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RESEARCH

Temporal trend and factors associated with post-endoscopic retrograde cholangiopancreatography pancreatitis in children in the USA: a nationwide, retrospective cohort study

Ronghui Zhu[1] · Shengyong Wu[1] · Jinfang Xu[1] · Rui Wang[1] · Yi Cheng[1] · Yetao Xu[2] · Chenxin Chen[1] · Cheng Wu[1]

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Abstract

Pancreatitis is the most common adverse event following endoscopic retrograde cholangiopancreatography (ERCP). Meanwhile, the national temporal trend of post-ERCP pancreatitis (PEP) in children remains to be reported. The purpose of this study is to investigate the temporal trend and factors associated with PEP in children. We conducted a nationwide study using data from the National Inpatient Sample database during 2008–2017 and included all patients aged ≤ 18 years who underwent ERCP. The primary outcomes were temporal trends and factors associated with PEP. The secondary outcomes were in-hospital mortality, total charges (TC), and total length of stay (LOS). A total of 45,268 hospitalized pediatric patients who underwent ERCP were analyzed; of whom, 2043 (4.5%) were diagnosed with PEP. The prevalence of PEP decreased from 5.0% in 2008 to 4.6% in 2017 ($P = 0.0002$). In multivariable logistic analysis, adjusted risk factors of PEP were hospitals located in the West (aOR 2.09, 95% CI 1.36–3.20; $P < .0001$), bile duct stent insertion (aOR 1.49, 95% CI, 1.08–2.05; $P = 0.0040$), and end-stage renal disease (aOR 8.05, 95% CI 1.66–39.16; $P = 0.0098$). Adjusted protective factors of PEP were increasing age (aOR 0.95, 95% CI 0.92–0.98; $P = 0.0014$) and hospitals located in the South (aOR 0.53, 95% CI 0.30–0.94; $P < .0001$). In-hospital mortality, TC, and LOS were higher in patients with PEP than those without PEP.

Conclusion: This study shows a decreasing national trend over time and identifies multiple protective and risk factors for pediatric PEP. Endoscopists can use the insights from this study to evaluate relevant factors before performing ERCP in children to prevent PEP and reduce the medical-care burden.

What is Known:
- *Although ERCP has become indispensable procedure in children as they are in adults, education and training programs for ERCP in children are underdeveloped in many countries.*
- *PEP is the most common and most serious adverse event following ERCP. Research on PEP in adults showed rising hospital admission and mortality rates associated with PEP in the USA.*

What is New:
- *The national temporal trend of PEP among pediatric patients in the USA was decreasing from 2008 to 2017.*
- *Older age was a protective factor for PEP in children, while end-stage renal disease and stent insertion into the bile duct were risk factors.*

Keywords Endoscopic retrograde cholangiopancreatography · Biliary tract · Pancreatitis · Nationwide study · Children · Prevalence

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Ronghui Zhu and Shengyong Wu contributed equally to this study.

✉ Cheng Wu
wucheng@smmu.edu.cn

[1] Department of Military Health Statistics, Naval Medical University, No. 800 Xiangyin Road, Shanghai 200433, China

[2] Department of Rehabilitation, Children's Hospital of Fudan University, No. 399 Wanyuan Road, Shanghai 201102, China

Abbreviations

aOR	Adjusted odds ratio
CI	Confidence interval
ERCP	Endoscopic retrograde cholangiopancreatography
HCUP	Healthcare Cost and Utilization Project
ICD-9-CM	International Classification of Diseases, 9th revisions-Clinical Modification

ICD-10-CM	International Classification of Diseases, 10th revisions-Clinical Modification
IQR	Interquartile range
LOS	Length of stay
NIS	National Inpatient Sample
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PEP	Post-ERCP pancreatitis
TC	Total charges

