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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Incidence, Management, and Outcomes of Pulmonary Embolism at Tertiary Pediatric Hospitals in the United States

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ABSTRACT

BACKGROUND Pediatric pulmonary embolism (PE) is rare and potentially life-threatening. Though thrombolysis and thrombectomy are increasingly used in adult PE, trends in pediatric treatment and outcomes remain incompletely described.

OBJECTIVES The purpose of this study was to describe the incidence of PE, proportion of cases treated with anticoagulation alone, systemic thrombolysis, and directed therapy (local thrombolysis and thrombectomy), clinical outcomes, and total costs.

METHODS A multicenter observational study was performed using administrative data from the Pediatric Health Information System database to study PE treated at U.S. pediatric hospitals from 2015 to 2021. Outcomes by treatment were evaluated using multivariable generalized linear mixed effects models.

RESULTS Of 3,136 subjects, 70% were at least 12 years of age, and 46% were male. Sixty-two percent had at least 1 comorbidity, and congenital heart disease of any kind was the most prevalent (20%). Eighty-eight percent of subjects received anticoagulation alone, 7% received systemic thrombolysis, and 5% received directed therapy. Overall in-hospital mortality was 7.5%. Treatment approach did not change over time ($P = 0.98$). After adjusting for patient characteristics, directed therapy was associated with a lower risk of mortality (adjusted percentage −3%, [95% CI: −5% to 0%]) than anticoagulation alone. Systemic thrombolysis was associated with a greater total cost of hospitalization ($113,043 greater [95% CI: $62,866, $163,219]). Length of hospital stay did not differ by treatment.

CONCLUSIONS Pediatric patients with PE have a high incidence of underlying chronic disease. Anticoagulation alone remains the mainstay of treatment, with thrombolysis and thrombectomy rarely being used. Given the relative rarity of pediatric PE, additional research requiring innovative study designs is paramount. (JACC Adv 2024;3:100895) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CVC = central venous catheter

DOAC = direct oral anticoagulant

DTI = direct thrombin inhibitor

ECMO = extracorporeal membrane oxygenation

ICD-10 = International Classification of Disease-10th Version

LOS = length of stay

PE = pulmonary embolism

PHIS = Pediatric Health Information System

Pulmonary embolism (PE) is rare in children, with best estimates of incidence between 0.07 and 0.14/10,000 patients/year and as high as 9.2/10,000 hospitalized patients in the United States.[1-3] This is likely an underestimate because of the difficulties in diagnosis and limited reporting. Reported incidence has increased due to earlier detection and treatment and an increasing prevalence of conditions that pose a higher risk of PE,[2,3] including chronic inflammatory diseases (eg, inflammatory bowel disease [IBD]), congenital heart disease, malignancy, and obesity, as well as increasing use of central venous catheters across all diagnoses.[4] The public health impact of PE is out of proportion to its rarity because of the high risk of mortality (~8%) and morbidity,[1,2] including chronic thromboembolic pulmonary hypertension.

Progress in the treatment of PE in adults has focused on early intervention and a more aggressively directed approach (transcatheter site-directed thrombolysis and transcatheter or operative thrombectomy) based on risk stratification. The European Society of Cardiology and Pulmonary Embolism Response Team Consortium[5,6] suggests that adult PE patients with right heart strain and elevated troponin (intermediate-high risk PE) and contraindications to systemic thrombolysis and those with hemodynamic compromise (high risk PE) should receive site-specific thrombolysis or thrombectomy instead of anticoagulation alone. Observational studies have demonstrated that in adults with PE, there has been increased use of these "directed therapies" (site-specific thrombolysis and/or transcatheter or operative thrombectomy)[7,8] with associated improvement in outcomes.[8,9]

A recent pediatric recommendation and treatment algorithm extrapolate adult data for both risk stratification and risk-related management, recommending consideration of operative embolectomy or systemic thrombolysis in high-risk PE vs catheter-based intervention or low-dose systemic thrombolysis in intermediate-risk PE.[10] A dearth of data about the epidemiology of PE in pediatric patients and the outcomes of directed therapies are major obstacles to determining optimal management in young patients. Observational studies of pediatric PE from 2000 to 2014 reported wide variation in thrombolytic therapy (systemic, catheter-based, combination of site-directed thrombolysis with mechanical disruption) with increasing use of low molecular weight heparin, direct oral anticoagulants (DOAC), and direct thrombin inhibitors (DTI).[1,11-13] To our knowledge, there have been no studies that have specifically evaluated trends in the use of directed therapies in comparison to systemic thrombolysis or anticoagulation in pediatric patients, nor have there been studies comparing the outcomes of these strategies.

