Pediatric RESEARCH

REVIEW ARTICLE

Etiology, case fatality, recurrence, and severity in pediatric acute pancreatitis: a meta-analysis of 48 studies

Guo Tian[1,2], Lu Zhu[1], Shuochun Chen[1], Qiyu Zhao[1,2] and Tian'an Jiang[1,2]

For children, there are very few published reviews focusing on severe acute pancreatitis (AP). PubMed, EMBASE, Web of Science, Scopus, Chinese National Knowledge Infrastructure (CNKI), Wanfang data, EBSCO, and Cochrane Library were searched from inception until March 2020. Meta-regression analyses were used to estimate the etiology, case fatality, recurrence, and severity of pediatric AP in different regions (North America, Asia, South America, Europe, and Oceania). Pooled data from 47 papers (48 studies) found that main causes of pediatric AP were gallstones in Asia; trauma in Oceania; and idiopathic in Europe, North America, and South America. The case-fatality rate (CFR) of pediatric AP is 4.7% (North America), 6.2% (Europe), 2.4% (Asia), 3.1% (South America), and 7.4% (Oceania). The incidence rates of recurrent acute pancreatitis (RAP) in children who have had an episode of acute pancreatitis in North American, Asia, and Europe were 15.3, 13.1, and 13.8%, respectively. The incidence of severe acute pancreatitis (SAP) in different regions was 30.3% (Oceania), 29.2% (South America), 20.8% (Europe), 15.8% (Asia), and 13.7% (North America). It suggests that physicians should notice the etiology of pediatric AP for the initial assessment, diagnosis, prediction of relapse, and appropriate treatment at a later stage.

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IMPACT:

- It indicates the etiology of pediatric acute pancreatitis for the initial assessment, diagnosis, and prediction of relapse.
- Main causes of pediatric AP were gallstones in Asia; trauma in Oceania; and idiopathic in Europe, North America, and South America. The case-fatality rate of pediatric AP is diverse worldwide.
- It suggests that physicians noticed the etiology of pediatric AP for the initial assessment, diagnosis, prediction of relapse, and appropriate treatment at a later stage.

INTRODUCTION

Acute pancreatitis (AP) is a rare disease among children,[1] characterized by the appearance of inflammatory cells and inducing reversible structural and functional changes within a short duration.[2] The yearly incidence of pediatric AP has increased in decades, approximately 3–13 cases per 100,000 children per year.[3] Recently, many management strategies were based on evidence in adults, but there was a lack of pediatric-specific management options. It was beneficial to find high-risk patients by knowledge of the etiology of pediatric AP and helpful for interventions to improve treatment by its potential pathogenesis. In a previous study, it was reported that there were obvious differences in the etiology of AP among different regions and AP-associated case-fatality rate (CFR) was rising with age in adults. This rate was rapidly elevated above the age of 59 years.[4] But for children, the etiology, case fatality, and recurrence rates of AP were still widely various in the existing publication. In particular, there were very few published reviews focusing on severe acute pancreatitis (SAP) in children. The summary of pediatric AP in different regions about etiology, case fatality, recurrence rates, and SAP was especially lacking. We therefore carried out this systematic review and meta-analysis to estimate the epidemiology of developing pediatric AP in terms of the etiology, case fatality, recurrence, and severity rates in different regions (North America, Asia, South America, Europe, and Oceania).

METHODS

Literature search

We conducted this systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[5] Eight electronic databases, including PubMed, EMBASE, Web of Science, Scopus, CNKI, Wanfang data, EBSCO, and Cochrane Library, were searched for studies published without language restrictions from database inception to March 2020. The search strategy is detailed in the Appendix Text using terms such as acute pancreatitis, children, pediatric, juvenile, teenager, adolescent, etiology, pathogeny, recurrent, relapse, case fatality, mortality, and death. Titles and abstracts were independently checked for potential suitability by two individuals. We resolved any disagreement of investigators through discussion. Additional search was performed using the bibliographies of the included studies and related systematic reviews.

