Acute pulmonary embolism in children and adolescents in the USA (2016 and 2019): a nationwide retrospective cohort study

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Summary

Background Epidemiological data on acute pulmonary embolism among children and adolescents are sparse and only date back to the 2000s. We aimed to establish annual estimates and age-stratified and sex-stratified indicators of acute pulmonary embolism among children and adolescents aged 0–19 years.

Methods We did a retrospective, nationwide, patient-level analysis of the Kids' Inpatient Database, including 5733 patients with acute pulmonary embolism aged 0–19 years admitted to hospital in the USA in 2016 and 2019. The database includes data of all children admitted to hospital during the 2 years available. We also accessed the US Multiple Cause of Death database and population data from the US Census Bureau for the same 2 years. We estimated the incidence, mortality, case fatality, and proportional mortality rates, provided data on the annual pulmonary embolism burden, and provided data on clinical events recorded during hospitalisation.

Findings In the years 2016 and 2019, 5733 patients (3353 [58.5%] female and 2380 [41.5%] male) were admitted to hospital with acute pulmonary embolism as the primary diagnosis or a concomitant diagnosis. The annual incidence of acute pulmonary embolism was 3·5 (95% CI 3·4–3·6) per 100 000 people. Two peaks in the incidence rate were observed—one in infants younger than 1 year and one in adolescents aged 15–19 years. The in-hospital case fatality rate was 4·5% (4·0–5·1). The crude odds ratio for in-hospital death among patients with (*vs* without) acute pulmonary embolism was 9·3 (7·9–10·9). The association between acute pulmonary embolism and death persisted across different multivariable models. Patients with acute pulmonary embolism with high-risk (*vs* no high-risk) features had the highest risk of death: 25·3% (20·6–30·5) among patients aged 0–9 years and 13·9% (11·9–16·2) among patients aged 10–19 years. In patients without high-risk features, risk of death was 4·9% (3·1–7·6) among patients aged 0–9 years and 0·7% (0·5–1·0) among patients aged 10–19 years. The risk of intracranial bleeding was also highest in the presence of pulmonary embolism with high-risk features: 8·1% (5·5–11·7) among patients aged 0–9 years and 3·6% (2·6–4·9) among patients aged 10–19 years. In patients without high-risk features, the risk of intracranial bleeding was 2·5% (1·3–4·6) among those aged 0–9 years and 0·5% (0·3–0·8) in those aged 10–19 years. Reperfusion treatments beyond systemic thrombolysis were rarely used among children and adolescents with acute pulmonary embolism.

Interpretation Acute pulmonary embolism is rare during childhood and adolescence. The high pulmonary embolism-related fatality among specific subgroups of patients can be interpreted in the context of severe comorbidities and pulmonary embolism events with high-risk features.

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Introduction

Pulmonary embolism rarely occurs in children and adolescents. Incidence, risk factors, pathophysiology, presenting symptoms, and management strategies differ from those observed in adults and show substantial heterogeneity between infants, children, and adolescents.[1] For instance, identifiable risk factors for pulmonary embolism, such as central venous catheters and hormonal contraception, can be identified in up to 95% of children, compared with 50–70% of adults.[1–4] Furthermore, the severity of acute pulmonary embolism and the root causes leading to venous thromboembolic events are known to vary substantially across the age spectrum in infants, children, and adolescents.[3,5–7]

The epidemiological burden of pulmonary embolism in children remains poorly studied. 20 years ago, autopsy studies reported a prevalence of pulmonary embolism from 0·05% to 4·2% for children deceased for any cause.[2,8,9] Data from the US National Hospital Discharge survey from 1979 to 2001 described an annual incidence rate of 0·9 pulmonary embolism cases per 100 000 children and adolescents.[10] Between 2001 and 2007, the incidence rate of venous thromboembolism (VTE) in children in the USA was 34–58 cases per 10 000 hospital admissions, with pulmonary embolism accounting for 10% of these

Research in context

Evidence before this study

We searched PubMed, Web of Science, and Google Scholar for epidemiological studies and reviews published in English from Jan 1, 1980, to Jan 1, 2024, using the search terms "mortality", "incidence", "epidemiology", "pulmonary embolism", "venous thromboembolism", "children", and "adolescents". In 2021, the Pediatric and Neonatal Thrombosis and Hemostasis Subcommittee of the International Society on Thrombosis and Haemostasis called for research on paediatric pulmonary embolism to improve our knowledge about the disease and to guide future research.

The incidence rate of acute pulmonary embolism in children and adolescents has been estimated based on studies of venous thromboembolism, encompassing pulmonary embolism and deep vein thrombosis, covering the years 1979–2001 and 2001–07. In most cases, epidemiological studies have not focused specifically on children and adolescents, often presenting data in the context of the general population. Finally, no ad hoc epidemiological studies of pulmonary embolism-related mortality in children and adolescents have been carried out over the past four decades, as recent studies looked at populations of individuals older than 15 or 20 years.

Added value of this study

Our study provides the largest comprehensive analysis of the epidemiological burden of acute pulmonary embolism among children and adolescents. Furthermore, we calculated the prevalence of 119 clinically selected concomitant disorders described in patients with versus without pulmonary embolism. We revealed substantial age-specific and sex-specific differences in epidemiological parameters, possibly larger than those observed in adults, and concomitant disorders. This finding could be related to the differential exposure to triggers of pulmonary embolism among the three main age groups of infants (aged <1 years), children (aged 1–9 years), and adolescents (aged 10–19 years). We showed that the fatality rate was at least 2-times higher in patients with acute pulmonary embolism versus those without, even after conditioning for key demographic parameters and comorbidities. Both the risk of death and intracranial bleeding were very high, particularly in patients with acute pulmonary embolism with high-risk features, possibly due to the minimal evidence concerning acute management.

Implications of all the available evidence

Further research is needed to dissect disease-specific risks of venous thromboembolic complications in children and adolescents. We showed large heterogeneity in the genesis and prognosis of acute pulmonary embolism across age–sex groups: therefore, it is crucial to recognise potential risk factors and implement tailored preventive measures and therapeutic strategies. We showed the frequency of intracranial bleeding and case fatality rate across patients stratified according to the presence of high-risk features and advanced pulmonary embolism treatment. Acute pulmonary embolism in children is rare, and substantial barriers to generating evidence at any level of clinical development are anticipated.

cases.[11] However, no comprehensive investigation of key epidemiological indicators of pulmonary embolism in children and adolescents is currently available, including the frequency of age-specific comorbidities. Understanding the epidemiology of acute pulmonary embolism among children and adolescents is essential for quantifying age-specific and sex-specific disease burdens, as it allows us to identify factors contributing to poor outcome and study trends in prevalent comorbidities, rather than focusing solely on the incidence of the disease. Ultimately, this understanding will help to identify knowledge gaps and inform future research on new treatment (and preventive) strategies.