Challenges for effective pediatric PE research include low incidence, a heterogeneous population, and interhospital variation in the utilization of relatively novel directed therapies. To overcome these obstacles, we performed a retrospective multicenter observational study of children with PE at U.S.-based primary pediatric hospitals contributing data to the Pediatric Health Information Systems Database (PHIS) with the following objectives: 1) to characterize patterns of pharmacologic and intervention-based management, hypothesizing that the use of directed therapy would have increased during the study period as it has in adults; and 2) to evaluate contemporary clinical outcomes among pediatric PE patients. This information is critical to guide future efforts, including the creation of clinical registries and the design of clinical trials evaluating treatment approaches.

METHODS

DATA SOURCE. PHIS contains administrative data from inpatient, emergency department, ambulatory surgery, and observation encounters from 49 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Overland Park, Kansas, USA). Data quality and reliability are assured through a joint effort between Children's Hospital Association and participating hospitals. Participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures, as well as utilization data (eg, pharmacy products, radiologic studies, and laboratory studies). Data are deidentified

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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at the time of data submission and are subject to a number of reliability and validity checks.

The Children's Hospital of Philadelphia Institutional Review Board has determined that all analyses using PHIS data are exempt from review under the Common Rule. Data use agreements prohibit the sharing of patient-level data. Statistical methods and code will be shared on request, provided the requestor pledges that they will be used for academic purposes and an appropriate citation is applied.

STUDY POPULATION. We conducted a retrospective observational study of children (age ≤18 years) treated at PHIS hospitals between September 1, 2015 and June 30, 2021 with PE identified by International Classification of Diseases-10th version (ICD-10) diagnostic codes (Supplemental Table 1) at any point during the encounter. Centers that withdrew from PHIS during the study period were excluded. For patients with multiple admissions, the first admission during which PE-specific treatment was administered was included, and subsequent admissions were excluded. However, since we did not have information about prior admissions, the first admission during the time period may represent a repeat admission for the patient.

STUDY MEASURES. Data were extracted directly from PHIS using ICD-10 codes for diagnoses and procedures and clinical transaction codes for pharmaceutical products.

The exposure of interest is the treatment modality used, specifically: anticoagulation alone, systemic thrombolysis, or directed therapy (use of site-directed thrombolysis or thrombectomy, catheter-based or surgical). Additional information about therapies was also collected. Anticoagulant agents were divided by mechanism of action and mode of delivery. Pharmaceuticals were identified using PHIS-specific drug codes (Supplemental Table 2). Systemic thrombolysis was defined as the administration of thrombolytic medication along with thrombolysis procedure code(s) (Supplemental Table 3). Site-directed thrombolysis and thrombectomy were identified using procedure codes (Supplemental Table 3).

The outcomes are in-hospital mortality (yes or no), hospital length of stay (LOS) (in days), and total cost of hospitalization (in dollars). As described previously,[14-17] several steps were taken to ensure cost data were comparable between hospitals and across the entire study period. PHIS receives billing data directly from hospitals and converts these charges to costs using hospital- and department-specific ratios of costs to charges. Costs are also adjusted for regional wage-price indices to provide comparable costs between hospitals across the country. Total costs for an entire hospitalization/encounter can be retrieved within the confines of our data-use agreement, but more detailed cost reports (ie, department-level or itemized costs) are not released. We further adjusted cost data to account for inflation using the Consumer Price Index for medical care, as compiled by the United States Bureau of Labor Statistics.