[1]Department of Ultrasound Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China and [2]Zhejiang Provincial Key Laboratory of Pulsed Electric Field Technology Medical Transformation, Hangzhou, Zhejiang, China
Correspondence: Tian'an Jiang (tiananjiang@zju.edu.cn)

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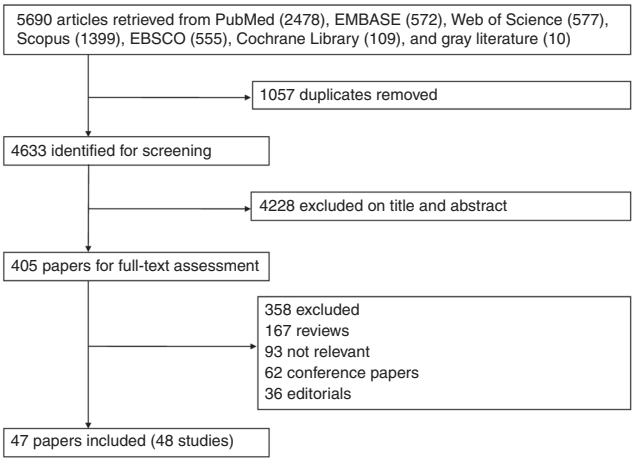

Fig. 1 Flowchart depicting the selection process of included studies for the meta-analysis. A total of 5643 papers were removed and 47 papers including 48 studies were finally enrolled in this meta-analysis.

Selection of studies for inclusion in the review

Studies were eligible with the following characteristics. (1) Pediatric patients aged 0–18 years with AP. (2) Outcome: the epidemiology of the etiology, case fatality, recurrence, or severity rates. (3) To be included, there was a minimum observational size of ten cases for inclusion studies. Exclusion criteria were as follows: (1) only abstract or posters and (2) if multiple studies were retrieved with overlapping cohorts, the latest study was included. Eligibility assessment was conducted by two investigators to check appropriateness for inclusion in the final analysis, with disagreements arbitrated through a third investigator.

Data extraction and quality assessment

Two independent investigators extracted data from each included study, such as author, country, study period, gender, age, and the number of pediatric AP. Severe pancreatitis was defined as a sum of the scores between 6 and 10 points with Ranson's Criteria.[6] The outcomes were assessed via the epidemiology of the etiology, case fatality, recurrence, and SAP in children. For observational studies, the Newcastle–Ottawa Scale (NOS) was used to evaluate bias in studies across three dimensions, including selection, comparability, and outcome. A study was recorded as high quality if it scored 7 out of 9 and medium when the score achieved 5.[7]

Statistical analysis

Through Stata 12.0 (StataCorp LLC), a random-effects model was used for estimating the incidence rate of case fatality, recurrence, and SAP of pediatric AP in this study due to significant heterogeneity between the studies. The incidence rate of etiology was presented graphically on the *y* axis and specific etiology on the *x* axis using the Microsoft Excel 2016 and R softwares. The random-effects meta-regression analyses for outcomes were applied to estimate the potential sources of heterogeneity, for example, age. Between-study heterogeneity was appraised using I^2 and Cochran's *Q* test.[8] The I^2 values of 25, 50, and 75% indicated the low, moderate, and high degree of heterogeneity, respectively. Publication bias for exploring small-study effects was assessed by Egger's test.[9] We evaluated the overall certainty in pooled effect estimates using Grading of Recommendations, Assessments, Development and Evaluation (GRADE),[10] which estimated quality of evidence by analyzing its risk of bias, imprecision, inconsistency, indirectness, and publication bias.

RESULTS

The review process and characteristics of included studies

The search verified 5690 possibly eligible articles. Based on further assessment, 5643 studies were excluded, and the study selection flow diagram is shown in Fig. 1. As a result, a total of 47 papers including 48 studies met the inclusion criteria and were finally enrolled in this meta-analysis.[11–57] Table 1 described the characteristics of the included studies. All these selected papers were published after 2005, in which the study period ranged from 1976 to 2017. The sample size for each study varied from 11 to 2127, with a total of 8873 patients.

Risk of bias assessment and certainty of evidence

Through NOS quality assessment, the risk of bias assessment for the included studies is listed in Table 1 and Supplemental Table 1, showing medium-to-high quality with scores of 4–8. Using GRADE approach, the overall certainty of evidence supporting the etiology, case fatality, recurrence, and SAP in pediatric AP was rated moderate.