The aim of this study was to investigate annual estimates and age-stratified and sex-stratified indicators of pulmonary embolism among children and adolescents aged 0–19 years, as well as the prevalence of clinically selected comorbidities in patients with (*vs* without) pulmonary embolism.

Methods

See Online for appendix

Data source

We did a retrospective, nationwide, patient-level analysis using the Kids' Inpatient Database (KID), provided by the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality,[12] including all patients aged 0–19 years admitted to hospital in the USA. The KID dataset provided data for selected years at regular intervals, of which we used the two available years (2016 and 2019) after the introduction of the ICD-10 in 2015. In 2016, 47 states submitted data to KID. In 2019, 48 states plus the District of Columbia submitted data. The data were sampled from 4200 community hospitals (including public hospitals and academic medical centres), excluding rehabilitation hospitals. Uncomplicated in-hospital births were sampled at a rate of 10% and complicated in-hospital births and other paediatric discharges were sampled at a rate of 80% via systematic random sampling. Using the provided weight for each patient, national estimates were calculated. Diagnoses were extracted from ICD-10 codes and pulmonary embolism was defined by code I26.x. We did not include obstetric codes for acute pulmonary embolism, as we anticipated a low count for those. ICD-10 codes for clinically selected disorders considered for analysis are listed in the appendix (pp 3–6).

We studied the frequency of intracranial bleeding and death across subgroups of patients stratified according

to age and features of pulmonary embolism severity. ICD-10 codes and ICD-10 procedure codes for the definition of pulmonary embolism with high-risk features encompass clinical characteristics (ie, shock or cardiac arrest) and advanced interventions (ie, reperfusion therapies or need for cathecolamines). The ICD-10 codes and procedures defining acute pulmonary embolism with high-risk characteristics and the definition of bleeding events are provided in the appendix (p 7).

Age–sex stratified mid-year estimates for the general population were extracted from the US Census Bureau for the same 2 years (2016 and 2019),[13] whereas the all-cause death counts were obtained from the US Centers for Disease Control and Prevention (CDC) Multiple Cause of Death (MCOD) database.[14] Ethnicities were defined as reported in the KID database: White, Black, Hispanic, and other (Asian or Pacific Islander, Native American, and other). This study was conducted in accordance with the RECORD standards.[15]

The only variable with a substantial number of missing data in the KID dataset was the ethnicity variable, for which approximately 10% of values were missing. Sex data were missing for five patients. Patients with missing data were excluded from the respective analyses. Death record files (MCOD database) were processed by a standard procedure and were considered 100% complete, with the exception of a small number of deaths for which registration was delayed (eg, Americans dying outside of the USA or missing people for whom courts had not yet assigned certification of death). As the mid-year population data provided by the US Census Bureau were official estimates, they required no strategies to address missingness.

Statistical analysis

The primary analysis of epidemiological indicators was performed for all pulmonary embolism-related cases, therefore it also included cases for which pulmonary embolism was reported as a concomitant disease. We calculated the crude age–sex-specific incidence rate as the number of pulmonary embolism-related hospitalisations per 100 000 people and the proportion of pulmonary embolism events per 10 000 hospital admissions. The crude pulmonary embolism-related mortality rate was defined as the number of pulmonary embolism-related deaths per 100 000 people and the proportion of pulmonary embolism-related deaths per 10 000 hospital admissions. The in-hospital case fatality rate was the number of pulmonary embolism-related deaths out of the total pulmonary embolism cases. The proportional mortality was defined as the number of pulmonary embolism-related deaths out of the total deaths from all causes. The frequency of in-hospital clinical events (intracerebral bleeding and death) was calculated as the number of pulmonary embolism patients with an event per 100 pulmonary embolism cases.

Patients were divided into 5-year age groups (age 0–4 years, 5–9 years, 10–14 years, and 15–19 years). The 0–4 year age group was further divided into patients aged 0 years and 1–4 years. Analyses per 10 000 hospital admissions excluded births, as births represented almost all hospitalisations in this age group. Epidemiological indicators were calculated for the overall population, for each age-stratified and sex-stratified group, for different ethnicities, and for the years 2016 and 2019 as a sensitivity analysis.

We performed two sets of inferential analyses. In the first set, we studied whether patients with acute pulmonary embolism had a higher fatality than those without pulmonary embolism. We performed univariate logistic regression analysis in the overall population and age–sex stratified subgroups. Then, we ran three multivariable models with different conditioning variables (age, sex, and clinically identified comorbidities) added in stages. In the second set, we studied potential predictors of death among patients with acute pulmonary embolism. A penalised logistic regression model was built based on the Akaike information criterion, starting from a small set of clinically selected covariates characterised by reasonable prevalence and potential prognostic relevance. The comprehensive list of ICD-10 codes used in these regression models is provided in the appendix (p 8).

In a hypothesis-generating analysis, we calculated the absolute prevalence difference (APD) for each clinically selected disorder in pulmonary embolism (*vs* non-pulmonary embolism) patients overall and for each age group. In the APD calculation, children aged 1–9 years were grouped together to reach adequate numerosity.

Data are presented either as n (%) or as median (IQR). Continuous variables were visually inspected for data distribution. Rates are presented as crude annual nationwide estimates. All rates and frequencies are presented with appropriate 95% CIs.

To comply with HCUP regulation, data with ten or fewer cases per cell were either aggregated or not reported. No individual patient-level data on readmission were available; therefore patients could not be traced over multiple hospitalisations and our estimates refer to individual pulmonary embolism events rather than to individual patients. The statistical analysis was performed using R version 4.3.1.[16]

Due to the use of anonymised data, approval by an institutional review board was not necessary.

Role of the funding source

There was no funding source for this study.

