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ORIGINAL ARTICLE

A population-based analysis of children with pneumonia among intensive care units in Taiwan



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Background: Pneumonia is a major diagnosis in children that requires intensive care and is a major cause of mortality in critically ill children. A survey on current epidemiology and case fatality-associated conditions is crucial for the care of critically ill children with pneumonia in an intensive care unit (ICU).

Methods: The sex, age, seasonality of admission, area of distribution, and case fatality rate of children younger than 18 years who had pneumonia and were admitted to an ICU during the period 2006–2010 were obtained from the National Health Insurance Research Database (NHIRD) of Taiwan. The enrolled children were grouped by age (0–2 years, 3–5 years, 6–11 years, and 12–17 years). The need for invasive procedures such as endotracheal tube (ET) insertion, mechanical ventilation (MV), tracheostomy, central venous catheter (CVC) insertion, chest tube insertion/drainage, chest surgery, and extracorporeal membranous oxygenation (ECMO) were analyzed to clarify their association with case fatality in critically ill children with pneumonia.

Results: Of the 12,577 children enrolled, 7131 (56.7%) were boys and 5446 (43.3%) were girls. The younger age groups had more cases of pneumonia, but less often required invasive procedures. Children 0–2 years old ($n = 6083$) accounted for approximately one-half (48.4%) of all

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enrolled children. This group had the lowest case fatality rate (3.1%; 187/6083 children) and lowest need for invasive procedures (31.1%; 1892/6083 children), whereas children in the 12–17 year-old group had the highest case fatality rate (9.9%; 140/1417 children) and the highest need for invasive procedures (59.8%; 847/1417 children) ($p < 0.001$). The percentage of pneumonia cases was highest in the spring (30.1%) and lowest in the summer (21.7%). The invasive procedures associated with case fatality were ET/MV (OR, 14.31; $p < 0.001$), CVC insertion (OR, 7.46; $p < 0.001$), ECMO intervention (OR, 4.59; $p < 0.001$), and chest tube insertion/drainage (OR, 1.87; $p < 0.001$).

Conclusion: The number of cases of pneumonia that required ICU admission was greater among younger children than among older children. Factors associated with the higher case fatality rate included older age at presentation, the need for invasive procedures (e.g., ET/MV, CVC insertion, chest tube insertion/drainage, and ECMO), underlying comorbidities and complications.

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Introduction

Pneumonia is a common infectious disease worldwide that can occur at any age. It causes severe complications and has a poor prognosis, and can result in death. In pediatric patients, it is also a major infectious disease that results in children being diagnosed as critical, which requires intensive care. The incidence of community-acquired pneumonia is reportedly 36–40 episodes per 1000 children per year in children younger than 5 years and 11–16 episodes per 1000 children per year in children 5–14 years.¹ In Europe alone, 2.5 million cases of pneumonia occur annually.¹ The etiology of community-acquired pneumonia has been analyzed in many previous studies to allow adjustments in the administration of antibiotics.^{1–7} *Streptococcus pneumoniae* is the leading bacterial etiology of pediatric pneumonia, particularly among children younger than 5 years.^{4,8} This bacterial species accounts for an estimated 17–44% of pediatric pneumonia admissions.^{7,9}

Since 2000, a pneumococcal conjugated vaccine has been used nationwide in the United States to prevent invasive pneumococcal diseases; this has led to a 39% decline in the admission rate of children younger than 2 years old with all-cause pneumonia.⁹ There are nevertheless many other pathogens that can cause pneumonia or similar severe infections.¹⁰ Hospital-acquired pneumonia is also a major subset of pediatric pneumonia because it causes severe complications that require invasive procedures as interventions. A previously published report also demonstrates that the implementation of routine vaccination with the conjugated pneumococcal vaccine resulted in an 84% reduction of *Streptococcus pneumoniae* bacteremia and 67% reduction in overall bacteremia in United States.¹⁰ Previous studies in 1997–2004 in Taiwan have shown higher incidences and case fatality rates in hospitalized children with pneumonia who were younger than 5 years old.^{11,12} A heptavalent pneumococcal conjugated vaccine was introduced in Taiwan in 2005. The age distribution, disease severity, and the case fatality rate after the introduction of the vaccine may differ from these factors prior to the use of pneumococcal conjugated vaccine in critically ill children with pneumonia who were admitted to an intensive care

unit (ICU). Thus, a detailed investigation of the post-pneumococcal vaccination period in critically ill children is crucial in Taiwan.