The etiology of the AP

The main causes of pediatric AP resulted from trauma, systemic disease, alcohol, medication, genetics, gallstones, infection, post-endoscopic retrograde cholangiopancreatography, idiopathic, anatomic anomalies, oncology, and metabolic disease. However, these factors differed among various continents (Fig. 2). The top three causes in different continents were gallstones (33%), systemic disease (31%), and infection (29%) in Asia; trauma (32%), idiopathic (25%), systemic disease (16%), and infection (16%) in Oceania; idiopathic (26%), systemic disease (13%), and infection (13%) in Europe; idiopathic (25%), systemic disease (16%), alcohol (16%), medication (16%), genetics (16%), gallstones (16%), and infection (16%) in North America; idiopathic (29%), medication (19%), and anatomic anomalies (15%) in South America. Gallstones were present in 33% of children with AP in Asia while trauma was the main cause (32%) in Oceania. The main etiology of pediatric AP, accounting for 25–29% of all cases, was idiopathic pancreatitis, which had the highest incidence in Europe, North America, and South America.

The prevalence of the AP-related death

The overall pooled prevalence of the pediatric AP-related death in children from 30 studies based on 7347 samples was 3.9% (95% confidence interval (CI), 3.5–4.4), with significant heterogeneity present ($I^2 = 100\%$; $p = 0$). According to region groups, they showed various prevalence of pediatric AP-related death as 4.7% (95% CI, 4–5.4), 6.2% (95% CI, 3.7–8.7), 2.4% (95% CI, 1.9–2.9), 3.1% (95% CI, 0.1–6), and 7.4% (95% CI, 5–9.8) in North America, Europe, Asia, South America, and Oceania, respectively (Fig. 3). In meta-regression analysis, after adjusting for correlated incidence data and controlling for ages, it indicated that there was no significant correlation between mean age and CFR of pediatric AP ($tau^2 = 0.001$, $p = 0.159$; Supplemental Fig. 1). The solid line showed the weighted regression line according to variance-weighted least squares. The inner and outer lines displayed the 95% CI. The area of each circle was proportional to the inverse variance of CFRs (Fig. 3).

The prevalence of pediatric recurrent AP (RAP)

There were 23 studies reporting the prevalence of pediatric ARP, with pooled data of 13.9% (95% CI, 12.5–15.3). According to region groups, they showed similar prevalence of pediatric AP recurrence as 15.3% (95% CI, 12.5–18.1), 13.1% (95% CI, 11.1–15.1), and 13.8% (95% CI, 11.1–16.5) in children who underwent an episode of AP in North America, Asia, and Europe, respectively (Fig. 4). Through univariate meta-regression analysis, a trending positive association ($tau^2 = 0.006$, $p = 0.530$) was detectable between mean age of study population and recurrence rate (Supplemental Fig. 2).

Table 1. Summary of the included studies.

