's criteria.[22,29,30] Since no definitive criteria are known for the diagnosis of FES, we chose a more standard approach by including ICD9 codes for the inclusion criteria of FES. To assess the presence of any fractures, the following ICD-9 codes were collected: skull fracture (800, 801, 802, 803, 804), spinal fracture (805, 806), rib fracture (807), pelvis fracture (808), clavicle fracture (810), scapular fracture (811), humerus fracture (812), radio-ulnar fracture (813), carpal fracture (814, 815, 816, 817), femoral neck fracture (820), other femoral fracture (821), patella fracture (822), tibiofibular fracture (823), ankle fracture (824), foot fracture (825, 826), and unspecified fracture (809, 818, 819, 827, 828, 829). To identify the procedures required to treat the sustained fractures, the following ICD-9-CM procedural codes included: bone graft (780), external fixation (781), limb shortening procedures (782), limb lengthening procedures (783), internal fixation without fracture reduction (785), closed reduction without internal fixation (790), closed reduction with internal fixation (791), open reduction without internal fixation (792), open reduction with internal fixation (793), and joint replacement of lower extremity (815). Patients were excluded from the cohort who were diagnosed with FES that resulted in death before hospital admission.

To assess the incidence of FES, patients were stratified by age group: <40 (G1), 40–65 (G2), and ≥65 years old (G3). The age stratification cut-off point was according to the most affected patient age for FES, which is less than 40.[23] The elderly cut-off point was according to the general definition of old age from the literature.[31] Patient-level demographic covariates included: sex, race; insurance status; comorbidities, injury mechanism, injury type, type of fracture, GCS, Injury Severity Score (ISS). The primary outcome evaluated was in-hospital mortality. Secondary outcomes included length of (i) total hospital and (ii) ICU stay (iii) ventilation use and (iv) non-home discharge.

Clinical information is stored in NTDB in de-identified form and available for quality improvement and research; therefore, individual patient consent was not required. To date, the NTDB is the world's largest trauma data repository, with more than 7.5 million electronic records from more than 900 trauma centers.[32] This study was approved by the Institutional Review Board of the Johns Hopkins Medicine (IRB00053752) and Chang Gung Memorial Hospital (202100187B0). The authors followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Statistical Analysis

Descriptive statistics were computed for patient-level and hospital characteristics. Missing data was based on a complete case analysis.[33] Categorical and continuous variables were compared using Chi-square and 2-sample t-tests. A multivariable logistic regression model was used to evaluate in-hospital mortality and hospital discharge disposition. Multivariable linear regression was fitted for lengths of stay (ICU days) as well as ventilation days with age groups of fat embolism syndrome patients as the primary predictor. Both regression models were adjusted for the following variables: age, sex, race, insurance, injury severity score, pre-admission interhospital transfer, GCS on admission, comorbidities (hypertension, diabetes, cerebrovascular accident, hemodialysis, and cancer with chemotherapy), type of fractures, and type of procedures. Adjustments were based on the guidelines suggested in the article by Haider et al[34] and Stein et al.[23] Adjusted odds ratios and coefficients with 95% confidence intervals were calculated from the logistic regression analysis. For the length of stay, the outcome of interest was the adjusted mean difference (in days) along with 95% confidence intervals. Subgroup analysis was done among the elderly population over age 65 to identify the most common fracture type, its hospital course, and mortality rates. P-values were two-sided and statistical significance was established at p≤0.05. All statistical analyses were performed using "Stata MP" statistical software version 14.2, 1985–2015, StataCorp LLC, College Station, Texas 77,845 USA.

Results

Between 2007 and 2014, a total of 5,836,499 patients were registered in the NTDB. The incidence rate for FES was 8 out of 100,000 (n=451) patients (Figure 1). Of these patients, 97.6% (n=440) sustained an orthopedic fracture (Table 1). Demographic and clinical variables of the study population are presented in Table 1. Of 451 individuals with fat embolism syndrome, 67% (n=302) and 33% (n=149) were male and female. When assessing the distribution of FES diagnosis by age group, 56.1% (n=253), 21.3% (n=96), and 22.6% (n=102) were <40, 40–65, and older than 65 years old respectively.

Upon evaluation of patient demographics, a statistically significant trend was noted in terms of sex distribution by age group. Fewer men were diagnosed with FES as patients age group increased (G1:187 [74.2%]; G2: 67 [70.5%]; G3: 48 [47.1%], p<0.001). When assessing the racial distribution, more Black and Hispanic patients contributed to the age group <40 years, while more White patients were older than 65 years old (p<0.001) (Table 1). Comorbid illnesses typically presented among patients older than 65 years old included bleeding disorders (14.9%, n=13), COPD (16.1%, n=14), and hypertension (48.3%, n=42) (Table 1). Furthermore, no significant difference was seen regarding age in patients presenting with adult respiratory distress syndrome (p=0.064) (Table 1). Among all patients, more than half of the individuals (51.7%, n= 233) diagnosed with FES presented to university hospitals. Most of the fat embolism patients were treated at level 1 trauma centers.

