RESEARCH ARTICLE

Risk Factors for Fractures in Children Hospitalized in Intensive and Intermediate Care Units

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ABSTRACT

BACKGROUND AND OBJECTIVES: Fragility fractures are increasingly recognized in hospitalized children. Our study aim was to identify risk factors for fracture in children hospitalized in intensive and intermediate care units.

METHODS: We conducted a retrospective, case-control study comparing the clinical characteristics of children with fractures (cases) to children without fractures (controls) matched for age, sex, hospital unit, admission quarter and year, ICU length of stay, severity of illness, and resource utilization. Bivariate comparisons and matched multivariable logistic regression modeling were used to determine associations between potential risk factors and fracture.

RESULTS: Median age at fracture for the 35 patients was 5.0 months (interquartile range 2.0 to 10.0 months) and at a comparable interval for the 70 matched controls was 3.5 months (interquartile range 2.0 to 7.0 months). In bivariate analyses, factors associated with fracture included: primary diagnosis of tracheoesophageal fistula, esophageal atresia and stenosis; diagnosis of kidney disease; and per 5-day increase in median cumulative ICU days at risk. In the final model, a respiratory disease diagnosis (odds ratio 3.9, 95% confidence interval 1.1–13.7) and per 5-day increase in median cumulative ICU days at risk (odds ratio 1.3, 95% confidence interval 1.0–1.6) were significant independent risk factors for fracture.

CONCLUSIONS: Children prone to fracture in the hospital are young, medically complex patients who require extended periods of intensive level medical care and potentially life-sustaining treatment modalities. The children who would benefit most from fracture reduction efforts are those with respiratory disease and prolonged ICU stays.

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Fragility (low-impact) fractures are rare but are increasingly recognized in hospitalized pediatric patients, particularly those who are critically ill.[1–3] Hospitalized children possess multiple risk factors that can contribute to low bone mineral density and bone fragility, including prematurity, alterations in bone metabolism that are due to underlying medical disorders (eg, renal and gastrointestinal disease), certain medications (eg, glucocorticoids and loop diuretics), poor nutritional status, and immobilization.[1–9] Early recognition and management of risk factors are important to prevent fractures and associated morbidity.

In 2008, Boston Children's Hospital (BCH) required all fractures that occurred during the course of a child's hospitalization to be recorded in the hospital's Safety Event Reporting System (SERS), which is an electronic patient database for safety event reporting, surveillance, and analysis. In addition to this initiative, the BCH Program for Patient Safety and Quality appointed a task force that launched a hospital-wide fracture awareness and educational campaign. These efforts resulted in more reported fractures (typically identified clinically with radiographic confirmation or as an incidental radiographic finding if clinically asymptomatic) with the highest fracture rates occurring among infants and young children with prolonged hospitalizations in the intensive and intermediate care units.

Retrospective studies examining the risk factors for fracture in hospitalized patients have recently been performed at BCH.[2,3,8,9] In a descriptive study of patients captured within SERS and additional patients identified through a computer-assisted keyword search of medical records, the common clinical characteristics among patients with fractures were age ≤1 year, preterm birth, admission to an ICU, immobilization, and weight-for-age *z* score ≤−2.0.[3] In a study limited to patients with congenital heart disease and hospitalized in the cardiac ICU,[2] the patients with fractures had prolonged loop diuretic use, prolonged immobility, corticosteroid exposure, and renal insufficiency compared with patients who did not experience fractures. However, the controls in that study were selected on the basis of the presence of laboratory measures, and they were not matched for disease acuity that would affect fracture risk.[2] In another study of patients with long-gap esophageal atresia (LGEA) undergoing the Foker process, a cohort with a high percentage of fractures (39%), univariate analysis identified several variables that increased fracture risk, including the number of paralytic episodes, exposure to nonloop diuretics, cumulative loop diuretic dose, ICU stay, and total length of hospital stay.[8] However, in multivariable analyses, only the number of separate episodes of paralysis was shown to be an independent risk factor, and patients with more than 3 episodes of paralysis had an estimated risk of fracture 15 times higher than those patients paralyzed only once or twice.[8]

The aforementioned studies identified clinical risk factors for fracture, but they were descriptive, the control group was not matched with fracture cases for disease severity, and/or the findings were not generalizable to other populations of children potentially at risk for fracture in the hospital. Therefore, the aim of this case-control study is to identify specific risk factors for fragility fracture in at-risk children hospitalized across intensive and intermediate-level pediatric care units by using a control group that was closely matched for medical complexity and severity of illness.