A previous investigation in Taiwan indicated that approximately 20% of hospitalized children diagnosed with pneumonia require ICU admission. Despite this intervention, some children still have a poor outcome, especially children with pneumococcal pneumonia.¹³ Based on disease severity and complications that are present, these children may need invasive procedures for therapeutic purposes. In such circumstances, a detailed survey on current epidemiology and related factors associated with case fatality may help guide clinicians in the care of critically ill children with pneumonia.

The purpose of this study was to investigate the epidemiology and case fatality-associated conditions in critically ill children with pneumonia who are admitted to an ICU. This study was conducted by using 5 years (2006–2010) of data from the nationwide National Health Insurance Research Database (NHIRD) of Taiwan.

Methods

Data sources

In 1995, a universal compulsory national health insurance was introduced in Taiwan; in 2011, it provided coverage for 99.6% of the population living in Taiwan.¹⁴ The National Health Research Institute (NHI) of Taiwan maintains a large computerized administrative database from the National Health Insurance program that includes data on complete outpatient visits, hospital admissions, prescriptions, disease, and vital status for this population. Therefore, the National Health Insurance Research Database (NHIRD) of Taiwan is one of the largest and most comprehensive nationwide population-based databases available in the world.

All information from the NHIRD was double encrypted to exclude any possibility of identifying individual information.¹⁵ The Institutional Review Board of Taipei Veterans General Hospital approved this study (VGHIRB; No. 2012-06-006A).

Study population

The inpatient data file of the Taiwan NHIRD was searched to identify pediatric patients younger than 18 years old who had a recorded ICU stay during 2006–2010 and a diagnosis of pneumonia, based on the diagnosis codes (480.x, 481, 482.xx, 483.x, 484.x, 485, 486, and 487.0) of the *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM). These data were extracted from the database and analyzed.

Data analysis

The demographic characteristics (e.g., age, sex, seasonality of admission, and area distributions) of the enrolled population were collected for analysis. The enrolled children were divided into four age groups for further comparisons: 0–2 years, 3–5 years, 6–11 years, and 12–17 years. Seasonality was divided into spring (March, April, and May); summer (June, July, and August); autumn (September, October, and November); and winter (December, January, and February).¹⁶ The area distributions were divided into north, middle, south, and east of Taiwan.

Invasive procedures such as endotracheal tube (ET) insertion/mechanical ventilation (MV), tracheostomy, central venous catheter (CVC) insertion, chest tube insertion/drainage, chest surgery, and extracorporeal membranous oxygenation (ECMO) intervention were analyzed to clarify their association with the case fatality rate. Other diagnoses aside from pneumonia were also retrieved and the top ten diagnoses associated with pneumonia were analyzed.

Statistical analysis

The dataset from the NHIRD was retrieved by using the software (Microsoft SQL Server 2008 R2, Redmond, Washington, USA). The *Chi-square* test was used to compare differences in the case numbers and case fatality rates with respect to age, sex, seasonality of admission, and area distribution. Logistic regression analysis was used to identify case fatality-associated conditions of pediatric pneumonia that required ICU admission. Statistical significance was set at $p < 0.05$. The odds ratios (ORs) and their 95% confidence intervals (CIs) were also calculated to determine the association factors of case fatality.

Results

A total of 12,577 critically ill children younger than 18 years old who were diagnosed with pneumonia and admitted to an ICU were identified. Pneumonia accounted for 23.7% of all records of pediatric patients with an ICU admission.

Table 1 shows the demographic characteristics of the patients. There were 7131 (56.7%) boys and 5446 (43.3%) girls. There were 522 (4.2%) mortalities, which comprised 308 (59.0%) boys and 214 (41.0%) girls. There was no statistical difference between the male and female patients in

interventions involving an invasive procedure ($p = 0.324$) or in the case fatality rate ($p = 0.299$).