Interestingly, patients <40 were statistically more likely to sustain multiple orthopedic fractures compared to patients older than 65 years old, yet patients older than 65 years old (17.6%, n=18) were statistically more likely to have in-hospital mortality compared to patients between 40–64 years old (14.6%, n=14) as well as patients less than 40 years old (8.3%, n=21) (p=0.029) (Table 2).
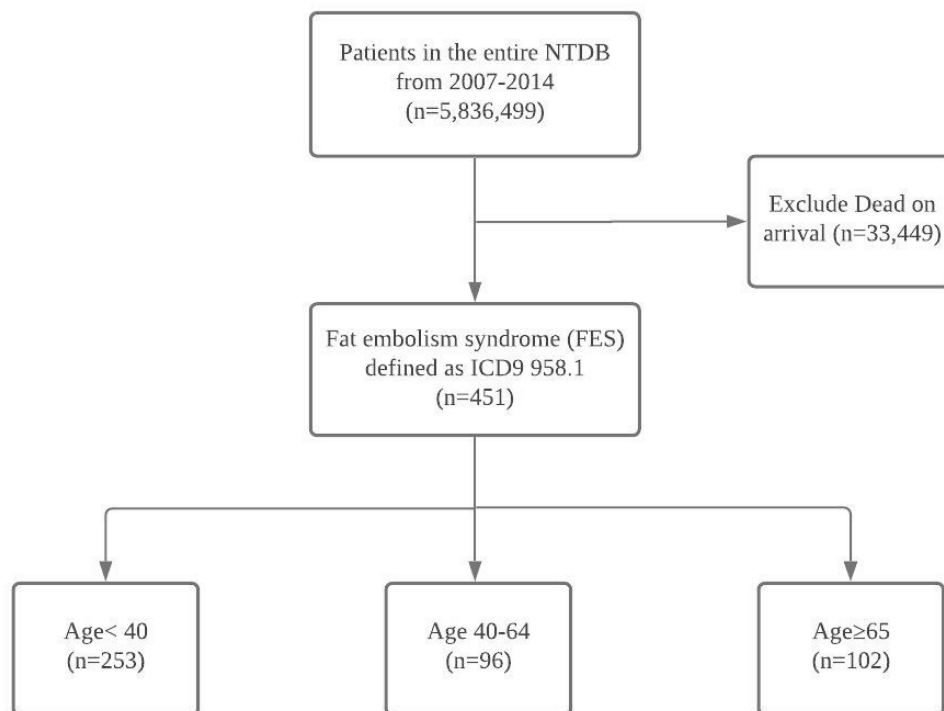
Figure 1 Patient selection and age stratification.
Abbreviations: NTDB, National Trauma Databank; ICD-9, International Classification of Diseases, Ninth Edition.

Overall, in-hospital mortality of the study population included 53 patients (11.8%). The mean (SD) length of hospital stay was 13.2 (0.6) days. Among patients that required ICU admission and ventilation use, the mean (SD) length of ICU stay was 6.0 (0.4) days, and the mean (SD) length of ventilation use was 3.8 (0.4) days (Table 2). No statistical difference was observed among total LOS, ICU admission, and ventilation use among the various age groups. With regards to the mechanism of injury, motor vehicle collisions (71.7%, n=180) and fall injuries (79.2%, n=80) were the most common modalities of injury in patients less than 40 and greater than 65 years old respectively (Table 3). Severely injured cases (ISS>16) were more commonly distributed in age less than 65 years old. (p<0.001) Among age cohorts, a statistically significant difference was noted among the following procedures: closed reduction without internal fixation (p=0.003), closed reduction with internal fixation (p<0.001), open reduction with internal fixation (p<0.001), external fixation (p=0.004), and joint replacement of the lower extremity (p<0.001). No significant difference was noted among patients that required bone grafting (p=0.63), internal fixation without fracture reduction (p=0.43), and open reduction without internal fixation (p=0.087).

Fracture type distribution by age group is presented in Table 4. Among patients <40, the most frequent diagnosis were 39.5% (n=100) with tibiofibular and 66.4% (n=168) with other femoral fractures. Patients between 40–65 years old were 46.9% (n=45) with femoral fractures, 31.3% (n=30) with tibiofibular ankle fractures, 37.5% (n=36) with rib fractures, 25.0% (n=24) with spinal fractures, and 24.0% (n=23) with pelvic fractures. Of patients >65 years old, the majority were femoral neck fractures with a proportion of 64.7% (n=66) (Table 4). Furthermore, a significant difference was observed among the number of fracture sites among each age cohort. 62.3% (n=159) patients less than 40 reported more than one fracture site location compared to 32.4% (n=33) with patients 65 years old and older (p<0.001) (Table 4).