METHODS

With institutional review board approval, we conducted a retrospective, matched case-control study comparing children with fractures (cases) to children without fractures (controls).

Patient Selection

Patients were selected from the SERS database at BCH and consisted of inpatients <18 years old who sustained a fracture and were hospitalized in an intensive or intermediate care unit at BCH between January 1, 2008 and June 30, 2013 ($N = 39$). If the exact fracture date was unknown for an incidentally discovered fracture, the date the fracture was reported in SERS was used. After excluding patients 18 years and older, the next oldest patient was 5 years old.

The Pediatric Health Information System (PHIS) database was used to identify potential controls who were fracture free and treated in the intensive or intermediate care unit at BCH.[10] Briefly, the PHIS database, developed by the Children's Hospital Association, includes demographic, billed transaction, and utilization data regarding inpatient admissions, observation hospital stays, ambulatory surgery visits, and emergency department visits from 47 free-standing, noncompeting children's hospitals located throughout the United States (including BCH).[10] In PHIS, both diagnosis and procedure codes use the *International Classification of Diseases, Ninth Revision* (*ICD-9*) format.

There were 15 912 potential candidates for controls. The potential control pool criteria included patients <18 years of age who were admitted to BCH between January 1, 2008 and June 30, 2013, and who required ICU-level care during their hospitalizations. Propensity score analysis was used to match cases to controls 1:2, accounting for the following covariates: age at admission (≤30 days, >30 days to <24 months, and ≥24 months), sex, hospital care unit, admission year and quarter (Q) (eg, Q1 of 2008), and total cumulative days in the ICU and total hospital length of stay as continuous variables. To account for medical complexity and severity of illness, cases were also matched to controls by using the National Association of Children's Hospitals and Related Institutions relative cost weights associated with the 3M All Patient Refined Diagnosis Related Group (APR DRG version 24)[11] and the severity of illness category assigned to them at discharge. These relative costs weights, referred to as case mix index (CMI) in the aggregate, are a proxy for patient severity and resource utilization.[12] The specific assigned APR DRG category was also used as a matching covariate in the model. The electronic medical records of potential controls were reviewed and cross-referenced

with the SERS database to verify the absence of fractures in the control group.

Data Abstraction

All clinical and demographic data for cases and controls were obtained from PHIS with the exception of physical therapy involvement and anthropometric data (length, height, and weight), which were abstracted from the electronic medical record. Based upon local expertise and review of the extant literature, potentially protective (eg, treatment with calcium, phosphate, vitamin D, a multivitamin, or physical therapy, etc) and harmful factors (eg, treatment with diuretics, glucocorticoids, muscle relaxants [excluding benzodiazepines], heparin, anesthetics, or anticonvulsants; receipt of diagnostic imaging studies [portable and nonportable] and operative procedures to capture potential risk from increased patient handling; or malnutrition, etc) were obtained from PHIS. Additional covariates including primary diagnosis, primary procedure, comorbidity, APR DRG code, National Association of Children's Hospitals and Related Institutions relative cost weights, intermediate care unit or ICU location, demographic, medication, length of stay, and disposition data were obtained by using PHIS. Primary diagnoses, comorbidities, and primary procedures were identified in PHIS by using *ICD-9* diagnostic codes. BMI data were calculated from lengths or heights and weights closest to the date of admission. BMI *z* scores were calculated by using the World Health Organization Child Growth Standards[13] for children <2 years old or the Centers for Disease Control and Prevention growth charts[14] for children age 2 years and older.

For cases, patient-days at risk for fracture was defined as admission date to fracture date. To maintain equivalent patient-days at risk across the matched cases and controls, the controls were assigned an index date that aligned with their matched case's patient-days at risk. If a control's length of stay was shorter than the matched case's patient-days at risk, then the control's total length of stay was used. Using this method, we found that 83% (29/35) of the 1:2 matched groups had patient-days at risk equivalent to their case for one or both of their 2 controls.

All potential predictors were assessed before fracture date (cases) or index date (controls). Exposure to medication was quantified as rates (number of days receiving medication per 100 patient-days at risk), as were total parenteral nutrition, extracorporeal membrane oxygenation, and operative procedures and diagnostic imaging studies (eg, number of surgical procedures or radiographic tests per 100 patient-days at risk). Intubation exposure was represented by any intubation event before the fracture or index dates. Any covariates occurring after the fracture date or index date were not included in the analyses.