Study	Country	Study period	Gender (M/F)	Age (mean ± sd)	Number of pediatric AP	NOS score
Vitale et al. 2019	United States	2013.3–2017.1	62/56	13.56 ± 13.47	118	6
Nauka et al. 2019	United States	2011.12–2016.3	46/33	14 ± 1.63	79	5
Vidal et al. 2019	Italy	NA	9/3	7.9 ± 5.19	12	5
Galai et al. 2019	Israel	1995.1–2016.6	56/61	13.2 ± 6.59	117	7
Cheng et al. 2019	China	2000–2013	1066/1061	11.91 ± 5.38	2127	8
Sweeny et al. 2019	United States	2003.3–2009.12	60/55	13.5 ± 1.65	115	7
Zheng et al. 2018	China	2012.1–2017.8	52/59	8.24 ± 3.3	111	6
Sag et al. 2018	Turkey	2005.1–2016	31/32	9.6 ± 4.8	63	6
Izquierdo et al. 2018	Colombia	2010–2015	49/81	12 ± 5	130	7
Grzybowska Chlebowczyk et al. 2018	Poland	2004.1–2013.12	36/40	12.07	76	6
Alabdulkareem et al. 2018	Saudi Arabia	NA	26/24	11.6	50	5
Suzuki et al. 2017	Japan	1986.1-2014.5	63/68	7.7 ± 4.3	131	6
Grover et al. 2017	United States	2010.1–2010.12	25/25	14 ± 7.41	50	6
Bierma et al. 2016	Australia	2000.1–2011.7	90/75	12.5 ± 4.74	165	7
Abu el haija et al. 2016	United States	2014.5–2014.12	12/26	13.95 ± 3.43	38	5
Hashimoto et al. 2016	Japan	2002–2012	15/18	6 ± 5.19	33	5
Hao et al. 2016	China	2003–2004	NA	6.16 ± 3.35	159	5
Majbar et al. 2016	United Kingdom	2013.4–2014.4	48/46	11.2 ± 3.4	94	6
Suzuki et al. 2015	Japan	1985–2011	57/88	7.3 ± 4.05	145	6
(a) Goday et al. 2015	United States	2009.7–2013.6	165/166	12 ± 1.85	331	6
(b) Goday et al. 2015	United States	2009.7–2013.6	820/875	11.5 ± 2.43	1695	6
Bolia et al. 2015	India	2001.1–2011.12	61/25	12	87	6
Terlizzi et al. 2014	Italy	2002.12–2012.12	79/106	11.4 ± 5.3	185	5
Guo et al. 2014	China	2002.1–2012.7	178/193	14.05	371	6
Boskovic et al. 2014	Serbia	2010.1–2013.7	15/21	10.08 ± 4.65	36	6
Antunes et al. 2014	Portugal	2010.1–2013.8	15/22	15 ± 2.5	37	5
Kim et al. 2013	Korea	2004.1–2012.12	17/10	9.3 ± 8.44	27	6
Javid et al. 2013	India	2000–2009	71/85	8.4 ± 1.5	156	6
Fabre et al. 2012	France	2003.1–2007.12	23/25	11.08 ± 12.88	48	5
Lautz et al. 2012	United States	2000–2009	NA	12.3	211	6
Chang et al. 2011	China	1993.9–2008.8	NA	8.5 ± 12.47	180	7
Zhu et al. 2011	China	2003.3–2009.12	67/54	6.82 ± 3.38	121	6
Park et al. 2009	United States	1994–2007	86/129	13.1 ± 5.6	215	6
Li et al. 2008	China	2005.5–2007.6	40/31	7.14 ± 3.38	71	5
Kandula et al. 2008	United States	1995.1–2004.12	45/42	1.67 ± 0.72	87	6
Nydegger et al. 2007	Australia	1993–2002	163/116	10 ± 3.93	279	5
Chen et al. 2006	China	1992–2002	36/39	10	75	5
Stringer et al. 2005	United Kingdom	1994.1–2004.1	19/14	12.8 ± 3	33	5
Laugel et al. 2005	France	1996.1–NA	7/4	10.14 ± 3.6	11	4
Alvarez Calatayud et al. 2003	Spain	NA	16/15	7.9 ± 3.25	31	5
Choi et al. 2003	Korea	1994.3–1999.3	NA	7.18 ± 4.16	56	6
Werlin et al. 2003	United States	1996.1–2001.12	83/97	12.5	180	6
Tiao et al. 2002	China	1986.7–2000.6	39/22	8.8 ± 4.8	61	5
Pezzilli et al. 2002	Italy	1998–1999	25/25	10.5 ± 3.75	50	6
DeBanto et al. 2002	United States	1976.4–2004.12	126/175	9.06 ± 1.27	301	6
Berney et al. 1996	Switzerland	1979.4–1993.3	9/12	10.8 ± 3.5	21	5
Yeung et al. 1996	China	1983–1992	23/20	9	43	5
Weizman et al. 1988	Canada	1978–1984	5/56	10.2	61	6

AP acute pancreatitis, *NA* not available, *NOS* Newcastle–Ottawa Scale.