Other patient-level data collected were age, sex, race, and insurance payer. Insurance payers were grouped into commercial, private, and other (eg, self-pay, charity, other), and unknown. Data about comorbid medical conditions were also collected, specifically congenital heart disease, malignancy, rheumatologic disease, IBD, nephrotic syndrome, chronic kidney disease, thrombophilia, prematurity, and low birth weight. The presence of a central venous catheter (CVC) was determined using procedure codes indicating insertion of an infusion, tunneled vascular access, and totally implantable vascular access devices (Supplemental Table 3). While CVC is a risk factor for thrombosis, we were unable to determine whether a CVC was present on admission or inserted during the admission, which could represent treatment for PE, and thus, CVC was not used as an adjustor in the analysis. Data regarding admission to the intensive care unit (ICU), use of extracorporeal membrane oxygenation (ECMO), and use of vasopressors were collected as markers of illness severity. Hospital characteristics, including admissions per year, were collected.

Risk-stratifying patients with PE into those with and without right heart strain and those with hemodynamic compromise is an important part of current guidelines.[18,19] This level of clinical detail is not available in PHIS. While there are different ICD-10 codes for PE and PE with evidence of strain (cor pulmonale), our preparatory work for this project yielded a reported incidence of cor pulmonale in <0.5% of cases within PHIS (data not shown). This incidence is not consistent with prior pediatric studies[20,21] or realistic based on clinical experience. To avoid misclassification, we did not divide the cohort based on this distinction. Clinical indicators of cor pulmonale (eg, imaging, electrocardiogram, and laboratory data) are not available in PHIS. Finally, using inotrope exposure or admission to an intensive care unit to determine disease severity was not performed, since these are choices made by care teams, and these choices are the subject of the current research.

STATISTICAL ANALYSIS. Descriptive statistics. The first aim of the study was to describe the general characteristics of the cohort and then stratify by treatment strategy. Incidence of PE was unable to be calculated as the true population at risk (ie, all children in the catchment area of the hospitals studied) could not be defined. Characteristics of patients with and without cardiac disease and those with and without in-hospital mortality were also compared. Continuous variables are presented as mean ± SD or median (IQR). Categorical variables are presented as counts and percentages. Comparisons in these characteristics by treatment strategy, cardiac disease status, and mortality were made using ANOVA and chi-squared tests.

Trends in treatment over time. The second aim of the study was to describe trends in treatment over time. Frequency of use of each treatment type was compared between study years using an ANOVA test.

Relationship between treatment and outcomes. The third aim was to test if the type of therapy was associated with differences in outcomes (mortality, LOS, and cost of encounters). Anticoagulation treatment was used as the reference group, and the effects of directed therapy and systemic thrombolysis compared to the reference treatment were examined. To account for correlated measurements between patients from the same hospital, a generalized linear mixed-effects model with a random intercept for each hospital was fit. The following distributions were chosen for each outcome: logistic distribution for mortality, negative binomial distribution for LOS, and gamma distribution (with log link) for cost-exponentiated coefficients and 95% confidence intervals for each outcome are presented. After exponentiating the raw estimates, the following estimates were obtained: ORs for mortality, incidence rate ratios for LOS, and ratio of costs between the 2 treatment groups for the cost outcome. To make the results more interpretable, postestimation predictive margins were also calculated to get the difference in marginal means for the effect of each treatment compared to the reference treatment.

For our 3 sets of mixed-effects generalized linear models, we examined regression diagnostics to ensure that our models fit the data well. For all models, we checked for multicollinearity amongst predictors, ensured that our observations were independent, and made sure that there were no outliers or extreme values that we were concerned about. Since our predictors are all categorical, we did not have to worry about the appropriateness of the linearity assumption for each predictor. For our logistic regression models, we checked the calibration of our models by plotting the estimated model against the true values.[22] For our generalized linear models for LOS, we chose a negative binomial distribution over a Poisson distribution to model the LOS outcome to mitigate against overdispersion. And finally, for our generalized linear models for LOS and cost, we plotted the predicted values against residuals and saw that the majority of the residuals were centered at 0.

Subgroup analysis. Three additional analyses were performed to test the relationship between type of treatment and outcome in 3 different subsamples. Given the suspicion that the clinical course, mechanism of PE, and outcomes would be qualitatively different in patients with cardiac disease, analyses were repeated: 1) excluding all patients with any cardiac disease; 2) including only patients with any cardiac disease; and 3) in patients from the top tertile of hospital volume. For the third approach, the average number of hospital admissions by hospital was calculated, and hospitals were ranked according to their place in this distribution. Hospitals were grouped into tertiles based on annual admissions averaged over the study period. Tertiles were chosen based on visual inspection of the distribution of center volumes in a histogram based on natural cut-points in the distribution of volume and number of centers in each potential group. As an exploratory analysis, the characteristics of PE patients who died were compared to those who did not using chi-squared and analysis of variance.