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic procedure required for the management of pancreatic and biliary diseases in adults and children [1]. ERCP has been performed for adults since the 1960s [2], while the first successful ERCP performed on a child using the standard adult cannulating instrument was reported in 1976 [3]. Meanwhile, magnetic resonance cholangiopancreatography has largely replaced diagnostic ERCP to avoid post-ERCP pancreatitis (PEP); therefore, mainly therapeutic interventions are performed with ERCP in the pancreaticobiliary tract [4, 5]. PEP is the most common adverse event after ERCP, which can lead to a significant increase in mortality and healthcare costs, with the prevalence ranging from 1.6 to 10.9% among children [6–10]. Some single-center studies explored the factors associated with PEP in children; however, the national temporal trend of PEP in pediatric patients has never been reported [6, 11]. Barakat et al. conducted a national study using data from the National Inpatient Sample (NIS) and National Readmission Database to analyze the outcome and utilization trends over time in children, which was focused on ERCP indications, utilization, and readmissions; they used the updated data until 2014 [12]. Herein, we present our nationwide analysis of children undergoing ERCP in the USA using the NIS database from 2008 to 2017 to investigate the temporal trend and factors associated with PEP in those children.

Materials and methods

Study design and data source

A nationwide, retrospective cohort study was conducted using data from the NIS database from 2008 to 2017. The NIS has been developed by the Agency for Healthcare Research and Quality for the Healthcare Cost and Utilization Project (HCUP) in the USA [13]. It is the largest public database of all-payer inpatient care data that is used to estimate the regional and national costs of inpatient utilization, access, charges, quality, and outcome, and contains data on 7 million hospital stays, capturing approximately 20% of all inpatient hospitalizations in the USA [14]. The HCUP comprised the quality-control procedures to assess data quality and edit individual data sources [15], which enables the accurate and reliable estimation based on the NIS database. Several articles about ERCP using the NIS database have been published in authoritative magazines [16–18]. Because the NIS databases were deidentified for public availability, our study was exempted from the requirement of institutional review board approval.

Study population

The study population included all children aged ≤ 18 years who underwent ERCP. The procedures were identified using the International Classification of Diseases, 9th and 10th revisions-Clinical Modification (ICD-9-CM and ICD-10-CM) diagnostic and procedural codes (Supplementary Table 1).

Outcomes

Our primary outcomes were the temporal trend and factors of PEP in children, and secondary outcomes were in-hospital mortality, total charges (TC), and total length of stay (LOS). TC was adjusted for inflation to currency rates ($) of 2017. To distinguish PEP from acute pancreatitis at admission, we followed the methodology described in prior studies [19–21]. Patients with a primary or secondary diagnosis of acute pancreatitis were deemed as not associated with ERCP to avoid confusion. Conversely, patients diagnosed with acute pancreatitis that was not a primary or secondary diagnosis were considered PEP.

Study variables

Demographic variables included age (years), age groups (0–4, 5–9, 10–13, and 14–18 years), sex (male/female), and race (race/ethnicity: White, Black, Hispanic, Asian/Pacific Islander, Native American, and other). Patient-associated variables comprised median household income (first quartile-fourth quartile), primary expected payer (Medicare, Medicaid, private insurance, self-pay, or other), and admission day (Monday–Friday, Saturday–Sunday). Hospital-related variables included bed size (small/medium/large), location status (rural/urban), teaching hospital, and hospital region (Northeast, Midwest, South, and West). The diagnosis parameters included chronic pancreatitis, biliary obstruction, cholangitis, and choledocholithiasis. ERCP-related parameters included ERCP type (diagnostic or therapeutic), dilation of the ampulla and biliary duct, sphincterotomy and papillotomy, stent insertion into the bile duct, removal of the stone from the biliary tract, and all stents insertion into the pancreatic duct. Comorbidity variables included end-stage renal disease, obesity, hypertension, diabetes mellitus, non-alcoholic fatty liver disease, acute kidney injury, asthma, and Sickle cell disease. Even the discharge weight and hospital stratum data were retrieved from the NIS database, as well as the HCUP hospital identification number. The HCUP website [22] describes how an individual data element is coded in the NIS database and the uniform values, for example, bed size categories are based on hospital beds, and are specific to the hospital's location and teaching status.

Statistical analysis

Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All reported probability values (P-values) were 2-tailed, and statistical significance was considered when $P<0.05$. The sample size was estimated using 10 events per variable approach for the regression model [23], requiring about 290 PEPs or more. As the NIS contains sampling and weight variables that can be used to obtain national estimates, all results reported are weighted by NIS sampling weights. For quantitative variables, data were summarized as means with standard deviations or medians with interquartile ranges (IQR), and for categorical variables, data were summarized as frequency with percentage. The outcome variables were compared using t-tests or Wilcoxon signed-rank test, and the Rao-Scott χ^2 test of patients with and without PEP in the univariate analysis. The temporal trends for PEP prevalence were tested with the Cochran-Armitage trend test.