Results

During the study period (2016 and 2019), 163 841 005 (48·9% female, 51·1% male) children and adolescents lived in the USA. A total of 4 367 589 hospital admissions and 83 873 deaths were recorded in patients aged 0–19 years. Of those, 5733 (58·5% female,

	Total (N=5733)	Males (N=2380)	Females (N=3353)
Pulmonary embolism as primary diagnosis	2296 (40·0%)	691 (29·0%)	1605 (47·9%)
Aged 0–9 years	30 (0·5%)	12 (0·5%)	18 (0·5%)
Aged 10–14 years	155 (2·7%)	61 (2·6%)	94 (2·8%)
Aged 15–19 years	2111 (36·8%)	618 (26·0%)	1493 (44·5%)
Hospitalisations for or with a pulmonary embolism diagnosis	5733	2380	3353
Neonatal (aged <28 days)	121 (2·1%)	63 (2·6%)	58 (1·7%)
Aged 28 days to <1 year	123 (2·1%)	75 (3·2%)	48 (1·4%)
Aged 1–4 years	214 (3·7%)	99 (4·2%)	115 (3·4%)
Aged 5–9 years	206 (3·6%)	129 (5·4%)	77 (2·3%)
Aged 10–14 years	677 (11·8%)	359 (15·1%)	318 (9·5%)
Aged 15–19 years	4392 (76·6%)	1655 (69·5%)	2737 (81·6%)
Median age of patients hospitalised for or with a pulmonary embolism diagnosis, years	17 (15–19)	17 (13–18)	18 (16–19)
Patients with acute pulmonary embolism with high-risk features	1273 (22·2%)	620 (26·1%)	653 (19·5%)
Neonatal (aged <28 days)	85 (1·5%)	43 (1·8%)	42 (1·3%)
Aged 28 days to <1 year	73 (1·3%)	39 (1·6%)	34 (1·0%)
Aged 1–4 years	85 (1·5%)	40 (1·7%)	45 (1·3%)
Aged 5–9 years	53 (0·9%)	35 (1·5%)	18 (0·5%)
Aged 10–14 years	149 (2·6%)	82 (3·4%)	67 (2·0%)
Aged 15–19 years	828 (14·4%)	381 (16%)	447 (13·3%)
Death with any mention of pulmonary embolism	258 (4·5%)	130 (5·5%)	128 (3·8%)
Neonatal (aged <28 days)	30 (0·5%)	≤10 (0·4%)	20 (0·6%)
Aged 28 days to <1 year	27 (0·5%)	12 (0·5%)	15 (0·4%)
Aged 1–9 years	36 (0·6%)	15 (0·6%)	21 (0·6%)
Aged 10–14 years	33 (0·6%)	18 (0·8%)	15 (0·4%)
Aged 15–19 years	132 (2·3%)	75 (3·2%)	57 (1·7%)
Median age at pulmonary embolism-related death, years	15 (2–18)	16 (5–18)	12 (0–17)

Data shown are n (%) or median (IQR).

Table 1: **Overview of pulmonary embolism cases and pulmonary embolism-related deaths per age group, stratified by sex**

41·5% male) hospital admissions had acute pulmonary embolism as the primary diagnosis or a concomitant diagnosis. Acute pulmonary embolism was the primary cause of hospitalisation in 2296 (69·9% female, 30·1% male) patients and was the primary or contributing cause of death in 258 patients. The median age of patients at the time of pulmonary embolism-related hospitalisation was 17 years (IQR 15–19), whereas the median age at pulmonary embolism-related death was 15 years (2–18; table 1).

The overall pulmonary embolism-related incidence rate was 3·5 (95% CI 3·4–3·6) pulmonary embolism-related hospitalisations per 100 000 people, corresponding to a proportion of 13 (12·7–13·4) pulmonary embolism events per 10 000 hospital admissions. The incidence rate showed a J-shaped curve, with the highest values recorded in infants younger than 1 year (3·2 [2·8–3·6] per 100 000 people) and in adolescents aged 15–19 years (10·4 [10·1–10·7] per 100 000 people). Among infants, the incidence rate was slightly higher in males (3·5 [3·0–4·1] per 100 000 people) than females (2·8 [2·3–3·4] per 100 000 people), whereas the opposite was observed among adolescents (7·7 [7·3–8·1] per 100 000 in males *vs* 13·3 [12·3–13·8] per 100 000 in females; figure 1; appendix p 9).

The proportion of pulmonary embolism-related hospitalisations increased from 2·2 (95% CI 2·0–2·6) pulmonary embolism events per 10 000 hospital admissions among infants to 28·9 (28·1–29·8) pulmonary embolism events per 10 000 hospital admissions among adolescents aged 15–19 years. Among female infants, the proportion was 2·3 [1·8–2·8] pulmonary embolism events per 10 000 hospital admissions, whereas among male infants it was 2·2 [1·9–2·7] per 10 000 hospital admissions. Among adolescents aged 15–19 years, there were 26·8 [25·8–27·8] pulmonary embolism events per 10 000 hospital admissions among females and 33·4 [33·8–35·0] per 10 000 hospital admissions among males (figure 1; appendix p 10).

The crude pulmonary embolism-related mortality rate was 0·16 (95% CI 0·14–0·18) in-hospital deaths per 100 000 people, corresponding to 0·6 (0·5–0·7) deaths per 10 000 hospital admissions. The mortality rate was highest among infants at 0·7 (0·6–1·0) per 100 000 general population. In the other age groups, the mortality rate did not exceed 0·3 per 100 000 people (appendix pp 11, 40). Compared with male infants, female infants had a slightly higher pulmonary embolism-related mortality rate and higher proportion of pulmonary embolism-related deaths out of total hospital admissions, whereas in adolescents aged 15–19 years, rates were slightly higher in males than females (appendix p 40). These epidemiological parameters appeared to be similar between the sexes among children and adolescents aged 0–14 years (appendix p 12).

The overall in-hospital case fatality rate was 4·5% (95% CI 4·0–5·1). The highest value (23·4% [18·5–29·1]) was observed in infants, with a progressive decrease across age groups down to 3·0% (2·5–3·6) in adolescents aged 15–19 years (figure 2; appendix p 13). The greatest sex-specific discrepancies in fatality rate were observed among infants (33·0% [24·8–42·4] in females *vs* 15·9% [10·8–23·0] in males) and adolescents (2·1% [1·6–2·7] in females *vs* 4·5% [3·6–5·6] in males; figure 2). The autopsy rate was overall higher than 30%, exceeding 50% in children aged 1–5 years (55·4%) and in those aged 15 to 19 years (60·5%; appendix pp 14, 41).