The univariable and multivariable regression analyses to assess risk factors associated with in-hospital mortality among FES patients who sustained an orthopedic fracture are displayed in Table 5. The univariable analysis indicated that patients greater than 65 years old reported a 237% increased rate of death compared to patients less than 40 (OR 2.37; 95% CI, 1.20–4.66; P =0.013) (Table 5). When the effect estimate was adjusted for potential confounders including sex, race, insurance status, ISS, mechanism of injury, ED GCS score, comorbidities, type of fracture, type of procedures,

Table 1 Demographic and Clinical Variables of the Study Population Stratified by Age Groups

Variable	Subgroup	Overall (n=451)	Age <40 (n=253)	Age 40–64 (n=96)	Age ≥65 (n=102)	p-value
Male (%)		302 (67.0%)	187 (74.2%)	67 (70.5%)	48 (47.1%)	**<0.001**
Race (%)	White	328 (72.7%)	163 (66.3%)	76 (84.4%)	89 (91.8%)	**<0.001**
	Black	50 (11.1%)	36 (14.6%)	9 (10.0%)	5 (5.2%)	
	Hispanic	36 (8.0%)	32 (13.0%)	4 (4.4%)	0 (0.0%)	
	Other	19 (4.2%)	15 (6.1%)	1 (1.1%)	3 (3.1%)	
Comorbid Illnesses (%)	Alcoholism	20 (4.4%)	14 (5.5%)	4 (4.2%)	2 (2.0%)	0.33
	Bleeding disorder	30 (6.7%)	13 (5.1%)	4 (4.2%)	13 (12.7%)	**0.018**
	Cerebrovascular accident	20 (4.4%)	7 (2.8%)	5 (5.2%)	8 (7.8%)	0.10
	Chronic Obstructive Pulmonary DIsease	41 (9.1%)	18 (7.1%)	9 (9.4%)	14 (13.7%)	0.15
	Chronic Renal Failure	5 (1.1%)	0 (0.0%)	4 (4.2%)	1 (1.0%)	**0.004**
	Liver Cirrhosis	2 (0.4%)	1 (0.4%)	1 (1.0%)	0 (0.0%)	0.54
	Congestive Heart Failure	23 (5.1%)	1 (0.4%)	8 (8.3%)	14 (13.7%)	**<0.001**
	Smoker	45 (10.0%)	26 (10.3%)	15 (15.6%)	4 (3.9%)	**0.022**
	Cancer with current chemotherapy	1 (0.2%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.16
	Dementia	3 (0.7%)	0 (0.0%)	0 (0.0%)	3 (2.9%)	**0.006**
	Dependent Status	10 (2.2%)	4 (1.6%)	1 (1.0%)	5 (4.9%)	0.11
	Hypertension	87 (19.3%)	5 (2.0%)	33 (34.4%)	49 (48.0%)	**<0.001**
	Steroid user	3 (0.7%)	1 (0.4%)	1 (1.0%)	1 (1.0%)	0.73
Insurance (%)		367 (81.4%)	201 (83.4%)	74 (89.2%)	92 (98.9%)	**<0.001**
Acute Respiratory Distress Syndrome (%)		40 (8.9%)	29 (11.5%)	7 (7.3%)	4 (3.9%)	0.064

Note: % as percentage, bold text are statistically significant p values.
Abbreviation: n, total numbers.

Table 2 Outcome Variables of the Study Population Stratified by Age Groups

Variable	Overall (n=451)	Age <40 (n=253)	Age 40–64 (n=96)	Age ≥65 (n=102)	p-value
In-hospital mortality (%)	53 (11.8%)	21 (8.3%)	14 (14.6%)	18 (17.6%)	**0.029**
Hospital discharge non home (%)	309 (68.5%)	180 (71.1%)	57 (59.4%)	72 (70.6%)	0.094
Length of stay (%)	13.2 (0.6)	13.2 (0.7)	15.1 (1.6)	12.1 (0.9)	**<0.001**
Require ICU stay (%)	344 (76.3%)	203 (80.1%)	79 (82.2%)	62 (61.2%)	**<0.001**
Require ventilation use (%)	273 (60.6%)	150 (59.2%)	65 (67.9%)	58 (57.1%)	**<0.001**

Note: % as percentage, bold text are statistically significant p values.
Abbreviation: n, total numbers.

Table 3 Injury Mechanism, Severity, and Type of the Study Population Stratified by Age Groups

Variable	Subgroup	Overall (n=451)	Age <40 (n=253)	Age 40–64 (n=96)	Age ≥65 (n=102)	p-value
Mechanism of Injury	Stab	2 (0.4%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	**<0.001**
	Falls	129 (28.6%)	20 (8.0%)	29 (30.9%)	80 (79.2%)	
	GSW	10 (2.2%)	8 (3.2%)	1 (1.1%)	1 (1.0%)	
	MVA	246 (54.5%)	180 (71.7%)	48 (51.1%)	18 (17.8%)	
	Pedestrian	4 (0.9%)	2 (0.8%)	2 (2.1%)	0 (0.0%)	
	Struck-by	15 (3.3%)	12 (4.8%)	3 (3.2%)	0 (0.0%)	
	Other	40 (8.9%)	28 (11.2%)	10 (10.6%)	2 (2.0%)	
ISS	1 to 8	46 (10.2%)	29 (11.5%)	10 (10.5%)	7 (6.9%)	**<0.001**
	9 to 15	255 (56.5%)	126 (49.8%)	48 (50.5%)	81 (79.4%)	
	16 to 24	84 (18.6%)	57 (22.5%)	19 (20.0%)	8 (7.8%)	
	25 to 75	65 (14.4%)	41 (16.2%)	18 (18.9%)	6 (5.9%)	
GCS	3	24 (5.3%)	18 (7.5%)	5 (5.8%)	1 (1.2%)	0.058
	4 to 5	5 (1.1%)	5 (2.1%)	0 (0.0%)	0 (0.0%)	
	6 to 8	8 (1.8%)	6 (2.5%)	2 (2.3%)	0 (0.0%)	
	9 to 12	10 (2.2%)	6 (2.5%)	4 (4.7%)	0 (0.0%)	
	13 to 15	364 (80.7%)	205 (85.4%)	75 (87.2%)	84 (98.8%)	
Injury type	Blunt	426 (94.5%)	239 (95.2%)	88 (93.6%)	99 (98.0%)	0.19
	Penetrating	12 (2.7%)	9 (3.6%)	2 (2.1%)	1 (1.0%)	
	Others	8 (1.8%)	3 (1.2%)	4 (4.3%)	1 (1.0%)	