When the different age groups were explored, the 0–2 year-old group ($n = 6083$, 48.4%) had the largest number of ICU admissions for pneumonia, followed by the 3–5 year-old group ($n = 2906$, 23.1%). The smallest number of ICU admissions for pneumonia was in the 12–17 year-old group ($n = 1417$; 11.3%; Table 1 and Fig. 1A). In patients requiring invasive procedures, more than one-third of patients (37.4%; 4702/12517 children) received one or more procedures. The number of pneumonia cases was greater in younger children—especially in the 0–2 year-old group (40.2%; 1982/4702)—than in the older children (Fig. 1B). However, the trend of the need for invasive procedures and the case fatality rate was higher for the older age groups, and highest for the 12–17 year-old group (invasive procedure, 59.8%; case fatality rate, 9.9%; $p < 0.001$; Table 1 and Fig. 1C).

The distribution of patients across the four geographical regions of Taiwan showed that east Taiwan had the fewest children enrolled. The need for invasive procedures was highest for children from north Taiwan (47.6%) and lowest for children from the middle of Taiwan (30.7%; $p < 0.001$). However, there was no significant difference in the case fatality rate among the different geographical areas.

In regard to the seasonality of ICU admissions for pneumonia, admissions were highest in the spring (30.1%; especially in April) and lowest in summer (21.7%; especially in July; Table 1 and Fig. 2). The need for administering invasive procedures was lowest in the spring (34.4%; $p < 0.001$). There was no significant difference in the case fatality rates among the different seasons ($p = 0.082$).

An analysis of the case fatality-associated conditions showed that age was a significant factor. There were significantly higher ORs for older children, specifically the 6–11 years (OR, 1.99) and 12–17 years groups (OR, 3.46; $p < 0.001$). The examination of the use of invasive procedures showed that case fatality was significant for children who had undergone ET/MV (OR, 14.31; $p < 0.001$), CVC insertion (OR, 7.46; $p < 0.001$), ECMO intervention (OR, 4.59; $p < 0.001$), and chest tube insertion/drainage (OR, 1.87; $p < 0.001$; Table 2).

Table 3 lists the top ten diagnoses associated with pneumonia and the ORs for case fatality among the enrolled critically ill children. Respiratory failure was the most common diagnosis, followed by cerebral palsy and epilepsy. Positively significant diagnoses included respiratory failure, cerebral palsy, epilepsy, septicemia, congenital heart disease, and gastrointestinal hemorrhage ($p < 0.05$). Inversely significant diagnoses included asthma, pleural effusion, and volume depletion ($p < 0.05$). Convulsions were also a common diagnosis, but there was no significant influence on case fatality.

Discussion

The present study demonstrates that there are a greater number of children of younger age among critically ill children with pneumonia who are admitted to an ICU. The number of patients requiring invasive procedure interventions were also higher in the younger age groups.

Table 1 Demographic characteristics, percentage of patients undergoing invasive procedures, and the case fatality rate among critically ill children with pneumonia who were admitted to an ICU in Taiwan (in 2006–2010)

Variable	No. of patients	Invasive procedures,	<i>p</i> (χ^2 test)	Case fatality	<i>p</i> (χ^2 test)
Total	12,577 (100)	4702 (37.4)		522 (4.2)	
Sex					
Male	7131 (56.7)	2639 (37.0)	0.324	308 (4.3)	0.299
Female	5446 (43.3)	2063 (37.9)		214 (3.9)	
Age (y)					
0–2	6083 (48.4)	1892 (31.1)	<0.001*	187 (3.1)	<0.001*
3–5	2906 (23.1)	1047 (36.0)		66 (2.3)	
6–11	2171 (17.3)	916 (42.2)		129 (5.9)	
12–17	1417 (11.3)	847 (59.8)		140 (9.9)	
Area of Taiwan					
North	4589 (36.5)	2185 (47.6)	<0.001*	218 (4.8)	0.082
Middle	3548 (28.2)	1088 (30.7)		138 (3.9)	
South	4128 (32.8)	1302 (31.5)		155 (3.8)	
East	312 (2.5)	127 (40.7)		11 (3.5)	
Season					
Spring	3786 (30.1)	1301 (34.4)	<0.001*	136 (3.6)	0.231
Summer	2725 (21.7)	1043 (38.3)		121 (4.4)	
Autumn	2924 (23.2)	1155 (39.5)		129 (4.4)	
Winter	3142 (25.0)	1203 (38.3)		136 (4.3)	

Data are presented as *n* (%).

* Indicates a statistical significance ($p < 0.05$).

ICU = intensive care unit.

However, the percentage of invasive procedures and the case fatality rate in each age group were higher among the older age groups. The need for invasive procedures was furthermore associated with a higher ratio of case fatality in critically ill children.