All analyses were conducted using R Studio (R Foundation) or STATA version 17. The primary analysis was prespecified. Secondary analyses are exploratory, so no penalization for multiple comparisons was performed.

RESULTS

Of 3,237,752 admissions at PHIS hospitals between September 1, 2015 and June 30, 2021, 3,811 (0.1% of admissions) included a diagnosis of PE. Of the 3,811 admissions, 546 (8.5%) were of subjects who had at least 1 subsequent admission for PE during the study period. After excluding the subsequent admissions and subjects for whom cost data was missing, the final cohort consisted of 3,136 subjects, of which 69% (2,178) were ≥12 years of age, 46% (1,442) were male, and 59% (1,848) were White. Of the total, 62% had at least 1 comorbid condition, of which the

TABLE 1 Treatment Over Time

	Admission Year							
	2015[a] (N = 157)	2016 (N = 492)	2017 (N = 476)	2018 (N = 586)	2019 (N = 558)	2020 (N = 591)	2021[b] (N = 276)	*P* Value
Number of medications per subject	1.80 ± 0.9	1.91 ± 0.9	1.95 ± 0.92	1.98 ± 0.93	2.01 ± 0.92	2.10 ± 0.96	2 ± 0.88	0.003
Warfarin	9.6 (15)	7.5 (37)	10.5 (50)	7.3 (43)	7.0 (39)	3.9 (23)	4.7 (13)	0.001
Heparin	69.4 (109)	75.6 (372)	71.2 (339)	72.4 (424)	77.1 (430)	76.0 (449)	69.2 (191)	0.058
Low molecular weight heparin	70.7 (111)	73.8 (363)	74.2 (353)	77.5 (454)	69.9 (390)	72.3 (427)	75.0 (207)	0.123
Direct thrombin inhibitor	1.3 (2)	2.4 (12)	2.3 (11)	2.2 (13)	3.9 (22)	7.3 (43)	6.2 (17)	<0.001
Direct oral anticoagulant	0.6 (1)	1.2 (6)	3.6 (17)	3.4 (20)	8.1 (45)	16.4 (97)	16.3 (45)	<0.001
Antiplatelet agents	13.4 (21)	14.2 (70)	16.6 (79)	14.0 (82)	14.5 (81)	14.4 (85)	11.2 (31)	0.63
Management approach								0.98
Anticoagulation alone	87.9 (138)	88.0 (433)	86.8 (413)	87.7 (514)	87.3 (487)	88.2 (521)	88.4 (244)	
Systemic thrombolysis	5.7 (9)	6.9 (34)	7.4 (35)	6.8 (40)	8.2 (46)	7.3 (43)	7.2 (20)	
Directed therapy	6.4 (10)	5.1 (25)	5.9 (28)	5.5 (32)	4.5 (25)	4.6 (27)	4.3 (12)	

Values are mean ± SD or % (n). [a]Data was collected from September 2015. [b]Data was collected until June 2021.

most common were congenital heart disease (including cyanotic and noncyanotic) (20%, n = 635), oncologic diagnoses (14%, n = 448), or thrombophilia (10%, n = 298).

TRENDS IN TREATMENT OVER TIME. In terms of therapy, 88% of patients received anticoagulation alone, 7% received systemic thrombolysis, and 5% received directed therapy (site-directed thrombolysis or transcatheter/operative thrombectomy). There was significant variation in rates of treatment among hospitals, with rates of systemic thrombolysis ranging from 0% to 21% and those of directed therapy from 0% to 15% ($P < 0.001$). Trends in treatment over time are presented in Table 1. Rates of each treatment approach have remained stable ($P = 0.99$). However, there were differences between types of anticoagulation used. Over the study period, patients received a greater number of medications during their hospitalization (1.8 medications/patient in 2015 vs 2.1 medications/patient in 2021, $P = 0.003$), were less likely to receive warfarin ($P = 0.001$), and were more likely to receive a DOAC ($P < 0.001$) or DTI ($P < 0.001$).