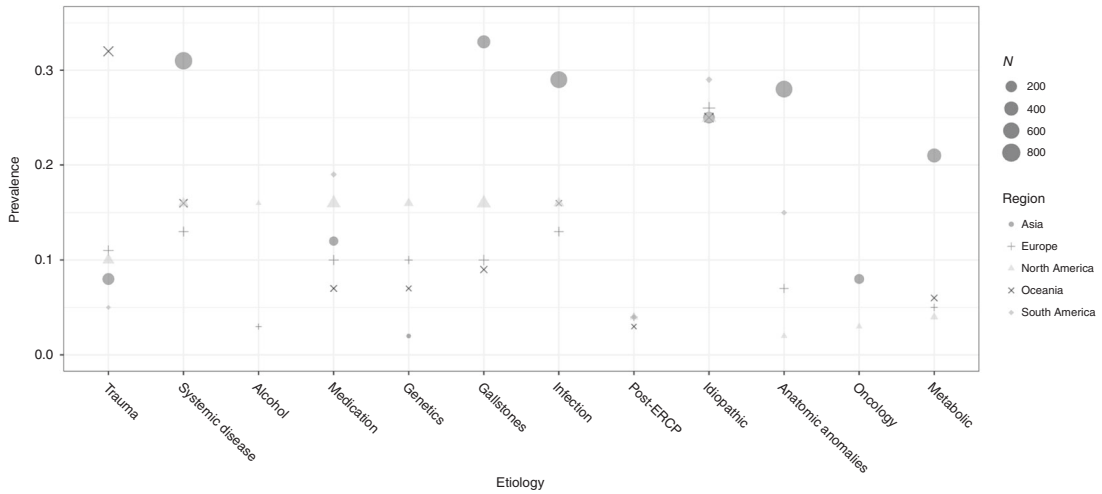

Fig. 2 The epidemiology of etiology of pediatric AP in different regions. The top three causes in different continents were gallstones (33%), systemic disease (31%), infection (29%) in Asia, trauma (32%), idiopathic (25%), systemic disease (16%), infection (16%) in Oceania, idiopathic (26%), systemic disease (13%), infection (13%) in Europe, idiopathic (25%), systemic disease (16%), alcohol (16%), medication (16%), genetics (16%), gallstones (16%), infection (16%) in North America, idiopathic (29%), medication (19%), anatomic anomalies (15%) in South America.