A total of 297 (44·5%) infants and children aged 0–9 years had high-risk features, the most prevalent of which were need for invasive ventilation (n=240), cardiac arrest and cardiopulmonary resuscitation (n=64), and need for veno-arterial extracorporeal membrane oxygenation (ECMO; n=55). A total of 978 (19·3%) adolescents aged 10–19 years had high-risk features, the most prevalent of which were need for invasive

ventilation (n=499), cardiac arrest or cardiopulmonary resuscitation (n=181), and need for systemic thrombolysis (n=324; table 2).

Patients with high-risk features had a much higher case fatality rate across age groups: 25·3% (95% CI 20·6–30·5) in infants and children aged 0–9 years and 13·9% (11·9–16·2) in adolescents aged 10–19 years (table 2). Patients requiring veno-arterial ECMO or presenting with cardiac arrest had the highest fatality, exceeding 40% in infants and children aged 0–9 years and 30% in adolescents aged 10–19 years. The case fatality rate in patients without high-risk features was 4·9% (3·1–7·6) in those aged 0–9 years and 0·7% (0·5–1·0) in those aged 10–19 years. In patients with high-risk features, the risk of intracranial bleeding was 8·1% (5·5–11·7) in infants and children aged 0–9 years and 3·6% (2·6–4·9) in adolescents aged 10–19 years (table 2).

The proportional mortality rate was 3·1 (95% CI 2·7–3·5) per 1000 overall deaths in the USA. The rate was 1·3 (1·0–1·7) per 1000 deaths among infants, and progressively increased across age groups up to 6·3 (5·3–7·4) per 1000 deaths among adolescents aged 15–19 years (appendix p 15). The proportional mortality was higher among females than males across all age groups (figure 2).

Differences in ethnicity-specific crude case fatality rates, age-stratified case fatality rates, and age-standardised case fatality rates were minimal and probably due to the low number of events in each subgroup (appendix p 16). Furthermore, the rates and proportions calculated for each available year (2016 and 2019) did not substantially differ (appendix pp 17–22).

The unadjusted odds ratios for death show that patients with acute pulmonary embolism had a 10–20-times higher risk of dying compared with patients without acute pulmonary embolism (figure 3; appendix p 23). The odds ratios for death progressively decreased with increasing age. The association between acute pulmonary embolism and death was present in an unadjusted model (9·3 [95% CI 7·9–10·9]) and remained in a multivariable model adjusting for age and sex (odds ratio 13·2 [11·3–15·5]) and in additional multivariable models adjusting for different severe comorbidities (2·0 [1·6–2·5] in the partially adjusted model and 2·5 [2·0–3·2] in the fully adjusted model).

We studied potential factors associated with death in the group of patients with acute pulmonary embolism. The analysis was limited to patients aged 10–19 years, as the number of events in younger patients was not enough for adjustment. In those aged 10–19 years, major comorbidities (sepsis, haematological tumours, thrombophilia, metabolic disorders, heart failure, cerebrovascular diseases, respiratory failure, and renal failure) were associated with in-hospital death in a multivariable penalised logistic regression model (appendix p 24).

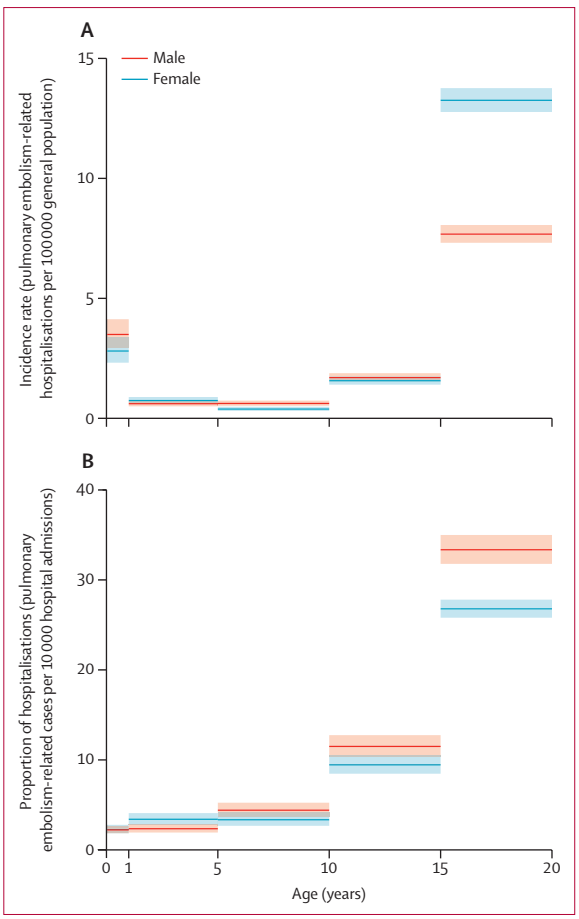

Figure 1: **Crude pulmonary embolism-related incidence rate across age groups**
Annual pulmonary embolism-related incidence (A) and proportion of hospitalisations (B) across age groups in male and female patients. Data are from the Kids' Inpatient Database and the Census Bureau. Shaded areas depict 95% CIs.

In patients for whom pulmonary embolism was reported as a concomitant diagnosis, the most commonly reported primary diagnoses were cardiovascular diseases (669 cases [19·5%]), infectious diseases (597 cases [17·4%]), and cancer (171 cases [5·0%]; appendix p 25). Irrespective of the position of pulmonary embolism code, the most common concomitant diseases were endocrine disorders (3014 cases [52·6%]), cardiovascular diseases (2730 cases [47·6%]), and respiratory diseases (2315 cases [40·4%]). Lemierre syndrome was identified in 72 (1·3%) patients with acute pulmonary embolism (appendix pp 26–27).