Patient characteristics stratified by management approach were compared (Table 2). Patients who received directed therapy were younger ($P < 0.001$) and more likely to have congenital heart disease ($P < 0.001$) than patients who received anticoagulation alone. No differences in race or insurance provider were noted between treatment groups.

RELATIONSHIP BETWEEN TREATMENT AND OUTCOME. For the entire cohort, median LOS was 10 days (IQR 4-26 days), in-hospital mortality was 7.5%, and median cost was $54,143 (IQR: $16,296-$161,662). Outcomes were compared by treatment group (Table 3). In adjusted analyses, directed therapy was associated with lower mortality compared to treatment with anticoagulation alone (adjusted OR: 0.55, 95% CI: 0.32-0.95). Systemic thrombolysis was not associated with significantly different odds of mortality compared to anticoagulation alone (OR: 0.87, 95% CI: 0.50-1.53). Systemic thrombolysis was associated with higher mean costs than anticoagulation alone (exponentiated $\beta = 1.64$, 95% CI: 1.38-1.94), while directed therapy was not. No significant association was found between treatment group and LOS.

Comparison of patient characteristics and treatment course by in-hospital mortality showed that patients who did not survive were more likely to be male (54% vs 45%, $P = 0.01$), younger (median age 7.3 [IQR: 0-14.5] years vs 12.5 [IQR: 10-17] years, $P < 0.001$), a different distribution of race (White: 54% vs 59%, Black: 21% vs 23%, Asian/Pacific Islander: 2% vs 3%, multiracial: 15% vs 11%, unknown race: 8% vs 4%, $P = 0.04$), and more likely to have public insurance (59% vs 52%, $P = 0.001$). Nonsurvivors were more likely to have at least 1 comorbidity (93% vs 60%, $P < 0.001$). They also differed in terms of the likelihood of comorbid medical conditions, with nonsurvivors more likely to have congenital heart disease (52% vs 18%, $P < 0.001$), oncologic disease (19% vs 14%, $P = 0.034$), and prematurity (8% vs 1%, $P < 0.001$). Nonsurvivors were more likely to be admitted to an ICU (89% vs 60%, $P < 0.001$) and receive ECMO (49% vs 4%, $P < 0.001$).

Compared to patients without cardiac disease, patients with cardiac disease were more likely to be male (57% vs 43%, $P < 0.001$), younger (median age 3 years vs 15 years, $P < 0.001$), differ by race (white: 56% vs 60%, black: 21% vs 23%, Asian/Pacific

TABLE 2 Demographics and Comorbidities by Management Approach

	Anticoagulation Alone (88%, n = 2,750)	Systemic Thrombolysis (7%, n = 227)	Directed Therapy (Local Thrombolysis, Thrombectomy) (5%, n = 159)	*P* Value
Male	46 (1,265)	41 (94)	52 (83)	0.11
Age group				<0.001
Neonates (0-30 d)	4 (117)	4 (10) (4.4)	12 (19)	
Infant (31-365 d)	4 (120)	2 (5)	22 (35)	
Toddler (1-3 y)	4 (105)	1 (2)	6 (9)	
School-aged (3-12 y)	17 (478)	9 (20)	25 (39)	
Adolescent (12-18 y)	70 (1,930)	84 (191)	36 (57)	
Race				0.52
White	59 (1,610)	64 (147)	57 (91)	
Black	23 (624)	20 (45)	21 (33)	
Asian/Pacific Islander	3 (79)	2 (5)	4 (7)	
Native American	11 (309)	11 (24)	15 (23)	
Other/multiracial	5 (128)	3 (7)	3 (5)	
Insurance				0.39
Commercial	44 (1,213)	52 (117)	42 (66)	
Public	53 (1,447)	46 (104)	55 (88)	
Other	3 (74)	2 (5)	3 (5)	
Unknown	1 (16)	1 (1)	0 (0)	
Comorbidities	62 (1,706)	58 (131)	83 (132)	<0.001
Congenital heart disease excluding ASD/VSD/PDA	13 (365)	10 (22)	52 (83)	<0.001
ASD/VSD	10 (263)	6 (13)	31 (51)	<0.001
PDA	4 (99)	2 (4)	17 (27)	<0.001
Oncologic disease	15 (419)	7 (15)	9 (14)	<0.001
Rheumatologic disease	4 (99)	2 (4)	1 (1)	0.05
Inflammatory bowel disease	1 (35)	1 (1)	2 (3)	0.42
Nephrotic syndrome	2 (48)	3 (7)	2 (3)	0.36
Chronic kidney disease	1 (4)	0 (0)	1 (1)	0.27
Thrombophilia	9 (245)	17 (38)	9 (15)	0.001
History of prematurity	2 (47)	1 (2)	4 (6)	0.09