Multivariable logistic regression accounting for the survey design was applied to investigate the independent factors of PEP. Variables with $P \leq 0.2$ in univariate analysis were used for multivariable logistic regression analysis, in which unadjusted odds ratios (ORs), adjusted odds ratios (aORs), and corresponding confidence intervals (CIs) were calculated. For the adjusted model, we used Wang's model selection macros for complex survey data to conduct the model selection (stepwise method, SL entry = 0.05, SL stay = 0.05) [24]. A forest plot was also provided with this model.

Missing variables and sensitivity analysis

If a variable had ≥ 5% missing rates, we would impute the missing value before conducting multivariable logistic regression in the sensitivity analysis. This was the case for one variable, i.e., race, which had an 8.9% missing rate (Table 1). We imputed missing values using mode imputation (White race), and then used the same covariates and methods in the adjusted model to evaluate the robustness of our results.

Results

Patient demographics

This study analyzed 45,268 hospitalized pediatric patients who underwent ERCP during 2008–2017. Of them, 2043(4.5%) were diagnosed with PEP. A selection flow diagram of the target population is shown in Fig. 1. Most patients who underwent ERCP were aged 14–18 years, female, and of White or Hispanic race. More than 90% of the expected primary payers were Medicaid or private insurance. The baseline characteristics are summarized in Table 2.

Temporal trends of PEP

The overall PEP prevalence in children was 4.5%, and the temporal trend of PEP prevalence decreased from 5.0% in 2008 to 4.6% in 2017 ($P=0.0002$) (Fig. 2).

Mortality, TC, and LOS

Of 2043 pediatric patients with PEP, 16 (0.8%) died during hospitalization, compared with 0.1% of patients without PEP ($P=0.0325$). The mean TC of PEP patients was \$132,356 ± 12.384.7, which was higher than that of patients without PEP (\$65,768 ± 1833.3; $P<0.001$). The median LOS of patients with PEP was 5.4 (IQR: 3.2–10.2) days, which was higher than that of patients without PEP (3.2 days, IQR: 1.9–5.4 days; $P<0.001$, Table 2).

Multivariable analysis of factors associated with PEP

By multivariable logistic regression analysis, unadjusted risk factors associated with PEP were the 0–4-year-old age group (OR 2.61, 95% CI 1.51–4.50; $P=0.0090$) compared with the 14–18 age group, hospitals located in the West (OR 1.94, 95% CI 1.26–2.98; $P<0.0001$) compared with hospitals in the Northeast, insertion of stent into the bile duct (OR 1.47, 95% CI 1.07–2.02; $P=0.0178$), and end-stage renal disease (OR 6.41, 95% CI 1.11–37.16; $P=0.0382$). Unadjusted protective factors associated with PEP were increasing age (OR 3.49, 95% CI 1.87–6.52; $P<0.0001$) and hospitals located in the South (OR 0.51, 95% CI 0.29–0.90; $P<0.0001$). The results are shown in Table 3.