The highest APD across all age groups was found for other venous thromboembolic events (excluding deep vein thrombosis), with an APD of 31·8% (95 % CI 30·6–33·0) among patients with versus without pulmonary embolism; this was followed by metabolic disorders (15·2% [14·0–16·5]) and obesity (14·7% [13·7–15·8]; appendix pp 28–31). A higher prevalence of some key conditions was observed in patients with acute pulmonary embolism versus those without: these included injuries,

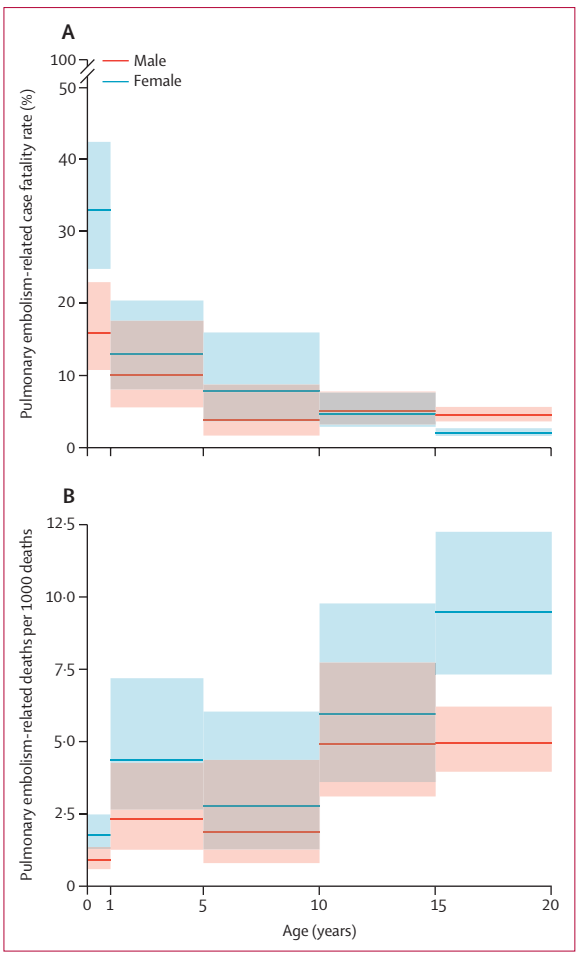

Figure 2: **Crude pulmonary embolism-related case fatality rate and crude pulmonary embolism-related proportional mortality rate across age groups**
Pulmonary embolism-related deaths per 100 diagnoses of pulmonary embolism (A) and pulmonary embolism-related proportional mortality (deaths per 1000 all-cause deaths; B) across age groups in male and female patients. Data are from the Kids' Inpatient Database and the Multiple Cause of Death database. Shaded areas depict 95% CIs.

coagulation defects or thrombophilia, sepsis, respiratory or renal failure, arterial disorders, neoplasms, and pneumonia.

Clinically relevant APD were found for some conditions, typically affecting specific age groups (appendix pp 32–39). The prevalence of malformations, injury or poisoning, renal failure, heart failure, and cerebrovascular diseases was highest among infants with (*vs* without) pulmonary embolism. In contrast, the prevalence of obesity, pneumonia, cancer, and asthma were typically higher among adolescents with (*vs* without) pulmonary embolism. Some conditions were more frequent among hospitalised females (*vs* males) with pulmonary embolism, such as obesity, systemic lupus erythematosus, and osteomyelitis. Most of the other clinically selected conditions were more frequent among hospitalised males (*vs* females) with pulmonary embolism, notably sepsis, multiorgan failure, and neoplasms.

Discussion

This analysis provides a comprehensive overview of the epidemiology of acute pulmonary embolism among children and adolescents in the USA for the years 2016 and 2019. We revealed substantial age–sex-specific differences for all studied estimators, possibly larger than those among adults.[17,18] This difference is probably related to the exposure to age-specific triggers of pulmonary embolism and underlying risk factors in infants, children, and adolescents. We explored this hypothesis by calculating the prevalence of 119 clinically selected concomitant disorders in children with (*vs* without) pulmonary embolism. We showed that the risk of dying is much higher in patients with (*vs* without) acute pulmonary embolism: this association was partly driven by severe comorbidities, but remained after conditioning for several covariates, suggesting an independent role of pulmonary embolism. Finally, we provided the absolute risks of intracranial bleeding and death in patients with acute pulmonary embolism with (*vs* without) high-risk features and across groups of patients receiving advanced treatments.

We estimated an overall incidence rate of 3·5 pulmonary embolism-related hospitalisations per 100 000 general population. Stein and colleagues[10] described an overall lower incidence rate of 0·9 cases per 100 000 people among children and adolescents aged 0–17 years in the period 1979–2001, with no sex-specific data been presented. In a Canadian study performed between 1990 and 1992 reporting on the incidence of acute VTE, the authors estimated an overall incidence rate of 0·7 cases per 100 000 people, with possibly no more than 50% of patients having acute pulmonary embolism.[1] In adults, the incidence of acute pulmonary embolism has been increasing for the past four decades.[19] In children and adolescents, an increasing frequency of pulmonary embolism-related hospitalisations has been described at selected institutions between 2001 and 2014.[20]

In our study, incidence of acute pulmonary embolism progressively increased between ages 5 and 19 years, peaking among adolescents aged 15–19 years (10·4 pulmonary embolism-related hospital admissions per 100 000 people). Among children and adolescents, venous catheters, surgery, and trauma have been described as the most common predisposing factors for acute pulmonary embolism.[21] We showed that, compared with patients without acute pulmonary embolism, the difference in the prevalence of comorbidities decreased with increasing age (exceptions were noted, such as obesity, cancer, and pneumonia). Similar to a previous study,[10] we found a second, smaller incidence peak among infants (3·2 pulmonary embolism-related hospital admissions per 100 000 people); this might represent an underestimation, as imaging is rarely performed in this age group.[22] As infants have several competing risks for hospital admission, we observed no peak in the frequency of pulmonary embolism-related hospital