Islander: 4% vs 3%, multiracial: 13% vs 11%, unknown race: 7% vs 4%, $P = 0.003$), and have public insurance (57% vs 51%, $P = 0.018$). Patients without cardiac disease were more likely to have other comorbidities, including rheumatologic disease (4% vs 1%, $P < 0.001$), IBD (1.5% vs 0.3%, $P = 003$), and thrombophilia (10% vs 6%, $P = 0.001$). Cardiac patients were more likely to be premature (8% vs 0.2%, $P < 0.001$) and have higher healthcare utilization, with a higher likelihood of ICU admission (81% vs 57%, $P < 0.001$) and ECMO (20% vs 4.2%, $P < 0.001$).

SENSITIVITY ANALYSES. The sensitivity analyses do not confirm all of the findings from the primary analyses (see exponentiated coefficients in Supplemental Tables 4 to 6 and predictive margins in Supplemental Tables 4 to 6). The adjusted relationship found between directed therapy (vs anticoagulation alone) and a lower risk of mortality in the full sample was also found in the sensitivity analyses, but these relationships were not statistically significant. There was a relationship found between directed therapy and shorter LOS in the patients without cardiac disease (−4 fewer days, 95% CI: −8 to 0), but this relationship was not found in the full sample. The relationship between systemic thrombolysis and higher average costs of hospitalization was found in all 3 subsamples.

DISCUSSION

In this retrospective multicenter observational study of pediatric PE patients treated at U.S.-based primary pediatric hospitals, we demonstrated that current therapy remains focused on anticoagulation and systemic thrombolysis. Within anticoagulation medications, DOAC use increased notably in 2019, which coincides with the primary completion date of

TABLE 3 Outcomes by Management Approach

	Mortality		LOS		Cost of Hospitalization	
	OR (95% CI)		IRR (95% CI)		Ratio of Costs (95% CI)	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Effect of systemic thrombolysis (vs anticoagulation alone)	0.83 (0.50-1.39)	0.87 (0.50-1.53)	0.81 (0.59-1.10)	0.98 (0.77-1.26)	1.05 (0.80-1.39)	1.64 (1.38-1.94)
Effect of directed therapy (vs anticoagulation alone)	2.04 (1.26-3.29)	0.55 (0.32-0.95)	2.11 (1.73-2.58)	1.00 (0.82-1.22)	2.42 (2.03-2.89)	1.14 (0.93-1.22)
	Mortality		**LOS (in d)**		**Cost (in Dollars)**	
	Marginal Effect (95% CI)		**Marginal Effect (95% CI)**		**Marginal Effect (95% CI)**	
	Unadjusted	**Adjusted[a]**	**Unadjusted**	**Adjusted[b]**	**Unadjusted**	**Adjusted[b]**
Effect of systemic thrombolysis (vs anticoagulation alone)	−1% (−4% to 2%)	−1% (−4% to 2%)	−4 (−10 to 2)	−0.4 (−7 to 6)	8,129 (−36,773 to 53,032)	113,043 (62,866-163,219)
Effect of directed therapy (vs anticoagulation alone)	6% (1%-12%)	−3% (−5% to 1%)	25 (16-35)	0 (−5 to 5)	218,653 (146,504-290,801)	24,532 (15,024-64,088)

[a]Age, presence of congenital heart disease, use of vasopressors, and use of ECMO. [b]Sex, age, race, insurance, presence of congenital heart disease, oncologic diagnosis, rheumatologic diagnosis, inflammatory bowel disease, nephrotic disease, prematurity, use of vasopressors, and use of ECMO.

ECMO = extracorporeal membrane oxygenation; IRR = incidence rate ratio; LOS = length of stay; OR = odds ratio.