The present study focuses on critically ill children who were diagnosed with pneumonia and admitted to an ICU during the period 2006–2010. This is the first report to use the nationwide population-based NHI database to investigate critically ill pediatric patients admitted to an ICU for pneumonia. The present study reveals that the incidence of pneumonia in ICU-admitted children is higher in boys than in girls and is higher in younger children (especially children who are 0–2 years old) than in older children (Fig. 1). These findings are consistent with a previous report by Lin et al.¹⁷ that was performed in a single center in the middle part of Taiwan and covered the period of 2002–2005, and reports by Wu et al.,^{11,12} who used the NHI database that covered the period of 1997–2004. However, these three studies investigated all hospitalized children and did not focus on critically ill patients. A European study examining the period of 1981–1982 also reported that the incidence of pneumonia was significantly higher in children younger than 5 years.¹⁸ Thus, young children are the most vulnerable population for pneumonia. This remains true for critically ill children who are admitted to an ICU.

The most common causes of pneumonia—other than viruses—in children younger than 5 years is bacterial pneumonia.^{1,2,4,6} *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, and *Staphylococcus aureus* are the primary causes of pneumonia.^{1,4} In older children and adolescents, *Mycoplasma pneumoniae* is the most frequent cause.^{5,19,20}

The use of invasive procedures in critically ill children with pneumonia in an ICU is much higher in younger children than in older children. This is consistent with the total case numbers of each age group (Table 1). Of the enrolled patients, 37.4% (4702/12,577 children) of the patients required one or more invasive procedures during their ICU stay. Furthermore, 2939 children (62.5% of all enrolled children) who were aged 0–5 years required invasive procedures. This was much higher than the total number of pneumonia cases among children aged 6–17 years old (1763 patients; 37.5% of all enrolled cases). However, the ratio of children requiring invasive procedures and the case fatality rate were higher in the 6–17 year-old children than in the 0–5 year-old children. These results are compatible with previous investigations^{11,17,21} and imply that, even though fewer older critically ill children are admitted to an ICU for pneumonia, their disease severity may be worse in comparison to the disease severity in younger children.

The critical pneumonia-related case fatality rate is highest in the children aged 12–17 years. In a report of Wu et al.¹¹ on children hospitalized with pneumonia in the period of 1997–2004, the population-based mortality rate was much higher in children younger than 5 years than in older children. The biphasic pneumonia-related case fatality rate was also markedly high in children aged 12–17 years.¹¹ Therefore, the high pneumonia-related case fatality rate in 12–17 year-old children was consistent prior to and after 2005. Clinicians should pay more attention to older children who are admitted to an ICU for pneumonia, especially children with critically ill presentations.

It is generally believed that younger children are more likely to get sick and are more vulnerable to more severe

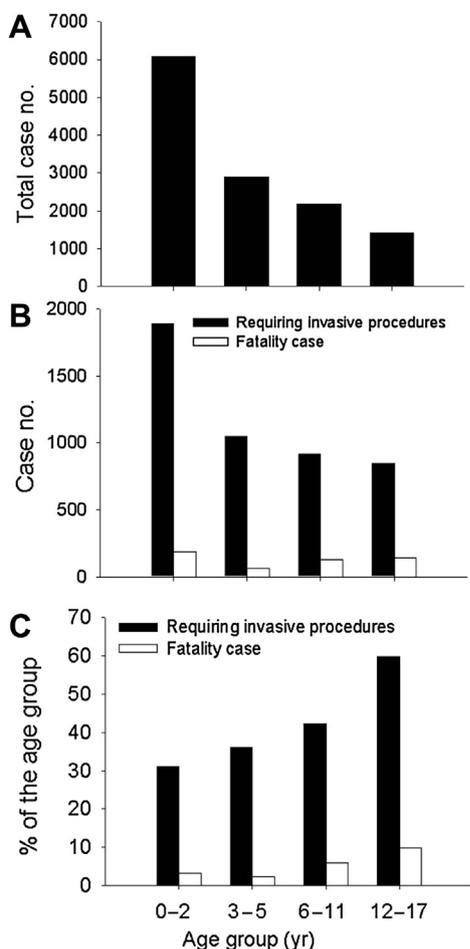


Figure 1. Total number of cases, patients requiring invasive procedures, and case fatalities in the different age groups of critically ill children with pneumonia who were admitted to an intensive care unit. (A) Total number of enrolled cases. (B) Number of children requiring invasive procedure interventions and number of fatalities. (C) Percentage of patients per age group who required invasive procedure intervention and fatalities (i.e., case fatality rate).