	Aged 0–9 years (N=664)						Aged 10–19 years (N=5069)					
	Count	Prevalence	Intracranial bleeding cases	Frequency of intracranial bleeding	Deaths	Case fatality rate	Count	Prevalence	Intracranial bleeding cases	Frequency of intracranial bleeding	Deaths	Case fatality rate
ECMO	55	8·3%	14	25·5% (15·8–38·3)	29	52·7% (39·8–65·3)	58	1·1%	≤10	5·2% (1·8–14·1)	26	44·8% (32·7–57·5)
Catheter-directed reperfusion therapies	≤10	0·8%	0	0	≤10	20·0% (3·6–62·4)	90	1·8%	≤10	1·1% (0·2–6·0)	≤10	1·1% (0·2–6·0)
Systemic thrombolysis	24	3·6%	≤10	4·2% (0·7–20·2)	≤10	16·7% (6·7–35·9)	324	6·4%	≤10	0·9% (0·3–2·7)	22	6·8% (4·5–10·1)
Shock	47	7·1%	≤10	14·9% (7·4–27·7)	19	40·4% (27·6–54·7)	145	2·9%	≤10	4·8% (2·4–9·6)	35	24·1% (17·9–31·7)
Surgical embolectomy	33	5·0%	≤10	3·0% (0·5–15·3)	≤10	3·0% (0·5–15·3)	25	0·5%	≤10	12·0% (4·2–30·0)	≤10	16·0% (6·4–34·7)
Invasive ventilation	240	36·1%	17	7·1% (4·5–11·0)	61	25·4% (20·3–31·3)	499	9·8%	31	6·2% (4·4–8·7)	106	21·2% (17·9–25·0)
Vasopressor use	18	2·7%	0	0	≤10	27·8% (12·5–50·9)	59	1·2%	≤10	6·8% (2·7–16·2)	15	25·4% (16·1–37·8)
Cardiac arrest or CPR	64	9·6%	11	17·2% (9·9–28·2)	29	45·3% (33·7–57·4)	181	3·6%	≤10	4·4% (2·3–8·5)	59	32·6% (26·2–39·7)
Any of the above	297	44·7%	24	8·1% (5·5–11·7)	75	25·3% (20·6–30·5)	978	19·3%	35	3·6% (2·6–4·9)	136	13·9% (11·9–16·2)
None of the above	367	55·3%	≤10	2·5% (1·3–4·6)	18	4·9% (3·1–7·6)	4091	80·7%	21	0·5% (0·3–0·8)	29	0·7% (0·5–1·0)

Data shown are n, %, and frequency (95% CI). CPR=cardiopulmonary resuscitation. ECMO=extracorporeal membrane oxygenation.

Table 2: **Frequency of intracranial bleeding and case fatality rate, stratified by age**

admissions.[23] Indeed, infants were characterised by a higher prevalence of organ failure and severe systemic diseases compared with patients without pulmonary embolism, which translated to a worse prognosis. In relative terms, infants with pulmonary embolism had 20-times higher odds of dying than infants without pulmonary embolism. In adults, the detection of proximal deep vein thrombosis or an acute pulmonary embolism event has been associated with higher in-hospital fatality.[24,25]

The reliability of fatality data in children and adolescents is supported by the high autopsy rate recorded, which is at least 2-times higher than in adults.[18,26] As in a previous study,[5] we showed that, compared with adolescents, children and infants with pulmonary embolism were more likely to have high-risk features and had much higher case fatality rates. In contrast, the pulmonary embolism-related fatality rate among adolescents was lower and more similar to that of younger adults.[27] We also obtained estimates for frequency of intracranial bleeding in patients with shock, undergoing different reperfusion treatment, requiring advanced haemodynamic support, or who underwent cardiopulmonary resuscitation. Indeed, we observed that the use of reperfusion treatments was overall rare, not exceeding 5% for ECMO, catheter-directed reperfusion therapies, or surgical embolectomy. Systemic thrombolysis remained the most frequently used reperfusion treatment with a prevalent use of 3·6% among patients aged 0–9 years and 6·4% among patients aged 10–19 years. The very high rate of complications, possibly higher than in adults, documented across the spectrum of patients with high-risk features reflects the lack of firm evidence concerning advanced pulmonary embolism management and comorbidities. This encompasses risk stratification, pharmacological therapies, and reperfusion strategies.

Our epidemiological estimates showed age–sex-specific differences. Pulmonary embolism diagnoses peaked in adolescents aged 15–19 years, possibly reflecting the maturation of the haemostatic system,[28,29] the progressive increase of oestrogen concentrations during adrenarche,[30] and the prevalent use of oral contraception.[31,32] The maturation of the haemostatic system starts at birth and evolves until around age 16 years; however, the precise age is unknown and might depend on sex-specific factors.[33,34] A typical cause of acute pulmonary embolism among adolescents, Lemierre syndrome (encompassing bacterial tonsillitis, septic jugular vein thrombosis, and septic embolism), was detected in approximately 1% of all acute pulmonary embolism cases.[35] The high prevalence of oral contraceptives and increasing oestrogen concentrations among patients aged 15–19 years explains the higher absolute number of pulmonary embolism cases observed among female patients compared with male patients. In adolescents, males had a 2-times higher in-hospital case fatality rate than females, reinforcing the different genesis of pulmonary embolism. In contrast, the high case fatality rate in males might indicate overlooked diagnoses and delay in initiation of appropriate treatment.[36] As a comparison, patients with acute pulmonary embolism had a higher in-hospital case fatality rate than those with

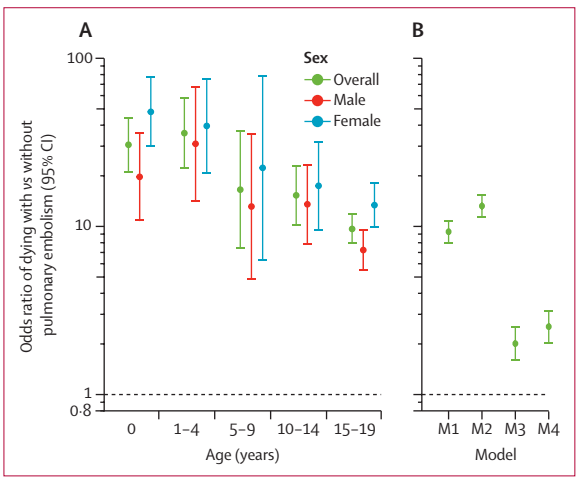

Figure 3: **Odds ratio for in-hospital death among children and adolescents with versus without pulmonary embolism by age (A) and model (B)**
The y axis is provided as a logarithmic scale. Data are from the Kids' Inpatient Database. Model 1 is the univariate logistic regression model using data from the complete cohort. Model 2 is the multivariable logistic regression model adjusted for age and sex using data from the complete cohort. Model 3 is the multivariable logistic regression model adjusted for age, sex, sepsis, solid tumours, haematological tumours, thrombophilia, metabolic disorders, heart failure, cerebrovascular diseases, deep venous thrombosis or other venous thrombotic manifestations, respiratory failure, and renal failure using data from the complete cohort. Model 4 is the multivariable logistic regression model adjusted for age; sex; sepsis; solid tumours; haematological tumours; thrombophilia; metabolic disorders; heart failure; cerebrovascular diseases; deep venous thrombosis or other venous thrombotic manifestations; respiratory failure; renal failure; obesity; pneumonia; acute and subacute endocarditis; asthma; malformations; cerebrovascular diseases; epilepsy; malnutrition; rheumatological diseases; and injury, poisoning, and some other consequences of external causes using data from the complete cohort.

trauma or severe pneumonia, comparable to those with sepsis, and lower than those with acute bacterial meningitis.[37–40] Our analysis of prevalent conditions suggests that males more often presented with more severe comorbidities than females; this, along with our analysis on the prevalence of comorbidities, might serve to generate hypotheses. Further research is necessary to investigate diseases and disease groups associated with pulmonary embolism in children and specific risk factors for pulmonary embolism in children.