Table 1 Missing rate of variables in multivariable logistic regression

Variables	Missing rate (%)
Age	1.3
Age groups	1.3
Sex	1.0
Race	8.9

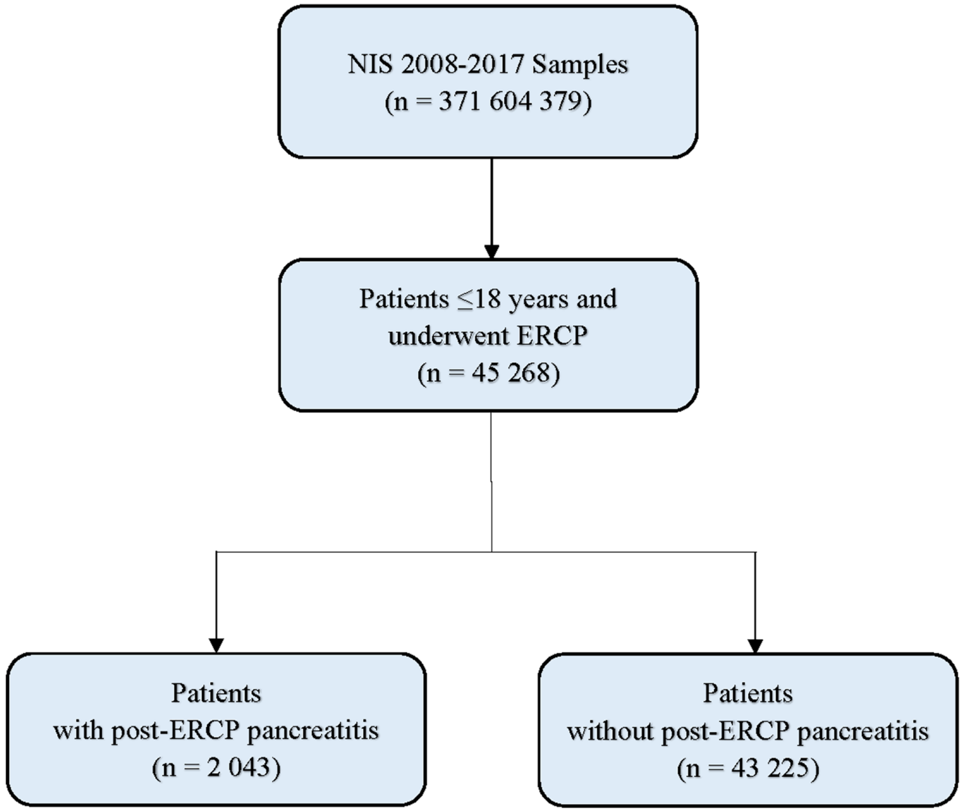

Fig. 1 Flow diagram of the target population

Adjusted risk factors associated with PEP were hospitals located in the West (aOR 2.09, 95% CI 1.36–3.20; $P<0.0001$), bile duct stent insertion (aOR 1.49, 95% CI, 1.08–2.05; $P=0.0040$), and end-stage renal disease (aOR 8.05, 95% CI 1.66–39.16; $P=0.0098$). Adjusted protective factors of PEP were increasing age (aOR 0.95, 95% CI 0.92–0.98; $P=0.0014$) and hospitals located in the South (aOR 0.53, 95% CI 0.30–0.94; $P<0.0001$). The results are summarized in Table 3 and Fig. 3. In the sensitivity analysis, the adjusted results were the same as above.

Discussion

In this nationwide, retrospective cohort study, we observed a decreasing prevalence of PEP in children of the USA during 2008–2017. We identified multiple risks and protective factors associated with PEP as well and noted that this is the first study to explore the national temporal trend of PEP in children.

Our study reported an overall prevalence of 4.5% for PEP in children, which is consistent with previous pediatric studies. The prevalence declined from 5.0% in 2008 to 4.6% in 2017; this downward trend may be beneficial because of several reasons. First, this may have stemmed from various mechanisms involving the interruption of biochemical reactions involved in proteolytic enzyme activation, acinar secretion impairment, autodigestion, and other key mechanisms that are central to the development of pancreatitis or pancreatic injury during ERCP, including damage from mechanical, thermal, chemical, hydrostatic, enzymatic, and microbiologic factors [25–27]. Second, the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), including diclofenac and indomethacin suppository to prevent PEP among adolescents as recommended by the European Society of Gastrointestinal Endoscopy, may have reduced the prevalence of PEP during the latter part of the study period. Third, the increase in the number of research studies on PEP prevention among children, which identified potential protective and risk factors of PEP, may have contributed to the declining prevalence [4, 6, 8, 11]. Therefore, these efforts would be useful for endoscopists to conduct pre-ERCP risk assessments.