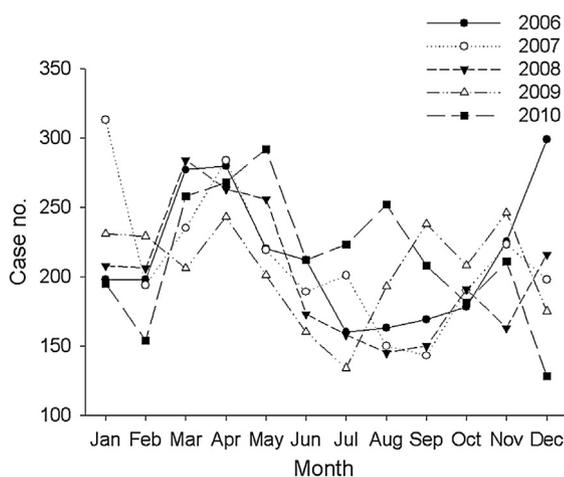


Figure 2. Seasonal distribution of intensive care unit admissions of critically ill children with pneumonia.

diseases. Parents and clinicians have been generally warned about this situation. As a result, parents often bring their sick children for medical help as soon as possible, and do so in Taiwan partly because of a convenient and nearly full-coverage national health insurance program. Furthermore, because of a pediatrician’s concerns, the admission criteria to a general ward or to an ICU for young children may not be as stringent as the criteria for older children. By contrast, older children may be brought to a hospital only when they are very sick because the parents or the children themselves think they are stronger than younger kids. They do not want to interrupt their schooling or other daily activities. However, the aforementioned are purely conjecture.

Since 2005 in Taiwan, the heptavalent pneumococcal conjugated vaccine was administered to young children. For younger children (0–5 years), it provides protection from fatal pneumococcal pneumonia and invasive pneumococcal diseases.²² The study period was 2006–2010; therefore, the influence of the heptavalent pneumococcal conjugated vaccine may play an important role in the finding that the severity of the disease among the younger children was not severe, although the number pneumonia cases was higher in younger children (0–5 years) than in older children. This may also explain the findings on the severity and the case fatality rate in critically ill children with pneumonia in which the younger children had a greater number of cases and the older children had a higher frequency of undergoing invasive procedures and a higher case fatality rate.

The use of invasive procedures was highest in northern Taiwan, although the case fatality ratio was not significantly different among the different sites (Table 1). Our hypothesis to explain this issue is that the number of tertiary medical centers is highest in northern Taiwan, and possibly so are the number of pediatric intensivists who are available to perform invasive procedures. To clarify this issue, a further study to investigate the differences in medical care behaviors of different medical centers and/or pediatric intensivists may be helpful in the future.

The seasonal distribution of pediatric pneumonia admissions to the ICU shows that the highest rate of admissions occurs in spring and the lowest rate occurs in summer. These findings are compatible with a previous study, although with less variation.⁴ The difference among the four seasons was not very apparent. One possible explanation is that the seasons in Taiwan have fewer variations because of its subtropical geographic location. The lower seasonal climate variations may reduce the variation in the incidence of pneumonia with complications requiring ICU admission. A further study to evaluate the causal organisms of critical pneumonia in children may help to elucidate the seasonal differences in Taiwan.

The odds ratios of the case fatality rate of critically ill children with pneumonia are significantly higher in the 6–11 year-old group and the 12–17 year-old group ($p < 0.001$), and significantly higher in children who receive any of the following invasive procedures: ET/MV, CVC insertion, chest tube insertion/chest tube drainage, and ECMO ($p < 0.001$). These findings suggest that an older age and higher degree of disease severity may be associated with a higher risk of mortality. This is the most important

Table 2 Analysis of case fatality-associated conditions in critically ill children who were admitted to an ICU with pneumonia