2 pediatric DOAC trials (DIVERSITY trial for dabigatran and EINSTEIN-Junior for rivaroxaban) and continued to rise through the end of the study period, with DOAC approval by the Food and Drug Administration in 2021.[23-25] Warfarin use declined over time, likely reflecting the lower patient burden associated with DOAC use. Trends in increasing utilization of site-directed thrombolysis and transcatheter or operative thrombectomy in adult patients have not mirrored the pediatric experience. Whether such a discrepancy is due to delayed application of new technology, risk in smaller patients, or other reasons, our findings highlight an important potential opportunity in the care of young patients with PE.

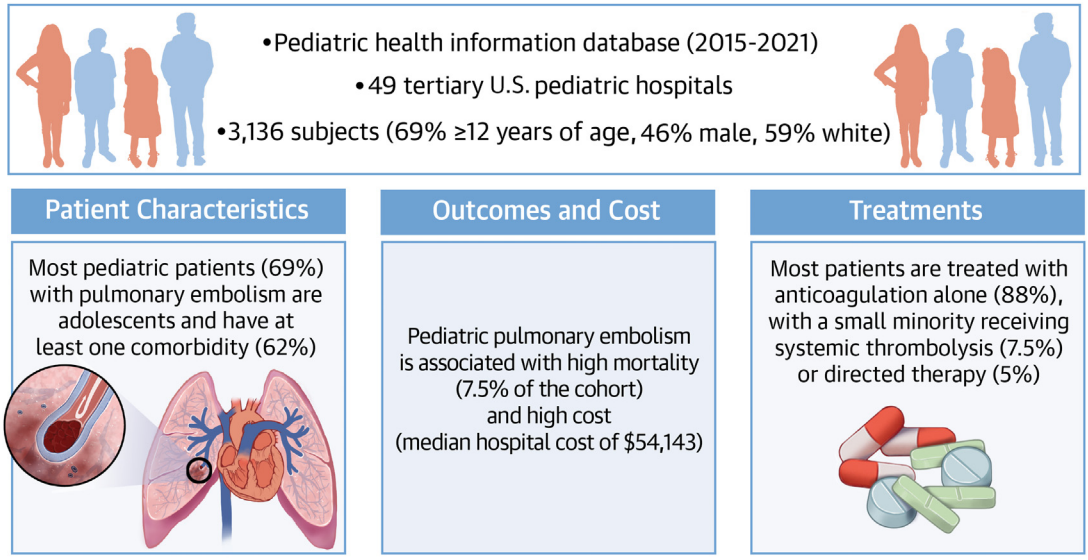
Our study period was notable for overlapping with the COVID pandemic. While we were unable to identify COVID-associated PE given the database-related limitations detailed below, several studies report rates of PE as high as 14% among pediatric patients with COVID, with notably high disease severity as well.[26-29] Further research is needed to identify the optimal therapy for this patient population.

There has been a significant shift in approach to adults with PE, sending an increasing number of adult patients for directed treatment.[5] Observational data demonstrate improved survival in adults with right ventricular strain or shock.[8,9] There are ongoing trials in the adult population to assess the safety of catheter-directed thrombolysis in intermediate-high-risk patients defined as those with confirmed PE with right ventricular dysfunction on imaging, positive troponin testing, and higher risk of early death or hemodynamic compromise, suggesting that more patients may have an indication for directed therapy in the future (NCT05591118).[30]

Extrapolating adult practices to children and adolescents is challenging for several reasons. Smaller patient size may be a limitation for transcatheter technologies that rely on large-caliber catheters. While there is a lower prevalence of medical frailty-associated age in pediatric patients (eg, secondary to atherosclerosis and diabetes mellitus), the pediatric PE population is characterized by a high prevalence of comorbid chronic medical conditions. This may increase their risk of an adverse outcome, potentially reflected in the high rates of PE-related morbidity and mortality,[1,2] and also (along with their younger age) change their lifetime risk of recurrent PE and the consequences of chronic thromboembolic pulmonary hypertension (CTEPH). Pediatric CTEPH remains an incompletely understood entity. As Ross et al comment, the prevalence of CTEPH in pediatric PE survivors is unknown, though they report a pooled incidence of 3.6% from 2 recent studies. Pediatric pulmonary hypertension guidelines comment only on diagnostic modalities for CTEPH,[31] and the 2019 update recommends chronic anticoagulation.[32] Benefits of surgical embolectomy have been reported in a pediatric case series.[10,33] Moreover, given the poorer functional status and quality of life among pediatric patients with pulmonary hypertension overall, preventing CTEPH must be prioritized.[34]