We identified several protective and risk factors associated with PEP. Among the protective factors, older age of children was a protective factor for PEP, while a younger age was associated with higher PEP prevalence. Our result was in line with the report of Limketkai et al. [28], who reported a higher prevalence of PEP in the youngest (0–6) age group than in the 7–12- and 13–17-year-old age groups. The bile and pancreatic ducts are more vulnerable in younger children, and they have unique anatomical challenges in the small duodenal lumen, smaller papillary orifice, and narrow caliber pancreatic duct that present technical difficulties in the cannulation of the intended duct and other therapeutic

Table 2 Baseline characteristics of children underwent ERCP

Variables	PEP		*P* value
	Present [2043 (4.5%)]	**Absent [43,225 (95.5%)]**	
Age, years, median (IQR)	16 (12–17)	16 (14–18)	< .0001
Age groups (years)			0.0009
0–4	225 (11)	2045 (4.8)	
5–9	175 (8.6)	2427 (5.7)	
10–13	269 (13)	5632 (13)	
14–18	1374 (67)	32,544 (76)	
Sex			0.1832
Male	611 (30)	10,931 (26)	
Female	1432 (70)	31,816 (74)	
Race			0.1595
White	681 (35)	17,848 (45)	
Black	299 (15)	4907 (12)	
Hispanic	822 (42)	13,268 (34)	
Asian/Pacific Islander	47 (2.4)	802 (2.0)	
Native American	30 (1.5)	611 (1.6)	
Other	79 (4.0)	1847 (4.7)	
Median household income			0.0001
First quartile	555 (28)	13,351 (32)	
Second quartile	596 (30)	11,440 (27)	
Third quartile	498 (25)	9394 (22)	
Fourth quartile	363 (18)	8087 (19)	
Primary expected payer			0.9197
Medicare	15 (0.7)	199 (0.5)	
Medicaid	1017 (50)	22,092 (51)	
Private insurance	853 (42)	17,039 (39)	
Self-pay	83 (4.1)	2055 (4.8)	
Other	76 (3.7)	1814 (4.2)	
Admission day			0.8904
Monday–Friday	1593 (78)	33,496 (78)	
Saturday–Sunday	451 (22)	9720 (22)	
Bed size of hospital			0.4602
Small	157 (7.7)	3911 (9.1)	
Medium	372 (18)	9180 (21)	
Large	1509 (74)	29,908 (70)	
Location status of hospital			0.7065
Rural	80 (3.9)	1456 (3.4)	
Urban	1959 (96)	41,542 (97)	
Teaching hospital	1427 (73)	31,510 (76)	0.3978
Region of hospital			< .0001
Northeast	304 (15)	7077 (16)	
Midwest	330 (16)	8514 (20)	
South	319 (16)	14,578 (34)	
West	1090 (53)	13,056 (30)	
Chronic pancreatitis	56 (2.7)	1318 (3.1)	0.7779
Biliary obstruction	149 (7.9)	2217 (5.1)	0.2275
Cholangitis	76 (3.7)	1399 (3.2)	0.7349
Choledocholithiasis	1136 (56)	25,591 (59)	0.3276
ERCP type			0.0945
Diagnostic	95 (4.7)	3182 (7.4)	
Therapeutic	1948 (95)	40,043 (93)	
Dilation of ampulla and biliary duct	234 (11)	4740 (11)	0.6944
Sphincterotomy and papillotomy	1464 (72)	29,987 (69)	0.5136
Insertion of stent into the bile duct	681 (33)	10,979 (25)	0.0165
Removal of the stone from biliary tract	1085 (53)	25,543 (59)	0.0994

Table 2 (continued)

Variables	PEP		*P* value
	Present [2043 (4.5%)]	**Absent [43,225 (95.5%)]**	
Stent insertion into pancreatic duct	472 (23)	8899 (21)	0.4626
End-stage renal disease	15 (0.7)	50 (0.1)	0.0173
Obesity	91 (4.5)	1061 (2.5)	0.0881
Hypertension	86 (4.2)	1255 (2.9)	0.3526
Diabetes mellitus	35 (1.7)	697 (1.6)	0.8687
Nonalcoholic fatty liver disease	74 (3.6)	1118 (2.6)	0.3232
Acute kidney injury	35 (1.7)	450 (1.0)	0.2870
Asthma	150 (7.3)	4076 (9.4)	0.3514
Sickle cell disease	73 (3.6)	1358 (3.1)	0.7469
In-hospital mortality	16 (0.8)	49 (0.1)	0.0325
TC, $, $\overline{X} \pm$ **Std**	132,356 ± 12,384.7	65,768 ± 1833.3	< .0001
LOS, d, median (IQR)	5.4 (3.2–10.2)	3.2 (1.9–5.4)	< .0001