Variable	Odds ratio	95% CI	<i>p</i>
Sex			
Male	1.10	0.92–1.32	0.278
Female	1.00	–	–
Age (y)			
0–2	1.00	–	–
3–5	0.73	0.55–0.97	0.032*
6–11	1.99	1.58–2.51	<0.001*
12–17	3.46	2.75–4.34	<0.001*
Area of Taiwan			
North	1.23	0.99–1.53	0.060
Middle	1.00	–	–
South	0.96	0.76–1.22	0.759
East	0.90	0.48–1.69	0.749
Season			
Spring	0.82	0.65–1.05	0.117
Summer	1.03	0.80–1.32	0.835
Autumn	1.02	0.80–1.31	0.874
Winter	1.00	–	–
Invasive procedure			
ET/MV	14.31	11.27–18.18	<0.001*
CVC	7.46	6.22–8.95	<0.001*
ECMO	4.59	3.29–6.41	<0.001*
Chest tube insertion/drainage	1.87	1.48–2.36	<0.001*
Chest surgery	1.20	0.49–2.97	0.686
Tracheostomy	0.64	0.24–1.73	0.378

* Indicates a significant difference ($p < 0.05$).

CI = confidence interval; CVC = central venous catheter; ECMO = extra-corporeal membranous oxygenation; ET = endotracheal tube; ICU = intensive care unit; MV = mechanical ventilation; OR = odds ratio.

finding of the present study: greater attention should be focused on the clinical condition of older children with complications who are admitted to an ICU for pneumonia.

Of the underlying comorbidities (Table 3), cerebral palsy, epilepsy, and congenital heart disease are the most common underlying diseases and are significantly correlated with high mortality in critically ill children with pneumonia ($p < 0.05$). Physicians should focus more attention on these patients in regard to their pulmonary condition. The highest odds ratios of the most common complications correlated with case fatality were for respiratory failure (OR, 7.04; CI, 5.87–8.46) and septicemia (OR, 7.07; CI, 5.88–8.50; $p < 0.001$). These are also often the most common reasons that patients require intensive care. The other significant complication correlated with case fatality is gastrointestinal hemorrhage, which is a common complication in critical patients. Pediatric intensive care specialists should remember the potential risk of mortality when these underlying comorbidities and complications are present in critically ill children with pneumonia.

A limitation of the present study is that it is a retrospective analysis based on the encrypted NHIRD. Thus, there was no detailed laboratory information on the organism causing the pneumonia. The causal organism may have influenced the severity of the disease, the complication rate, the need for invasive procedures, and the case fatality rate. A further multicenter hospital-based investigation that collects detailed laboratory data would be necessary to understand the influence of these factors.

In conclusion, in children diagnosed with pneumonia that requires an ICU admission, age is the most important factor in regard to incidence, requirement for invasive procedures, and survival. Children younger than 3 years had the highest number of episodes. Children aged 12–17 years old had the lowest number of episodes, but had the highest ratio of the need for invasive procedures and highest case fatality rate, compared to other age groups. Factors associated with the higher case fatality rate include an older presenting age (especially in children aged 12–17 years old), undergoing invasive procedures (e.g., ET/MV, CVC insertion, chest tube insertion/drainage, and ECMO), having underlying comorbidities (e.g., cerebral palsy, epilepsy, and congenital heart disease), and developing complications (e.g., respiratory failure, septicemia, and gastrointestinal hemorrhage).

Table 3 The top 10 associated diagnoses and odds ratios for case fatality among children with pneumonia who were admitted to an ICU in Taiwan (2006–2010)

Diagnosis	ICD-9-CM code	Total cases (<i>n</i>)	Case fatality (<i>n</i>)	OR	95% CI	<i>p</i>
Respiratory failure	518.8x	2296	304	7.04	5.87–8.46	<0.001
Cerebral palsy	343.x	2075	91	2.37	1.86–3.01	<0.001
Epilepsy	345.xx	1756	74	1.49	1.16–1.93	0.002
Septicemia	038.xx	1348	248	7.07	5.88–8.50	<0.001
Asthma	493.xx	1107	11	0.17	0.09–0.31	<0.001
Convulsions	780.3x	830	38	0.88	0.63–1.24	0.478
Pleural effusion	511.x	812	32	0.67	0.47–0.97	0.033
Congenital heart disease	745.xx	756	43	1.46	1.05–2.02	0.023
Volume depletion	276.5x	745	10	0.23	0.12–0.42	<0.001
Gastrointestinal hemorrhage	578.9	607	61	2.96	2.23–3.95	<0.001

CI = confidence interval; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ICU = intensive care unit; OR = odds ratio.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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