Statistical Analysis

We used a multivariate logistic regression model to generate propensity scores to match patients who fractured (cases) with clinically comparable patients who did not fracture (controls). The model included patient demographics (age at admission and sex), temporal data (admission year and quarter), location (neonatal, cardiac, medical or surgical ICUs, and intermediate cardiac care unit), and clinical severity surrogates (APR DRG and associated relative cost weights, ICU length of stay, and total length of stay). We used the Greedy matching algorithm to achieve 1:2 propensity score matching.[15]

Descriptive statistics were used to characterize cases and controls. Bivariate associations between potentially important clinical factors and the presence of a fracture were evaluated by using χ^2 and Fisher's exact tests for categorical variables and Wilcoxon Mann–Whitney *U* tests for continuous variables. Matched (conditional) logistic regression modeling[16] was used to determine unadjusted associations between relevant clinical factors and the presence of fractures. A score selection logistic regression model was used to identify which clinical predictors with a *P* value $\leq$ .2 in the bivariate analysis produced the highest likelihood χ^2 score statistic.[17] Because previous studies showed relationships between immobility[2] and episodes of paralysis[8,9] and fracture, we forced muscle relaxant utilization (days receiving muscle relaxants per 100 patient-days at risk) into the score selection model. We included the 3 highest-scoring subset covariates in combination with muscle relaxant utilization in the final multivariable conditional logistic regression model to assess clinical predictors of fracture. A fracture volume of 35 limited the number of covariates we could add to the model. Data analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC), and $P \leq .05$ was considered statistically significant.

RESULTS

Thirty-nine cases were deemed eligible; however, 4 cases could not be matched to controls because of outlier lengths of stays and case complexity. The final sample included 35 cases and 70 matched controls (Fig 1). The matched demographic and clinical characteristics of the cases and controls are presented in Table 1. Cases and controls were well matched according to sex, age, hospital unit, admission year and Q, ICU length of stay, total hospital length of stay, APR DRG category, and relative cost weights (Table 1). Both cases and controls were medically complex, as represented by their median CMI, and had prolonged

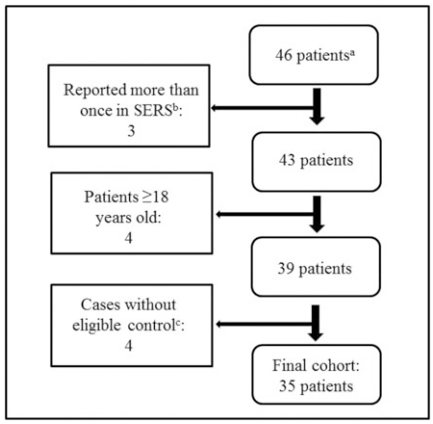

FIGURE 1 Assembly of case cohort. [a] Forty-six patients with fractures reported in SERS between January 2008 and June 2013. [b] Date the initial fracture was identified was used for analysis. [c] Outlier total lengths of stay and case acuity.

TABLE 1 Matched Demographic and Clinical Characteristics of Cases and Controls

	Cases (Fractures) $N = 35$	Controls (No Fractures) $N = 70$	P
	N (% of cases) or Median (25th to 75th IQR)	N (% of cases) or Median (25th to 75th IQR)	
Age category at admission			.72
≤30 d	13 (37)	31 (44)	
>30 d and <24 mo	19 (54)	35 (50)	
≥24 mo	3 (9)	4 (6)	
Age in months at admission	1.0 (0.0 to 9.0)	1.0 (0.0 to 4.0)	.30
Sex, female	17 (49)	27 (39)	.33
Admission year			.57
2008	2 (6)	4 (6)	
2009	1 (3)	8 (11)	
2010	5 (14)	11 (16)	
2011	13 (37)	16 (23)	
2012	9 (26)	22 (31)	
2013	5 (14)	9 (13)	
Event Q[a]			.59
Q1	12 (34)	18 (26)	
Q2	10 (29)	16 (23)	
Q3	6 (17)	17 (24)	
Q4	7 (20)	19 (27)	
Length of hospital stay, d	117.0 (69.0 to 194.0)	95.5 (40.0 to 144.0)	.16
Hospital unit			.30
NICU	18 (51)	43 (61)	
Medical or Surgical ICU	6 (17)	4 (6)	
Cardiac step-down unit	4 (11)	7 (10)	
Cardiac ICU	7 (20)	16 (23)	
Total days in ICU	82.0 (49.0 to 155.0)	78.5 (29.0 to 126.0)	.16
Case mix index	10.7 (6.9 to 19.8)	13.7 (5.6 to 23.3)	.71
APR DRG[b]			.18
Major stomach esophageal and duodenal procedures	8 (23)	4 (6)	
Other vascular procedures	4 (11)	0 (0)	
Neonate birth weight <1500 g with major procedure	4 (11)	8 (11)	
Tracheostomy with long-term mechanical ventilation with extensive procedure or extracorporeal membrane oxygenation	3 (9)	11 (16)	
Heart and/or lung transplant	2 (6)	6 (9)	