TC were adjusted for inflation to currency rates ($) of 2017, ERCP endoscopic retrograde cholangiopancreatography, *IQR* interquartile range, *LOS* length of stay, *PEP* post-ERCP pancreatitis, *TC* total charges

interventions. Among the risk factors, we identified end-stage renal disease as a risk factor for PEP, which has not been recognized as a risk factor in children until now but is a risk factor for adults [21]. Its association with higher PEP may be due to papillary edema from fluid overload, which causes difficult biliary cannulation [29]. Even stent insertion into the bile duct was concluded as a procedure-related risk factor. No previous study has reported any association

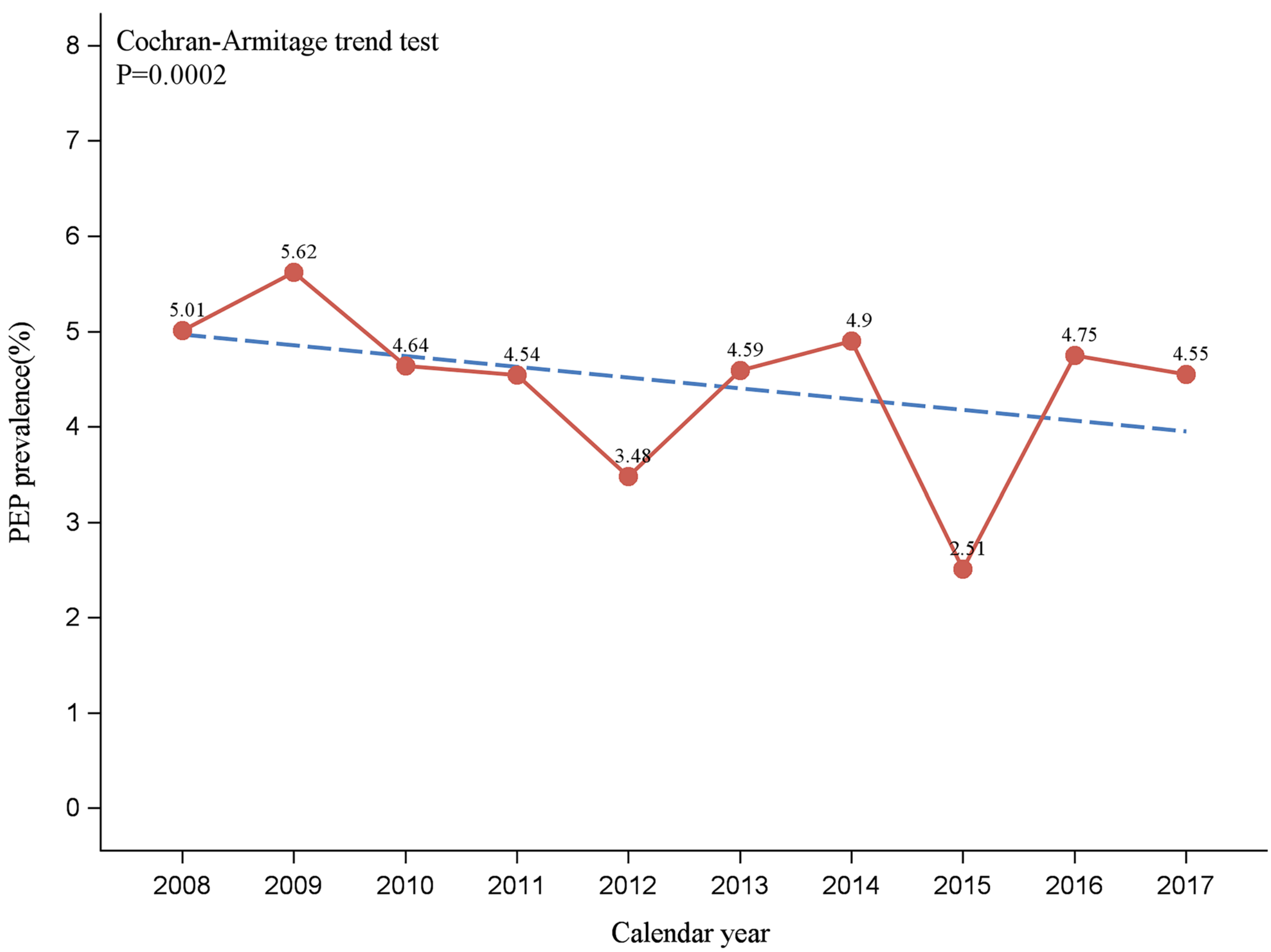

Fig. 2 Temporal trend of PEP prevalence

Table 3 Multivariable logistic regression results of factors associated with PEP

Variables	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age (years)	0.95 (0.92–0.98)	0.0008	0.95 (0.92–0.98)	0.0014
Age groups (years)				
0–4	2.61 (1.51–4.50)	0.0090		
5–9	1.71 (0.99–2.93)	0.5607		
10–13	1.13 (0.72–1.77)	0.1170		
14–18	Reference			
Sex				
Male	Reference			
Female	0.80 (0.58–1.11)	0.1839		
Race				
White	Reference			
Asian/Pacific Islander	1.53 (0.44–5.31)	0.7989		
Black	1.59 (0.97–2.62)	0.4526		
Hispanic	1.62 (1.13–2.34)	0.3187		
Native American	1.29 (0.39–4.27)	0.9398		
Other	1.12 (0.52–2.41)	0.6058		
Region of hospital				
Northeast	Reference		Reference	
Midwest	0.90 (0.54–1.52)	0.6497	0.95 (0.56–1.59)	0.6702
South	0.51 (0.29–0.90)	0.0004	0.53 (0.30–0.94)	0.0004
West	1.94 (1.26–2.98)	< .0001	2.09 (1.36–3.20)	< .0001
Median household income				
First quartile	Reference			
Second quartile	1.08 (0.70–1.68)	0.6945		
Third quartile	1.25 (0.83–1.88)	0.5013		