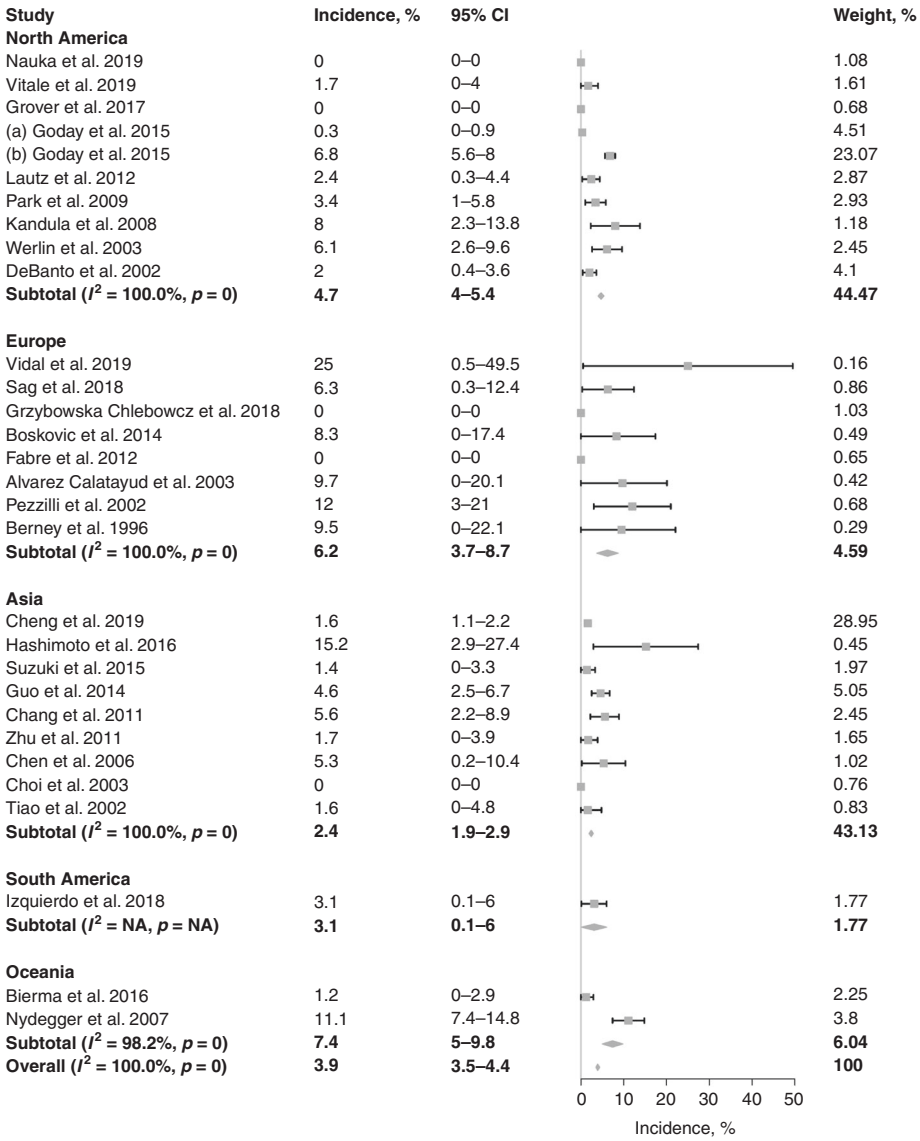

Fig. 3 Forest plot of case-fatality rates of pediatric AP in different regions. They showed various prevalence of pediatric AP-related death 4.7% (95% CI, 4 to 5.4), 6.2% (95% CI, 3.7 to 8.7), 2.4% (95% CI, 1.9 to 2.9), 3.1% (95% CI, 0.1 to 6), and 7.4% (95% CI, 5 to 9.8) in North America, Europe, Asia, South America, and Oceania, respectively.