[a] Fracture date for cases and index date for controls.
[b] Top 5 most common for cases shown.

hospitalizations (Table 1). Additional demographic and clinical characteristics of the cases and controls are presented in Table 2. Patients were hospitalized for a median of 61 days before fracture (25th, 75th interquartile range [IQR] 35.0 to 100.0). The patient-days at risk for the matched controls was 50 days (IQR 21.0 to 99.0). The difference in patient-days at risk between the cases and controls was not statistically significant ($P = .28$). Median age at fracture for the 35 cases was 5.0 months (IQR 2.0 to 10.0) and 3.5 months (IQR 2.0 to 7.0) at the index date for the 70 matched controls (Table 2). There were no statistically significant differences between the cases and controls with respect to self-reported race/ethnicity, primary procedure, primary diagnosis, and disposition (Table 2). The most common primary diagnoses and primary procedures for the cases and controls are presented in Table 2. The most common diagnosis in both groups was tracheoesophageal fistula, esophageal atresia, and stenosis (ICD-9 750.3). There were no statistically significant differences with regards to median BMI z score at admission or percent severe underweight (BMI z score ≤3 SDs below the mean for age and sex),[18] but 32 cases and only 50 controls had complete BMI data at or near admission (Table 2).

Highly prevalent diagnoses according to *ICD-9* grouping among all children included cardiovascular disease (ICD-9 420–429; 745–747.9) (77% of cases, 80% of controls), respiratory disease (ICD-9 510–519, Procedure Code 96.0) (83% of cases, 64% of controls), and nutritional deficiency (ICD-9 260–269, 275, 783) (63% of cases, 47% of controls) (Table 3). In bivariate analyses, factors that were significantly associated with fracture included the following: primary diagnosis of tracheoesophageal fistula, esophageal atresia, and stenosis (ICD-9 750.3) (odds ratio [OR] 4.2, 95% confidence interval [CI] 1.3–13.7); diagnosis of kidney disease (ICD-9 580–590) (OR 3.3, 95% CI 1.0–10.3); and per 5-day increase in median cumulative ICU days at risk for fracture (OR 1.3, 95% CI 1.0–1.5) (Table 3).

In the final multivariable model, which included the highest-scoring subset of 3 covariates and muscle relaxant utilization rate, only respiratory disease (OR 3.9, 95% CI 1.1–13.7) and per 5-day increase in median cumulative ICU days at risk (OR 1.3, 95% CI 1.0–1.6) were significant independent risk factors for fracture (Table 4). The primary diagnosis of tracheoesophageal fistula, esophageal atresia, and stenosis (ICD-9 750.3) and muscle relaxant rate were not significant.

DISCUSSION

Our findings build upon those from recent studies at our institution that characterized hospitalized patients with fractures and