Fourth quartile	1.28 (0.81–2.01)	0.4734		
ERCP type				
Diagnostic	Reference			
Therapeutic	1.62 (0.92–2.87)	0.0964		
Insertion of stent into the bile duct	1.47 (1.07–2.02)	0.0178	1.49 (1.08–2.05)	0.0145
Removal of the stone from Biliary tract	0.78 (0.59–1.05)	0.1012		
End-stage renal disease	6.41 (1.11–37.16)	0.0382	8.05 (1.66–39.16)	0.0098
Obesity	1.85 (0.90–3.80)	0.0932		

aOR adjusted odds ratio, *CI* confidence interval, *ERCP* endoscopic retrograde cholangiopancreatography, *OR* odds ratio, *PEP* post-ERCP pancreatitis

between biliary stent insertion and higher prevalence of PEP in children. However, in the adult population, several studies have found that biliary stent placement is associated with a high prevalence of PEP [30, 31]; this happens because biliary stent placement oppresses the orifice of the main pancreatic duct or common channel, which obstructs the pancreatic duct [32].

We also found associations between hospital locations and the PEP prevalence; hospitals located in the South were associated with a lower prevalence of PEP, while hospitals located in the West were associated with higher PEP prevalence in the USA. One study on adults with PEP that used the NIS database obtained similar results as ours [21], but they did not explain their results. To determine the possible reasons behind this result, we conducted an exploratory analysis. We found that the number of ERCP procedures and the proportion of teaching hospitals in the South region were both high, while in the West, the number of teaching hospitals was low even though a higher number of ERCP procedures had been conducted. Therefore, we ascribed that the number of ERCP procedures and that of teaching hospitals in different regions may be attributed for our obtained result.