Evidence guiding PE treatment in pediatrics remains sparse. Our findings describing the demographic and comorbidity characteristics of patients with PE identify factors that could be incorporated in the future in tools for risk stratification in pediatric

CENTRAL ILLUSTRATION **Key Points From This Multicenter Observational Study on Pediatric Pulmonary Embolism Utilizing Administrate Data**



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PE. While there is a shift toward thrombolysis and thrombectomy in adult guidelines,[5,6] we found that there were no changes in treatment approach over time and that anticoagulation alone remains the mainstay of treatment in children and adolescents. These findings suggest that either anticoagulation is adequate in the pediatric population or that the population that would benefit most has not been well defined and that clinicians perceive the risk-benefit ratio of directed therapies to be unfavorable. The former is unlikely, given the high mortality associated with PE, and thus, further study is needed to identify patients for whom directed therapy should be prioritized.

Our finding that mortality is lower among patients managed with directed therapy may reflect unaddressed confounding by indication since, at this stage, the most severely ill subjects may not be considered for directed therapy in pediatric hospitals. The etiology of differences in cost between anticoagulation, systemic thrombolysis, and directed therapy are difficult to evaluate in these small sample sizes and deserves further attention if utilization of directed therapy increases. These differences may be the result of confounding by indication and case mix. Sensitivity analyses separately evaluating subjects with and without any cardiac disease did not demonstrate differences in mortality by treatment strategy in either stratum. We cannot ascribe our initial finding of lower mortality in the population because of the presence or absence of cardiac disease. The discrepancies noted between our original and sensitivity analyses likely reflect a smaller sample size as well as differences in the patient population that may be incompletely captured by our cohort definition. The shorter LOS among noncardiac patients receiving directed therapy may reflect a healthier baseline for these patients as compared to the whole cohort.

STUDY LIMITATIONS. There are several additional limitations to our study. As noted, potentially important clinical covariates are not discernible (eg, right heart strain) or are poorly discernible (eg, obesity, tobacco use, and use of oral contraceptives) in the database, resulting in potential unmeasured confounding. Additionally, patients' clinical courses are incompletely reflected in such databases, and thus, we cannot know which factors contributed to patients receiving directed therapy, but we have tried to mitigate this by adjusting for patient characteristics. However, potentially important clinical covariates are not available in an administrative database such as PHIS,[35] and the potential for unmeasured confounding must be acknowledged. Although there are methods to overcome unmeasured confounding,[36] this was beyond the scope of this study. Similarly, it was difficult to ascertain nosocomial PE, which may represent a clinically

distinct entity from PE present on admission. Moreover, there remains a confounding indication as there are likely differences between patients who received medication alone vs intervention, though we are unable to control for those differences. Low event rates of thrombolysis and thrombectomy result in further confounding and risk of underestimation of outcomes. Finally, since the study uses a convenience sample, there is a risk of type II error with failure to reject the null hypothesis.

CONCLUSIONS

Despite these limitations, we conclude that PE is most commonly seen in adolescents with at least 1 comorbidity. Currently, most pediatric PE patients are treated with anticoagulation alone, with DOAC and DTI use increasing over time. Thrombolysis, systemic or local, and thrombectomy were used rarely. Extrapolating from adult data, careful use of these technologies may represent an important way to improve both acute and long-term outcomes in this population. Given the relative rarity of PE in children and adolescents, additional research, which may require innovative study designs, is critical (**Central Illustration**).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Most pediatric patients with PE have at least 1 chronic disease, of which cardiac disease is the most common.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Most pediatric patients with PE are treated with anticoagulation, though the choice of anticoagulation has shifted over time.

COMPETENCY IN PATIENT CARE: Though most pediatric patients with PE are treated with anticoagulation, thrombolysis and thrombectomy must also be considered as treatment modalities.

TRANSLATIONAL OUTLOOK: Though anticoagulation is the mainstay of pediatric PE treatment, better delineation of which patients may benefit from thrombolysis or thrombectomy is necessary.

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APPENDIX For supplemental tables, please see the online version of this paper.