Pulmonary embolism-related death was recorded in 258 children and adolescents and explained 3·1 of 1000 deaths, with higher rates recorded among adolescents and in females. In the same period, the three most frequent causes of death among children and adolescents were unintentional injuries (648 per 1000 deaths), congenital anomalies (307 per 1000), and homicide (124 per 1000).[14,41] We have previously shown that pulmonary embolism-related proportional mortality peaks among female individuals aged 30–34 years, explaining 15 of 1000 deaths in the USA,[18] and that pulmonary embolism-related mortality rate exponentially increases with increasing age. In this context, acute pulmonary embolism is a rare cause of death among children and adolescents, but might occur in concomitance and represent a marker of the severity of other conditions. The clinical effect of acute pulmonary embolism should also be evaluated in relation to its poor prognostic impact, anticoagulant-related bleeding risk, and patient burden (eg, long-term complications).[42]

Studies on predictors for pulmonary embolism and pulmonary embolism-related death in children and adolescents are scarce. One recent study found congenital heart disease or pulmonary surgery, known thrombophilia, previous VTE, nephrotic syndrome, and chest pain to be predictors of pulmonary embolism.[43] We showed an increased odds ratio for death in patients with pulmonary embolism aged 10–19 years with severe comorbidities (sepsis, haematological tumours, thrombophilia, metabolic disorders, heart failure, cerebrovascular diseases, respiratory failure, and renal failure), suggesting the need for closer monitoring of these patients and the consideration of early treatment. The current evidence calls for the development of age–sex-specific prediction models for pulmonary embolism occurrence and pulmonary embolism-related death.

Further research is warranted to improve our understanding of pulmonary embolism in children and adolescents. First, prospective studies would improve the understanding of the timing of adverse events occurring during hospitalisation and, therefore, the potential causal relationship between comorbidities and acute pulmonary embolism. Second, longitudinal studies focusing on the post-discharge phase could assess functional outcomes and the burden of long-term sequelae after pulmonary embolism.[44] Finally, interventional studies should identify optimal treatment regimens, including reperfusion strategies, across different age groups.

This study has limitations. First, KID consists of inpatient hospitalisations only, and no data on outpatient management of acute pulmonary embolism were available. Nonetheless, we do not expect that direct discharge is routinely adopted after pulmonary embolism diagnosis in this patient group. Second, proportionate mortality was calculated using data on deaths from KID as the numerator and data from the MCOD database as the denominator. Therefore, the proportionate mortality rate only represents the rate of deaths among hospitalised patients with pulmonary embolism. If out-of-hospital pulmonary embolism-related deaths were diagnosed and included, we would expect the proportionate mortality rate to be higher. Third, the study is based on ICD-10 coding of hospital admission data, which could have led to the inclusion of prevalent cases; this could have led to an underestimation of the case fatality rate (assuming that the reported recurrent pulmonary embolism events are less severe than the index events) and to an overestimation of the prevalence of mild chronic comorbidities that contributed to the genesis of acute pulmonary embolism. Additionally, pulmonary embolism-related deaths are based on the coding of death certificates, which are less reliable than autopsy

results, and we could not cross-check whether medication use was consistent with a diagnosis of acute pulmonary embolism, as this information is not available in KID.

We showed that acute pulmonary embolism is rare among children and adolescents, with an incidence rate of 3·5 pulmonary embolism-related hospitalisations per 100 000 people. The sex-specific differences observed for all epidemiological parameters reflected differences in the prevalence of severe comorbidities. The high pulmonary embolism-related fatality among specific subgroups of patients could be explained by severe comorbidities and a high proportion of pulmonary embolism events with high-risk features.

Contributors

SW contributed to the concept and design of the study, statistical analysis, interpretation of the results, writing of the manuscript, and final approval of the manuscript. LV, FAK, NK, SVK, ILMK, CHvO, CA, and SCC contributed to the interpretation of the results, critical revision of the manuscript, and final approval of the manuscript. SB contributed to the concept and design of the study, interpretation of the results, writing of the manuscript, and final approval of the manuscript. SW and LV had access to the raw data. All authors accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Statistical source code used to generate population estimates, calculation of rates, and prevalence difference can be obtained from SW (simon.wolf@usz.ch). Source data can be downloaded from the US Centers for Disease Control and Prevention website (National Center for Health Statistics: mortality multiple cause files) and the US Census Bureau website (National Population by Characteristics: 2010–20). The HCUP Kids' Inpatient Database can be accessed on the HCUP webpage.

References

1 Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood* 1994; **83:** 1251–57.

2 Ramiz S, Rajpurkar M. Pulmonary embolism in children. *Pediatr Clin North Am* 2018; **65:** 495–507.

3 van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr* 2001; **139:** 676–81.

4 Barco S, Klok FA, Mahé I, et al. Impact of sex, age, and risk factors for venous thromboembolism on the initial presentation of first isolated symptomatic acute deep vein thrombosis. *Thromb Res* 2019; **173:** 166–71.

5 Pelland-Marcotte MC, Tucker C, Klaassen A, et al. Outcomes and risk factors of massive and submassive pulmonary embolism in children: a retrospective cohort study. *Lancet Haematol* 2019; **6:** e144–53.

6 Rastogi R, Okunowo O, Faerber JA, et al. Incidence, management, and outcomes of pulmonary embolism at tertiary pediatric hospitals in the United States. *JACC Adv* 2024; **3:** 100895.

7 Rajpurkar M, Huang YV, Raffini L. Additional analysis of pediatric pulmonary embolism using the Pediatric Health Information System database. *Blood Adv* 2019; **3:** 2604–07.