In our study, the overall post-ERCP mortality was 0.14%, which was similar to that reported by Barakat et al. (0.1%) [12]. The mortality, TC, and LOS of PEP patients were significantly higher than those without PEP, which meant that PEP would result in higher mortality and more medical burden for children. Based on these results, we consider it

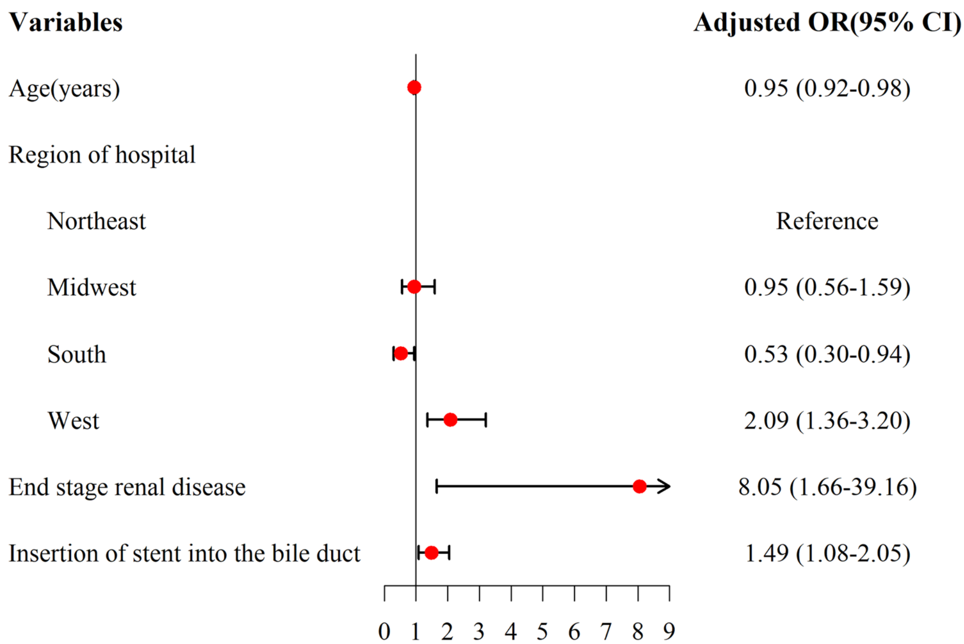

Fig. 3 Adjusted factors of PEP

critical for endoscopists to provide extensive care for preventing PEP and adopt appropriate clinical practice methods. Several studies have explored methods for preventing PEP in adults, including the assessment of patient-related factors, procedural techniques for prevention, and chemoprevention with NSAIDs. However, for children, especially non-adolescents, the effective chemoprevention of PEP has been seldom reported. Troendle et al. provided some encouragement that intravenous ibuprofen might help prevent PEP in children, but their evidence was very weak regarding the reduced rates of PEP with NSAIDs [33]. Therefore, assessing patient-related and procedure-related factors may most effectively prevent PEP in children.

Our study had several limitations. First, although ICD codes used for defining PEP were used by several previous studies, the methodology has not been validated. And potential coding errors in the database were inevitable. However, due to the large sample size of the NIS, these errors might be random. Second, because NIS was not specifically designed for our research, we were unable to analyze some uncollected covariates, such as use of NSAIDs, aggressive hydration, and prophylactic pancreatic duct stents. The frequencies of these means to decrease PEP may differ between younger and older children (especially adolescents), and may differ in Southern and Western hospital practices, which may contribute to differences in PEP rates between these groups. Third, we were unable to obtain detailed information on ERCP procedures and characteristics of endoscopists, such as which duct was intended to be treated, whether there were difficult cannulation situations, and qualifications of endoscopists, which might affect PEP rates. Further prospective and multicenter studies are warranted. Finally, the database does not capture patients who develop PEP after discharge; therefore, we may have underestimated the prevalence of PEP in children during the study period.

In conclusion, our study shows a decreasing temporal trend and identifies multiple protective and risk factors for PEP in children from 2008 to 2017. This study may help endoscopists evaluate the relevant protective and risk factors before performing ERCP in children to prevent PEP and reduce the associated healthcare economic burden.

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Authors' Contributions Ronghui Zhu and Shengyong Wu designed the research, had full access to the data, conducted all analyses, and wrote the draft of this paper. Jinfang Xu, Rui Wang, Yi Cheng, Yetao Xu, and Chenxin Chen revised the article critically. All the authors contributed to the manuscript writing, read, and approved the final manuscript. Cheng Wu was the guarantor.

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Data availability The data used in the study is publicly available.

Declarations

Ethical approval Because the NIS databases were deidentified for public availability, our study was exempted from the requirement of institutional review board approval.

Conflict of interest The authors declare no competing interests.

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