TABLE 2 Additional Characteristics of Cases and Controls

	Cases (Fractures) $N = 35$	Controls (No Fractures) $N = 70$	P
	N (% of cases) or Median (25th to 75th IQR)	N (% of cases) or Median (25th to 75th IQR)	
Age in months at fracture (cases) or index date (controls)	5.0 (2.0 to 10.0)	3.5 (2.0 to 7.0)	.14
Race/ethnicity			.89
White, Non-Hispanic	22 (63)	41 (59)	
African-American, Non-Hispanic	4 (11)	5 (7)	
Asian, Non-Hispanic	1 (3)	1 (1)	
Other, Non-Hispanic	3 (9)	9 (13)	
Hispanic/Latino	3 (9)	5 (7)	
Unknown	4 (11)	7 (10)	
BMI z score at admission[a]			
Median	−1.6 (−4.4 to −0.6)	−2.2 (−3.7 to −0.9)	.61
z score ≤ -3	12 (38)	22 (44)	.56
Length of stay (d) until fracture (cases) or index date (controls)	61.0 (35.0 to 100.0)	50.0 (21.0 to 99.0)	.28
Primary diagnosis[b]			.45
Tracheoesophageal fistula, esophageal atresia, and stenosis	9 (26)	5 (7)	
Patent ductus arteriosus	4 (11)	0 (0)	
Congestive heart failure, unspecified	2 (6)	1 (1)	
Hypoplastic left heart syndrome	2 (6)	5 (7)	
Extreme immaturity, 500–749 g	2 (6)	3 (4)	
Primary procedure[b]			.25
Other surgical occlusion of vessels, thoracic vessels	4 (11)	4 (6)	
Other repair of esophagus	3 (9)	1 (1)	
Closure of other fistula of trachea	2 (6)	2 (3)	
Open heart valvuloplasty of mitral valve without replacement	2 (6)	0 (0)	
Heart transplantation	2 (6)	5 (7)	
Extracorporeal membrane oxygenation	2 (6)	7 (10)	
Intrathoracic esophagoesophagostomy	2 (6)	0 (0)	
Disposition			.38
Discharged to home	17 (49)	34 (49)	
Discharged to other facility	12 (34)	30 (43)	
Expired	6 (17)	6 (9)	

[a] $N = 32$ for cases, $N = 50$ for controls.
[b] Top 5 most common for cases shown.

specifically examined risk factors among highly specialized groups of patients with congenital heart disease and LGEA. By using matched controls within a propensity score model that incorporated multiple clinical characteristics, we minimized selection bias and isolated specific risk factors for fracture in intermediate and ICUs at a tertiary pediatric care center. Similar to other studies, patients with fractures within our study population were young, had prolonged hospitalizations, and were medically complex. Fracture cases in our study had a median CMI of 10.7 (IQR 6.9 to 19.8), and for comparison, based on the available data in PHIS, the median CMI of patients admitted to a BCH ICU in 2014 was 3.3 (IQR 1.4 to 5.9). After matching for medical complexity and disease severity, fracture cases in our study also had higher odds of a diagnosis of respiratory disease and a greater per 5-day increase in median cumulative ICU days compared with controls.

To further investigate the finding related to respiratory disease and whether a specific diagnosis might be responsible for conferring the increased fracture risk, we performed additional post hoc analyses to determine the specific *ICD-9* codes that were most frequently billed for respiratory disease. The following respiratory diagnoses were the most common for cases and controls: unspecified pleural effusion (ICD-9 511.9) (45% of cases, 27% of controls); pulmonary collapse (ICD 518.0) (38% of cases, 44% of controls); acute respiratory failure (ICD-9 518.81) (21% of cases, 18% of controls); and other diseases of lung, not elsewhere classified (ICD-9 518.89) (24% of cases, 22% of controls). These findings suggest that intensivists and other care providers should have heightened awareness of patients with respiratory diseases such as pleural effusions as having an increased risk of fracture. Whether it is the respiratory disease itself or the associated therapeutic interventions or complications that confer the increased risk for fracture requires further study.

Fractures were also more likely to occur in the patients who spent more days in the ICU. The median number of days in the ICU before fracture was 53 (IQR 19.0 to 99.0). Other studies have also reported prolonged ICU stays in inpatient fractures, but they reported total ICU days.[8,9] Our study reports the number of ICU days at risk before fracture, which is more meaningful clinically to determine optimal timing for the implementation of fracture risk reduction and prevention protocols.