Note: % as percentage, bold text are statistically significant p values.
Abbreviation: n, total numbers.

patients greater than 65 years old reported 24.16 times increased odds of in-hospital mortality compared to patients less than 40 (aOR 24.16; 95% CI, 3.73 −156.59; P =0.001). Furthermore, patients between 40–64 reported 7.09 times increased odds of in-hospital mortality compared to patients less than 40 (aOR 7.09; 95% CI, 1.74–28.84; P =0.006) (Table 5). Patients between 40–64 were statistically more likely to be discharged home [hospital non-home discharge (unadjusted odds ratio [OR], 0.59; 95% CI, 0.36–0.97; p =0.036; adjusted odds ratio [aOR], 0.42; 95% CI, 0.19–0.93; P =0.032)] compared to patients less than 40. (Table 5)

Among FES fracture patients greater than 65 years of age, we further compared femoral neck fracture diagnoses to other femoral fractures as these diagnoses comprised most FES mortalities (Table 6). Overall, 33% underwent closed reduction alone, 26.7% underwent open reduction with internal fixation, 17% underwent internal fixation without reduction, and 25% underwent joint replacement of lower extremity. The in-hospital mortality rate among femoral neck fractures and other femoral fractures was 18% and 14% respectively; however, other femoral fractures compared to femoral neck fractures reported a longer total length of stay (16.29 days vs 9.77 days), ICU stay (7.2 days vs 2.97 days), ventilation use (5.06 days, vs 1.94 days), and non-home discharge (76% vs 64%).

Table 4 Fracture Location and Numbers Among Fat Embolism Syndrome Patients Stratified by Age Groups in the National Trauma Databank

	Overall (n=451)	Age <40 (n=253)	Age 40–64 (n=96)	Age ≥65 (n=102)	p-value
Spinal Fracture	84 (18.6%)	50 (19.8%)	24 (25.0%)	10 (9.8%)	**0.018**
Rib Fracture	94 (20.8%)	49 (19.4%)	36 (37.5%)	9 (8.8%)	**<0.001**
Pelvic Fracture	90 (20.0%)	52 (20.6%)	23 (24.0%)	15 (14.7%)	0.25
Clavicle Fracture	20 (4.4%)	12 (4.7%)	7 (7.3%)	1 (1.0%)	0.092
Scapula Fracture	13 (2.9%)	9 (3.6%)	3 (3.1%)	1 (1.0%)	0.42
Humerus Fracture	32 (7.1%)	17 (6.7%)	8 (8.3%)	7 (6.9%)	0.87
Radioulnar Fracture	61 (13.5%)	39 (15.4%)	16 (16.7%)	6 (5.9%)	**0.035**
Carpal Bone Fracture	28 (6.2%)	19 (7.5%)	7 (7.3%)	2 (2.0%)	0.13
Hip Fracture (Femoral Neck)	321 (71.2%)	26 (10.3%)	17 (17.7%)	66 (64.7%)	**<0.001**
Other Femoral Fracture	234 (51.9%)	**168 (66.4%)**	45 (46.9%)	21 (20.6%)	**<0.001**
Patella Fracture	26 (5.8%)	19 (7.5%)	5 (5.2%)	2 (2.0%)	0.12
Tibiofibular Fracture	134 (29.7%)	**100 (39.5%)**	26 (27.1%)	8 (7.8%)	**<0.001**
Ankle Fracture	39 (8.6%)	26 (10.3%)	9 (9.4%)	4 (3.9%)	0.15
Foot Fracture	35 (7.8%)	24 (9.5%)	10 (10.4%)	1 (1.0%)	**0.014**
Unspecified	2 (0.4%)	1 (0.4%)	0 (0.0%)	1 (1.0%)	0.57
Fracture site numbers					**<0.001**
No Fracture	11 (2.4%)	6 (2.4%)	4 (4.2%)	1 (1.0%)	
One Fracture site	191 (42.4%)	88 (34.8%)	35 (36.5%)	68 (66.7%)	
Two Fracture sites	83 (18.4%)	49 (19.4%)	14 (14.6%)	20 (19.6%)	
Three Fracture sites	70 (15.5%)	48 (19.0%)	15 (15.6%)	7 (6.9%)	
More than three fracture sites	96 (24.5%)	62 (24.5%)	28 (29.2%)	6 (5.9%)	

Note: % as percentage, bold text are statistically significant p values.
Abbreviation: n, total numbers.