8 Buck JR, Connors RH, Coon WW, Weintraub WH, Wesley JR, Coran AG. Pulmonary embolism in children. *J Pediatr Surg* 1981; **16:** 385–91.

9 Byard RW, Cutz E. Sudden and unexpected death in infancy and childhood due to pulmonary thromboembolism. An autopsy study. *Arch Pathol Lab Med* 1990; **114:** 142–44.

10 Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. *J Pediatr* 2004; **145:** 563–65.

11 Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics* 2009; **124:** 1001–08.

12 Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. 2016–2019. https://hcup-us.ahrq.gov/kidoverview.jsp (accessed Dec 18, 2023).

13 US Census Bureau. National population by characteristics: 2010–2020. https://census.gov/programs-surveys/popest/technical-documentation/research/evaluation-estimates/2020-evaluation-estimates/2010s-national-detail.html (accessed Dec 19, 2023).

14 US Centers for Disease Control and Prevention. Multiple Cause of Death database. https://wonder.cdc.gov/mcd-icd10.html (accessed Dec 19, 2023).

15 Benchimol EI, Smeeth L, Guttmann A, et al. The reporting of studies conducted using observational routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; **12:** e1001885.

16 R Core Team. R: a language and environment for statistical computing. https://www.R-project.org/.

17 Jarman AF, Mumma BE, Singh KS, Nowadly CD, Maughan BC. Crucial considerations: sex differences in the epidemiology, diagnosis, treatment, and outcomes of acute pulmonary embolism in non-pregnant adult patients. *J Am Coll Emerg Physicians Open* 2021; **2:** 12378.

18 Barco S, Valerio L, Agneo W, et al. Age–sex specific pulmonary embolism-related mortality in the USA and Canada, 2000–18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. *Lancet Respir Med* 2021; **9:** 33–42.

19 Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of pulmonary embolism: an update. *J Am Coll Cardiol* 2016; **67:** 976–90.

20 Carpenter SL, Richardson T, Hall M. Increasing rate of pulmonary embolism diagnosed in hospitalized children in the United States from 2001 to 2014. *Blood Adv* 2018; **2:** 1403–08.

21 David M, Andrew M. Venous thromboembolic complications in children. *J Pediatr* 1993; **123:** 337–46.

22 Bosch de Basea M, Salotti JA, Pearce MS, et al. Trends and patterns in the use of computed tomography in children and young adults in Catalonia—results from the EPI-CT study. *Pediatr Radiol* 2016; **46:** 119–29.

23 Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics* 1995; **96:** 939–43.

24 Raskob GE, Spyropoulos AC, Cohen AT, et al. Association between asymptomatic proximal deep vein thrombosis and mortality in acutely ill medical patients. *J Am Heart Assoc* 2021; **10:** e019459.

25 Imura M, Yamamoto T, Hiasa KI. Pulmonary thromboembolism developed during hospitalization: a nationwide retrospective observational study using claims data. *Cardiol Ther* 2023; **12:** 127–41.

26 Valerio L, Turatti G, Klok FA, et al. Prevalence of pulmonary embolism in 127 945 autopsies performed in cancer patients in the United States between 2003 and 2019. *J Thromb Haemost* 2021; **19:** 1591–93.

27 Stein PD, Matta F, Alrifai A. Case fatality rate in pulmonary embolism according to age and stability. *Clin Appl Thromb Hemost* 2013; **19:** 668–72.

28 Appel IM, Grimminck B, Geerts J, Stigter R, Cnossen MH, Beishuizen A. Age dependency of coagulation parameters during childhood and puberty. *J Thromb Haemost* 2012; **10:** 2254–63.

29 Kuhle S, Male C, Mitchell L. Developmental hemostasis: pro- and anticoagulant systems during childhood. *Semin Thromb Hemost* 2003; **29:** 329–38.

30 Witchel SF, Pinto B, Burghard AC, Oberfield SE. Update on adrenarche. *Curr Opin Pediatr* 2020; **32:** 574–81.

31 Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Exp Clin Cardiol* 2013; **18:** 129–38.

32 Abou-Ismail MY, Citla Sridhar D, Nayak L. Estrogen and thrombosis: a bench to bedside review. *Thromb Res* 2020; **192:** 40–51.

33 Toulon P. Developmental hemostasis: laboratory and clinical implications. *Int J Lab Hematol* 2016; **38** (suppl 1)**:** 66–77.

34 Ganrot P, Schersten B. Serum α2-macroglobulin concentration and its variation with age and sex. *Clin Chim Acta* 1967; **15:** 113–20.

35 Valerio L, Zane F, Sacco C, et al. Patients with Lemierre syndrome have a high risk of new thromboembolic complications, clinical sequelae and death: an analysis of 712 cases. *J Intern Med* 2021; **289:** 325–39.

36 Rajpurkar M, Warrier I, Chitlur M, et al. Pulmonary embolism—experience at a single children's hospital. *Thromb Res* 2007; **119:** 699–703.

37 Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003; **167:** 695–701.

38 Oliver J, Avraham J, Frangos S, Tomita S, DiMaggio C. The epidemiology of inpatient pediatric trauma in United States hospitals 2000 to 2011. *J Pediatr Surg* 2018; **53:** 758–64.

39 Lukšić I, Mulić R, Falconer R, Orban M, Sidhu S, Rudan I. Estimating global and regional morbidity from acute bacterial meningitis in children: assessment of the evidence. *Croat Med J* 2013; **54:** 510–18.

40 Bokade CM, Madhura AD, Bagul AS, Thakre SB. Predictors of mortality in children due to severe and very severe pneumonia. *Niger Med J* 2015; **56:** 287–91.

41 Goldstick JE, Cunningham RM, Carter PM. Current causes of death in children and adolescents in the United States. *N Engl J Med* 2022; **386:** 1955–56.

42 Bastas D, Brandão LR, Vincelli J, et al. Long-term outcomes of pulmonary embolism in children and adolescents. *Blood* 2024; **143:** 631–40.

43 Tiratrakoonseree T, Charoenpichitnun S, Natesirinilkul R, et al. Clinical prediction tool to identify children at risk of pulmonary embolism. *Thromb Res* 2024; **234:** 151–57.

44 Gwozdz AM, de Jong CMM, Fialho LS, et al. Development of an international standard set of outcome measures for patients with venous thromboembolism: an International Consortium for Health Outcomes Measurement consensus recommendation. *Lancet Haematol* 2022; **9:** e698–706.