A primary diagnosis of tracheoesophageal fistula, esophageal atresia, and stenosis was a significant risk factor for fracture in bivariate analyses but not in multivariable analyses. This may have to do with our study's small sample size because a primary

TABLE 3 Bivariate Associations of Clinical Characteristics Related to Fracture

	Cases (Fractures) ($N = 35$)	Controls (No Fractures) ($N = 70$)	Unadjusted OR	95% CI	*P*
	N (%) or Median (25th to 75th IQR)	*N* (%) or Median (25th to 75th IQR)			
Age, mo[a]	5.0 (2.0 to 10.0)	3.5 (2.0 to 7.0)	1.0[b]	1.0–1.1	.24
BMI *z* score[c]					
Admission	−1.6 (−4.4 to −0.6)	−2.2 (−3.7 to −0.9)	1.1	0.9–1.2	.46
BMI *z* score ≤−3					
Admission	12 (38)	22 (44)	0.6	0.2–1.5	.24
Days in ICU until fracture (cases) or index date (controls)	53.0 (19.0 to 99.0)	43.0 (18.0 to 93.0)	1.3[d]	1.0–1.5	.02
Comorbidities					
Cardiovascular disease	27 (77)	56 (80)	0.8	0.3–2.4	.72
Respiratory disease	29 (83)	45 (64)	2.5	1.0–6.4	.06
Kidney disease	19 (54)	25 (36)	3.3	1.0–10.3	.04
Nutrition deficiency	22 (63)	33 (47)	2.2	0.9–5.6	.10
Prematurity	11 (31)	27 (39)	0.7	0.3–1.8	.43
Primary diagnosis					
Tracheoesophageal fistula, esophageal atresia, and stenosis	9 (26)	5 (7)	4.2	1.3–13.7	.02
Medications[e]					
Anesthetics	26 (74)	46 (66)	1.6	0.6–4.4	.33
Rate	2.6 (0.0 to 6.9)	2.6 (0.0 to 5.5)	1.0[d]	0.8–1.2	.90
Muscle relaxants	27 (77)	48 (69)	1.5	0.6–3.8	.37
Rate	12.5 (1.5 to 44.3)	5.7 (0 to 19.6)	1.1[d]	1.0–1.2	.06
Diuretics	30 (86)	55 (79)	1.6	0.5–5.0	.38
Rate	67.4 (35.7 to 96.7)	50.7 (2.3 to 96.7)	1.0[d]	1.0–1.1	.24
Heparin	32 (91)	58 (83)	2.3	0.6–9.0	.23
Rate	42.1 (15.2 to 82.4)	21.0 (3.3 to 63.6)	1.0[d]	1.0–1.1	.17
Calcium	20 (57)	43 (61)	0.8	0.3–2.1	.61
Rate	2.2 (0.0 to 19.0)	2.2 (0.0 to 11.3)	1.0[d]	0.9–1.1	.67
Phosphate	7 (20)	9 (13)	1.7	0.6–5.1	.33
Rate	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	1.1[d]	0.6–1.9	.82
Multivitamin	8 (23)	11 (16)	1.6	0.6–4.3	.38
Rate	0.0 (0.0 to 0.0)	0 (0.0 to 0.0)	1.1[d]	1.0–1.2	.12
Glucocorticoids	18 (51)	32 (46)	1.3	0.5–3.1	.56
Rate	1.0 (0.0 to 16.9)	0.0 (0.0 to 18.9)	1.0[d]	0.9–1.1	.68
Anticonvulsants	1 (3)	8 (11)	0.2	0.0–1.9	.17
Rate	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.7[d]	0.3–1.6	.38
Interventions and studies					
Physical therapy	23 (66)	46 (66)	1.0	0.4–2.8	1.00
Extracorporeal membrane oxygenation	2 (6)	7 (10)	0.5	0.1–3.4	.40

diagnosis of ICD-9 750.3 made up a significant portion of our fracture cases, and a high percentage of fractures in patients with LGEA has been reported.[8,9] Additionally, because we matched cases and controls by APR DRG, it is possible that we biased our finding toward the null hypothesis. This finding, in addition to lack of significance of muscle relaxants in our final model, might also have to do with the potential colinearity of risk factors with respiratory disease and ICU length of stay. Therefore, we would not discount these or other risk factors and consider them potentially important to examine further in prospective studies.

Taken together, our study suggests that patients with prolonged ICU lengths of stay and a respiratory disease diagnosis deserve heightened surveillance, early detection of fractures, and fracture prevention strategies as demonstrated specifically in patients with congenital heart disease and esophageal atresia.[2,8,9] Such a protocol could similarly include signage at the bedside, handling precautions,[2] limiting medications (such as paralytics and muscle relaxants) that are detrimental to bone health,[8,9,19] and where possible reducing respiratory disease risk and length of stay in the ICU. More research is needed to identify additional prevention strategies for clinical circumstances when more conservative measures are insufficient.