Discussion

This study aimed to specifically evaluate in-patient mortality, epidemiology of associated fractures, hospital course among patients diagnosed with FES who sustained an orthopedic injury stratified by age. To our knowledge, this is the first and largest study to specifically report mortality rates of FES by age distribution. In this retrospective analysis of the NTDB, the overall in-hospital mortality rate of FES was 11.8%. When stratified by age, the in-hospital mortality rate was 8.3%, 14.6%, and 17.6% among patients less than 40, between 40–64, and greater than 65 years old respectively. Previous literature has reported FES mortality rates ranging from 1–20%;[5–7] however, much of the literature included a younger age demographic resulting in lower overall mortality rates relative to our findings. This study highlights that in-hospital FES mortality rates differ based on patient age.

Prior studies have reported that patients with long-bone fractures, specifically of the femur, are most likely to develop FES. Stein et al[23] observed that the majority of FES were patients between 10 and 39, with an incidence of FES 7.6% higher in patients with isolated fractures of the femur (excluding the neck) compared to patients with isolated fractures of

Table 5 Odds Ratios for in Hospital Mortality, Hospital Non-Home Discharge, and Coefficients for Length of Stay, ICU Days and Ventilation Days, with Stratified Age Groups as Predictor, Among Fat Embolism Syndrome Patients. Covariates Included Were Sex, Race, Insurance Status, ISS, Mechanism of Injury, Emergency Department GCS Score, Comorbidities, Type of Fracture, Type of Procedure, Hospital Teaching Status and Hospital Bed Count

	Age <40 (n=253); Age 40–64 (n=96); Age ≥65 (n=102)				
	Unadjusted OR (95% CI)	p-value	*Adjusted OR (95% CI)	p-value
In Hospital Mortality				
<40	Ref		Ref	
40–64	1.89 (0.92,3.88)	0.085	**7.09 (1.74,28.84)**	**0.006**
>65	2.37 (1.20,4.66)	**0.013**	**24.16 (3.73, 156.59)**	**0.001**
Total Length of Stay				
<40	Ref		Ref	
40–64	1.94 (−0.94,4.82)	0.186	2.29 (−1.53,6.12)	0.239
>65	−1.05 (−3.87,1.77)	0.463	3.50 (−1.46,8.45)	0.166
Total ICU Length of Days				
<40	Ref		Ref	
40–64	1.31 (−0.90,3.52)	0.244	1.02 (−1.90,3.93)	0.492
>65	−1.65 (−3.79,0.49)	0.13	0.79 (−2.94,4.54)	0.675
Total Ventilation Days				
<40	Ref		Ref	
40–64	0.27 (−1.67,2.20)	0.79	−0.25 (−2.88,2.37)	0.85
>65	−1.44 (−3.33,0.45)	0.13	−0.25 (−3.55,3.05)	0.88
Hospital non-home discharge				
<40	Ref		Ref	
40–64	0.59 (0.36,0.97)	**0.036**	0.42 (0.19,0.93)	**0.032**
>65	0.97 (0.59,1.61)	0.917	0.56 (0.20,1.61)	0.283

Notes: *Adjusted by sex, race, insurance status, ISS, mechanism of injury, emergency department GCS score, comorbidities, type of fracture, type of procedure. % as percentage, bold text are statistically significant p values.
Abbreviations: n, total numbers; Ref, reference.

Table 6 Femoral Neck Fractures Compared to Other Femoral Fractures in Patients 65 and Older Who Developed FES

Age ≥65 n=102 (Total)	Femoral Neck Fracture (n=66, 64.7%)	Other Femoral Fracture (n=21, 20.6%)
In Hospital Mortality	12 (18%)	3 (14%)
Total Length of Stay	9.77 (7.94, 11.61)	16.29 (10.50, 22.07)
Total ICU Length of Days	2.97 (1.30, 4.64)	7.2 (3.55, 10.85)
Total Ventilation Days	1.94 (0.35, 3.53)	5.06 (1.53, 8.58)
Hospital non-home Discharge	42 (64%)	16 (76%)

Note: % as percentage.
Abbreviation: n, total numbers.

the neck. Our findings demonstrate that the incidence of FES was also most common among patients less than 40. Yet, the incidence of fracture location varied by patient age. FES patients less than 65 years old were most likely to have sustained femur fractures other than femoral neck fractures, while patients greater than 65 years old were more likely to report fractures of the femoral neck compared to other types of femur fractures.

Furthermore, alongside fracture location, it is important to consider the number of fractures sustained during a trauma. Bone et al[16] conducted a prospective randomized study of 178 patients comparing early with delayed stabilization of acute femoral fractures in adults. Patients were categorized into two groups: isolated fractures of the femur and those who had multiple injuries. Patients who sustained multiple injuries were reported to have increased rates of adult respiratory distress syndrome, fat embolism, and pneumonia.[35] Similarly, our results also indicate that patients with two, three, or more than three distinct fracture sites were statistically more likely to develop FES compared to patients with one fracture. Contrary to the results presented by Bone et al,[16] we found no statistical difference in ARDS among different age groups. The difference can be explained by inclusion criteria. Bone et al[16] excluded all patients over 65 years old that sustained an isolated femur fracture; however, this study included patients over 65 years old.

Our findings indicate that 94.5% of patients diagnosed with FES had blunt trauma with regards to injury mechanism Mudd et al[36] evaluated the incidence of pulmonary fat embolism among blunt force fatalities compared to control subjects dying from natural causes/non-blunt force injury. 68% of patients with blunt force trauma were diagnosed with FES compared to 15% of the control cohort. In our cohort, patients less than 40 were statistically more likely to have sustained high energy trauma from a motor vehicle accident, report a greater ISS, and have fewer medical comorbidities as well as in-hospital mortality rates when compared to patients over 65 years old. Additionally, 61 (13.5%) of patients less than 40 years old received initial external fixation compared to 7 (6.9%) of patients over 65 years old. A proportion of these elderly patients might have been unfit for surgery and had severe comorbidities at risk to undergo surgery. The coupling of delayed surgery and more comorbidities could have resulted in a high incidence of FES in this age group. These epidemiological findings have been supported by previous literature. Neiman[37] reported that patients younger than 40 were more likely to sustain high energy trauma from a motor vehicle crash resulting in midshaft femur fracture while patients over 40 were more likely to sustain low energy trauma and fracture of the proximal third of the femur.

Even though, younger patients (<40) have a higher incidence of sustaining high energy blunt trauma, multiple fractures and FES, this does not necessarily translate into a higher in-hospital mortality. When assessing age as a major risk factor for FES related in-hospital mortality, patients between 40–64 and patients older than 65 years old showed a respective 7.09 and 24.16 times increased odds of in-hospital mortality compared to patients less than 40 after adjusting for sex, race, insurance status, ISS, mechanism of injury, emergency department GCS score, comorbidities, type of fracture, type of procedures, hospital teaching status, and hospital bed count. More pre-existing comorbidities among the elderly may also have been a factor that contributed to the higher mortality rates among this population subgroup and the results of delayed surgery from unfit or high risk of surgery may have caused a higher FES rate with mortality and morbidity. Among patients older than 65 years old who were either diagnosed with femoral neck fracture or other femur fracture, the in-hospital mortality rate was 18% and 14% respectively. Femoral neck fractures have been reported a mortality as high as 30% in the literature.[38,39] The associated complications induced by the fracture including FES, urinary tract infection and pneumonia may further contribute to the mortality of this group of patients. It should be noted that no statistical difference was observed among total LOS, ICU admission, and ventilation use among age groups. This may be explained by in-hospital mortality acting as a competing factor for LOS and ventilation management. Overall, these findings reinforce that age is a strong predictor of mortality, especially among those diagnosed with FES.

Although this study demonstrates that age is a major independent risk factor for FES-related in-hospital mortality among patients who sustained orthopedic injuries, some limitations must be addressed. Firstly, although the NTDB includes a large sample of trauma centers from across the United States, it is a retrospective convenience sample that consists of data only submitted by participating hospitals. Second, the quality of data entered in the NTDB is dependent on the participants entering the data. Third, ICD-9 codes do not provide granular data in terms of either fracture pattern or precise anatomical location. For example, "other femur fracture" was not able to differentiate between a femoral shaft or distal femur fracture. Bilateral femur fractures were not easily identified from the ICD9 codes. We were not able to reassess and confirm the final diagnosis using the standard clinical criteria since symptoms were not documented in the database. Therefore, we were not able to identify autopsy diagnosed or clinically diagnosed FES. Subclinical and mild cases might be underestimated. Fourth, the ability to adjust for important confounding factors including time to surgery, time to FES, intramedullary reaming versus non-reaming procedures, procedures which involved increased versus decreased intramedullary pressures, cemented versus non-cemented procedures, intraosseous fluid resuscitation, as well as medications was not possible.[40,41] Residual unmeasured confounding is a bias.

However, potential immortal time bias was adjusted by excluding patients who died before hospital admission.[42] These patients may have less likely to receive treatment than other patients. Schmidutz et al[43] conducted a randomized trial with 30 patients and observed that secondary cement insertion was able to reduce severe embolic events. With regards to reaming technique, intramedullary reaming has the theoretical higher odds of increasing FES due to the increase in canal pressure and stimulation of an inflammatory response, yet studies have been limited by small sample sizes and this topic requires further investigation.[44–48] Bosse et al[49] compared reamed intramedullary nails with plate fixation among 453 patients who sustained a femur fracture and reported no significant differences in pulmonary complications or mortality rates. With regards to time to intervention, a meta-analysis conducted by El-Menyar et al[50] reported that large, pooled effects were in favor of early intramedullary nailing intervention compared to delayed intervention. Higher incidence of FES in the elderly with a femoral neck fracture is a significant finding of this study which necessitates the need for prospective studies to evaluate and analyze this finding.

Conclusion

This study highlights that age is a major determinant of FES in-hospital mortality after adjusting for other clinical and demographic factors. Femoral neck fracture patients over 65 years old should be carefully monitored for the development of FES. Future studies evaluating FES patients' outcomes at different hospital levels will be critical to see how their outcomes compare to those of patients included in large national databases; this will help better guide clinical decision-making.

Ethical Approval

This study was approved by the Institutional Review Board of the Johns Hopkins Medicine (IRB 00053752) and Chang Gung Memorial Hospital (202100187B0).

Acknowledgments

Disclosure

This research received no benefits from any agency in the commercial, public or non-profit organization related to the subject of the study. There is no conflict of interest of the study.