Our study has important limitations that should be considered. Because of the rare event of inpatient fractures, the absence of a specific billing code for fractures that occur during hospitalization, and the high acuity, young age, and prolonged hospitalizations of fracture cases, we were limited in our study design and selection of controls. Although the difference in patient-days at risk between cases and controls was not statistically significant, we cannot completely exclude possible selection bias as an explanation for this difference. By relying only on SERS to identify inpatient fractures, we did not capture all potential cases for inclusion in the study and might not have included patients who have a higher severity of illness.[3] Also, 4 of the 39

TABLE 3 Continued

	Cases (Fractures) ($N = 35$)	Controls (No Fractures) ($N = 70$)	Unadjusted OR	95% CI	*P*
	N (%) or Median (25th to 75th IQR)	*N* (%) or Median (25th to 75th IQR)			
Rate[f]	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.1[d]	0.0–33.4	.44
Intubation	17 (49)	33 (47)	1.1	0.4–2.6	.88
Total parenteral nutrition	29 (83)	52 (74)	1.8	0.6–5.2	.29
Rate[g]	10.4 (5.1 to 42.9)	10.4 (0.0 to 17.4)	0.9[d]	0.8–1.1	.47
Operative procedures	4.0 (1.0 to 8.0)	2.0 (0.0 to 6.0)	1.1	1.0–1.2	.11
Rate[h]	6.6 (2.3 to 9.1)	5.4 (0.0 to 9.6)	1.0[i]	1.0–1.0	.52
Imaging study	—	—	—	—	—
Rate[j]	101.8 (77.1 to 161.6)	115.0 (69.0 to 178.7)	1.0[i]	1.0–1.0	.83

[a] Age at fracture (cases) or at index date (controls).
[b] Per 1-mo increment.
[c] $N = 32$ for cases, $N = 50$ for controls.
[d] Per 5-U increment.
[e] Rate defined as number of days on medication per 100 patient-days at risk.
[f] Rate as days receiving extracorporeal membrane oxygenation per 100 patient-days at risk.
[g] Rate defined as number of days receiving total parenteral nutrition per 100 patient-days at risk.
[h] Rate defined as number of operative procedures per 100 patient-days at risk.
[i] Per 10-U increment.
[j] Rate defined as number of imaging studies per 100 patient-days at risk.

(10%) fracture cases from this study were excluded because of outlier lengths of stay and case acuity. This raises the possibility of selection bias and lack of generalizability to patients who may be at even higher risk of fracture than those represented in this study. On the other hand, this may bolster our findings that prolonged ICU length of stay is a significant risk factor for fracture in hospitalized youth. Administrative databases are valuable pooled sources of clinical information that can be analyzed for research, but the inaccuracy of billing codes is possible.[20] As a way to address this limitation, we incorporated diagnostic and procedural codes,[21] linked the administrative data to SERS, used the propensity score technique to match controls, and verified through chart review (N.M., unpublished observations) that the identified controls did not have fractures. There is also limited granularity in PHIS, so pharmacy data that were limited to bundling of certain drugs and exact doses could not be accurately measured. In addition, PHIS does not include laboratory data, so we were unable to explore biochemical differences in factors potentially related to fracture (eg, parathyroid hormone, 25-hydroxyvitamin D, etc). Missing data, especially with regard to BMI, could have introduced bias to the values of this variable because missing data may not be random. Lastly, our study's small sample size precluded our ability to examine all potentially clinically relevant covariates and limited power to detect potentially important differences between cases and controls.

TABLE 4 Matched Logistic Regression of Factors Associated With Fractures

	Adjusted OR	95% CI	*P*
Primary diagnosis of tracheoesophageal fistula, esophageal atresia, and stenosis	2.5	0.7–9.7	.18
Muscle relaxant rate (days on medication per 100 patient-days at risk)[a]	1.0	0.9–1.1	.54
Respiratory disease	3.9	1.1–13.7	.04
ICU days at risk[a]	1.3	1.0–1.6	.03

[a] Per 5-d increment.

CONCLUSIONS

Children prone to fracture in the hospital are young, medically complex patients who require extended periods of intensive level medical care and potentially life-sustaining treatment modalities. Children with respiratory disease and prolonged ICU stays have higher odds of fracture and should be targeted with increased surveillance and fracture prevention strategies. Larger, prospective studies are needed, and these may require collaboration across multiple pediatric centers because of the rare event of inpatient fractures.

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