References

1. Sevitt S. Fat embolism in patients with fractured hips. Br Med J. 1972 Apr 29;2(5808):257-62. doi: 10.1136/bmj.2.5808.257
2. Gauss H. The pathology of fat embolism. *Arch. Surg*. 1924;9(593):593. doi:10.1001/archsurg.1924.01120090110007
3. Lempert M, Halvachizadeh S, Ellanti P, et al. Incidence of fat embolism syndrome in femur fractures and its associated risk factors over time-a systematic review. *J Clin Med Res*. 2021;10:2733.
4. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome. A 10-year review. *Arch Surg*. 1997;132:435–439. doi:10.1001/archsurg.1997.01430280109019
5. Tzioupis CC, Giannoudis PV. Fat embolism syndrome: what have we learned over the years? *Traumatology*. 2011;13:259–281.
6. Mellor A, Soni N. Fat embolism. *Anaesthesia*. 2001;56:145–154. doi:10.1046/j.1365-2044.2001.01724.x
7. Rothberg DL, Makarewich CA. Fat embolism and fat embolism syndrome. *J Am Acad Orthop Surg*. 2019;27:e346–e355. doi:10.5435/JAAOS-D-17-00571
8. Kosova E, Bergmark B, Piazza G. Fat embolism syndrome. *Circulation*. 2015;131:317–320. doi:10.1161/CIRCULATIONAHA.114.010835
9. Chan KM, Tham KT, Chiu HS, Chow YN, Leung PC. Post-traumatic fat embolism—its clinical and subclinical presentations. *J Trauma Injury, Infect Crit Care*. 1984;24:45–49. doi:10.1097/00005373-198401000-00007
10. Gupta B, D'souza N, Sawhney C, et al. Analyzing fat embolism syndrome in trauma patients at AIIMS Apex Trauma Center, New Delhi, India. *J Emerg Trauma Shock*. 2011;4:337–341. doi:10.4103/0974-2700.83859
11. George J, George R, Dixit R, Gupta RC, Gupta N. Fat embolism syndrome. *Lung India*. 2013;30:47–53. doi:10.4103/0970-2113.106133
12. Newbigin K, Souza CA, Torres C, et al. Fat embolism syndrome: state-of-the-art review focused on pulmonary imaging findings. *Respir Med*. 2016;113:93–100. doi:10.1016/j.rmed.2016.01.018
13. Lackner I, Weber B, Baur M, et al. Complement activation and organ damage after trauma-differential immune response based on surgical treatment strategy. *Front. Immunol*. 2020;11(64). doi:10.3389/fimmu.2020.00064
14. Sears BW, Stover MD, Callaci J. Pathoanatomy and clinical correlates of the immunoinflammatory response following orthopaedic trauma. *J Am Acad Orthop Surg*. 2009;17:255–265. doi:10.5435/00124635-200904000-00006

15. Godoy DA, Di Napoli M, Rabinstein AA. Cerebral fat embolism: recognition, complications, and prognosis. *Neurocrit Care*. 2018;29:358–365. doi:10.1007/s12028-017-0463-y

16. Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. *J Bone Joint Surg Am*. 1989;71:336–340. doi:10.2106/00004623-198971030-00004

17. Shaikh N. Emergency management of fat embolism syndrome. *J Emerg Trauma Shock*. 2009;2:29–33. doi:10.4103/0974-2700.44680

18. He Z, Shi Z, Li C, et al. Single-case metanalysis of fat embolism syndrome. *Int. J. Cardiol*. 2021;345:111–117. doi:10.1016/j.ijcard.2021.10.151

19. Kainoh T, Iriyama H, Komori A, et al. Risk factors of fat embolism syndrome after trauma: a nested case-control study with the use of a nationwide trauma registry in Japan. *Chest*. 2021;159:1064–1071. doi:10.1016/j.chest.2020.09.268

20. Vetrugno L, Bignami E, Deana C, et al. Cerebral fat embolism after traumatic bone fractures: a structured literature review and analysis of published case reports. *Scand J Trauma Resusc Emerg Med*. 2021;29(1). doi:10.1186/s13049-021-00861-x

21. Tsai I-T, Hsu C-J, Chen Y-H, et al. Fat embolism syndrome in long bone fracture—clinical experience in a tertiary referral center in Taiwan. *J. Chin. Med. Assoc*. 2010;73:407–410. doi:10.1016/S1726-4901(10)70088-5

22. Gurd AR. Fat embolism: an aid to diagnosis. *J Bone Joint Surg Br*. 1970;52:732–737. doi:10.1302/0301-620X.52B4.732

23. Stein PD, Yaekoub AY, Matta F, Kleerekoper M. Fat embolism syndrome. *Am J Med Sci*. 2008;336:472–477. doi:10.1097/MAJ.0b013e318172f5d2

24. Lynch MJ. Nephrosis and fat embolism in acute hemorrhagic pancreatitis. *AMA Arch Intern Med*. 1954;94:709–717. doi:10.1001/archinte.1954.00250050023004

25. Scroggins C, Barson PK. Fat embolism syndrome in a case of abdominal lipectomy with liposuction. *Md Med J*. 1999;48:116–118.

26. Taviloglu K, Yanar H. Fat embolism syndrome. *Surg Today*. 2007;37:5–8. doi:10.1007/s00595-006-3307-5

27. Blacker E, Tsitsikas D. Fat embolism syndrome in sickle cell disease: a case series. *Br J Soc Econ Res*. 2018;181:124.

28. Macmahon HE, Weiss S. Carbon tetrachloride poisoning with macroscopic fat in the pulmonary artery. *Am J Pathol*. 1929;5:623–630.

29. Lindeque BG, Schoeman HS, Dommisse GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. *J Bone Joint Surg*. 1987;69-B:128–131. doi:10.1302/0301-620X.69B1.3818718

30. Schonfeld SA, Ploysongsang Y, Dilisio RA, et al. Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. *Ann Intern Med*. 1983;99:438–443. doi:10.7326/0003-4819-99-4-438

31. Victorino GP, Chong TJ, Pal JD. Trauma in the elderly patient. *Arch Surg*. 2003;138:1093–1098. doi:10.1001/archsurg.138.10.1093

32. Hashmi ZG, Kaji AH, Nathens AB. Practical guide to surgical data sets: National Trauma Data Bank (NTDB). *JAMA Surg*. 2018;153:852–853. doi:10.1001/jamasurg.2018.0483

33. Pigott TD. A Review of Methods for Missing Data. *Educ Res Eval*. 2001;7:353–383. doi:10.1076/edre.7.4.353.8937

34. Haider AH, Hashmi ZG, Zafar SN, et al. Developing best practices to study trauma outcomes in large databases: an evidence-based approach to determine the best mortality risk adjustment model. *J. Trauma Acute Care Surg*. 2014;76:1061–1069. doi:10.1097/TA.0000000000000182

35. Pfeifer R, Heussen N, Michalewicz E, Hilgers R-D, Pape H-C. Incidence of adult respiratory distress syndrome in trauma patients: a systematic review and meta-analysis over a period of three decades. *J Trauma Acute Care Surg*. 2017;83:496–506. doi:10.1097/TA.0000000000001571

36. Mudd KL, Hunt A, Matherly RC, et al. Analysis of pulmonary fat embolism in blunt force fatalities. *J Trauma Injury, Infect Crit Care*. 2000;48:711–715. doi:10.1097/00005373-200004000-00020

37. Neiman R. Antegrade nailing for midshaft femur fractures. *J Orthop Trauma*. 2020;34:S29–S30. doi:10.1097/BOT.0000000000001822

38. Elliott J, Beringer T, Kee F, et al. Predicting survival after treatment for fracture of the proximal femur and the effect of delays to surgery. *J. Clin. Epidemiol*. 2003;56:788–795. doi:10.1016/S0895-4356(03)00129-X

39. Arshi A, Su L, Lee C, et al. Comparison of complication profiles for femoral neck, intertrochanteric, and subtrochanteric geriatric Hip fractures. *Arch Orthop Trauma Surg*. 2021. doi:10.1007/s00402-021-03978-x

40. Lari A, Abdulshakoor A, Zogheib E, et al. How to save a life from macroscopic fat embolism: a narrative review of treatment options. *Aesthet. Surg. J*. 2020;40:1098–1107. doi:10.1093/asj/sjz277

41. Pape H-C, Halvachizadeh S, Leenen L, et al. Timing of major fracture care in polytrauma patients - An update on principles, parameters and strategies for 2020. *Injury*. 2019;50:1656–1670. doi:10.1016/j.injury.2019.09.021

42. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340(b5087):b5087–b5087. doi:10.1136/bmj.b5087

43. Schmidutz F, Düll T, Voges O, et al. Secondary cement injection technique reduces pulmonary embolism in total Hip arthroplasty. *Int. Orthop*. 2012;36:1575–1581. doi:10.1007/s00264-012-1537-2

44. Högel F, Kamer L, Schlegel U, et al. Fat extravasation due to unreamed and experimentally reamed intramedullary nailing of the sheep femur. *Injury*. 2009;40:718–721. doi:10.1016/j.injury.2008.10.044

45. Högel F, Gerlach UV, Südkamp NP, Müller CA. Pulmonary fat embolism after reamed and unreamed nailing of femoral fractures. *Injury*. 2010;41:1317–1322. doi:10.1016/j.injury.2010.08.019

46. Pape H-C, Giannoudis P. The biological and physiological effects of intramedullary reaming. *J Bone Joint Surg Br*. 2007;89-B:1421–1426. doi:10.1302/0301-620X.89B11.19570

47. Alobaidi AS, Al-Hassani A, El-Menyar A, et al. Early and late intramedullary nailing of femur fracture: a single center experience. *Int J Crit Illn Inj Sci*. 2016;6:143–147. doi:10.4103/2229-5151.190649

48. Pape H-C, Tornetta P, Tarkin I, et al. Timing of fracture fixation in multitrauma patients: the role of early total care and damage control surgery. *J Am Acad Orthop Surg*. 2009;17:541–549. doi:10.5435/00124635-200909000-00001

49. Bosse MJ, Mackenzie EJ, Riemer BL, et al. Adult respiratory distress syndrome, pneumonia, and mortality following thoracic injury and a femoral fracture treated either with intramedullary nailing with reaming or with a plate. A Comparative Study*. *J Bone Joint Surg*. 1997;79:799–809. doi:10.2106/00004623-199706000-00001

50. El-Menyar A, Muneer M, Samson D, et al. Early versus late intramedullary nailing for traumatic femur fracture management: meta-analysis. *J Orthop Surg Res*. 2018;13(160):1.