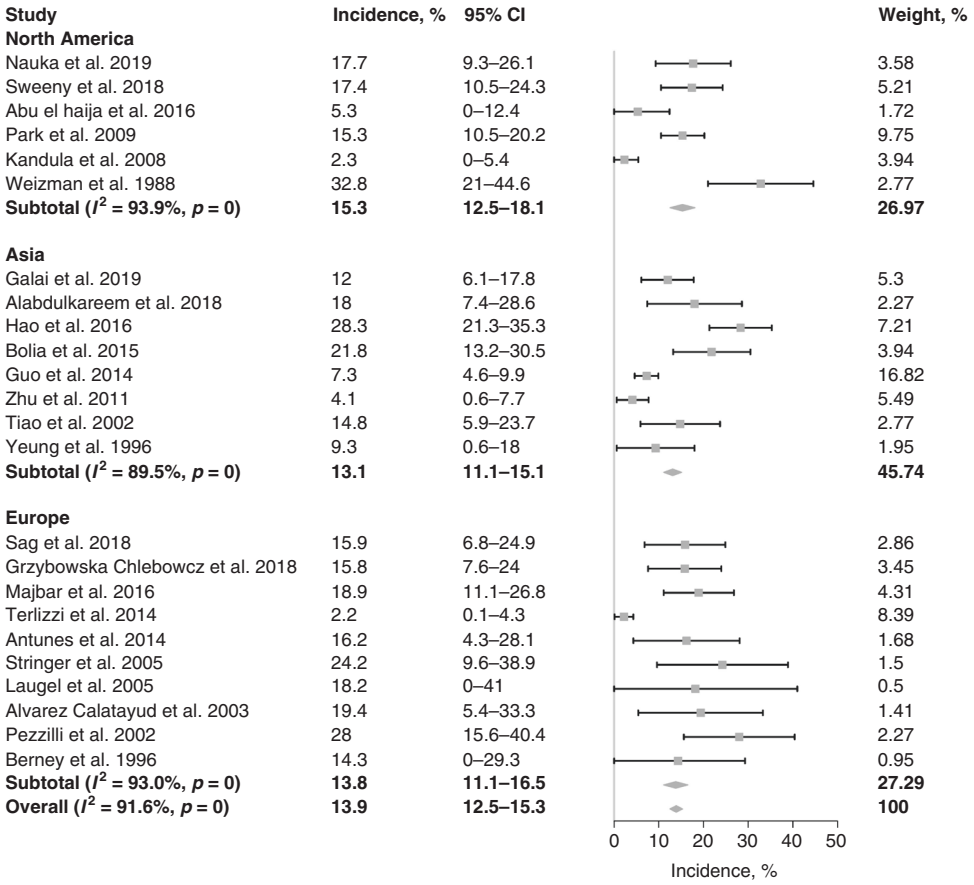

Fig. 4 Forest plot of acute recurrent pancreatitis rates of pediatric AP in different regions. They showed similar prevalence of pediatric AP recurrence 15.3% (95% CI, 12.5 to 18.1), 13.1% (95% CI, 11.1 to 15.1), 13.8% (95% CI, 11.1 to 16.5) in children who underwent an episode of acute pancreatitis in North America, Asia, and Europe, respectively.

The prevalence of pediatric SAP

The prevalence of pediatric SAP was reported in 24 studies, with pooled data of 17.2% (95% CI, 15.8–18.6). According to region groups, they had similar prevalence of pediatric SAP as 13.7% (95% CI, 11.5–15.9), 15.8% (95% CI, 13.8–17.8), 29.2% (95% CI, 21.4–37), 20.8% (95% CI, 16.2–25.5), and 30.3% (95% CI, 23.3–37.3) in North America, Asia, South America, Europe, and Oceania, respectively (Fig. 5). Heterogeneity assessment via meta-regression analyses showed that the age was not the main contributor ($tau^2 = 0.015$, $p = 0.442$) to the high between-study variability (Supplemental Fig. 3).

Assessment of sensitivity analysis and publication bias

No significant changes were detectable based on each outcome when any one study was removed. Egger's regression asymmetry tests were performed to evaluate publication bias for the prevalence of the case fatality, recurrence, and SAP of pediatric AP. There was significant publication bias in them, with p values of <0.01.

DISCUSSION

The incidence of AP in children is gradually increasing in recent years, which was close to that of adults.[58,59] AP could develop into chronic pancreatitis after several months to years. In the late-stage disease, pancreatic structural changes, pain, and pancreatic exocrine or endocrine insufficiency appear to be irreversible, depending on the etiology.[60] Moreover, there was also a clear correlation between the cause of AP and case fatality.[61] For the different etiology, the treatment of pediatric AP is also different. Therefore, clarifying the etiology of AP is of great importance for the initial assessment, diagnosis, slowing the progression, and treatment.

It was reported that the etiological composition of pediatric AP was different from that of adults. According to the existing reports, the most common causes of pediatric AP included bile or obstructive factors, drugs, and systemic diseases.[59] In adults, the leading causes of AP are mainly calculous gall bladder disease and alcohol abuse.[62] Furthermore, most causes of AP biliary obstruction are stones or tumors in adults, while in children, they mainly resulted from biliary tract silt.[2,59] Meanwhile, the metabolic etiology of children was significantly lower than that of adults. Only 2–7% pediatric AP has metabolic factors.[20,63] Recently, the emergence of new drugs, especially the continuous supply of chemotherapeutic drugs, has also led to an increase in the incidence of drug-induced pancreatitis (DIP). It was reported that the incidence of DIP was 0.3–5.3% in recent years,[64] but the drug-derived AP accounts for 10–40% in children.[59] Therefore, the etiology of adults AP is not suitable for the analysis of pediatric AP. It is urgent to understand the etiology of AP in children.

There are obvious differences in the etiology of pediatric AP among different regions.[15,26] This meta-analysis including 47 articles found that the main causes of pediatric AP were gallstones in Asia and trauma in Oceania, idiopathic in Europe, North America, and South America. These findings were conducive to target clinical preliminary assessment and diagnosis of pediatric AP in different races and regions.

The incidence of pediatric SAP in different regions is different. It may have a great relationship with different etiological proportion.[61] Studies have shown that idiopathic and hyperlipidemia

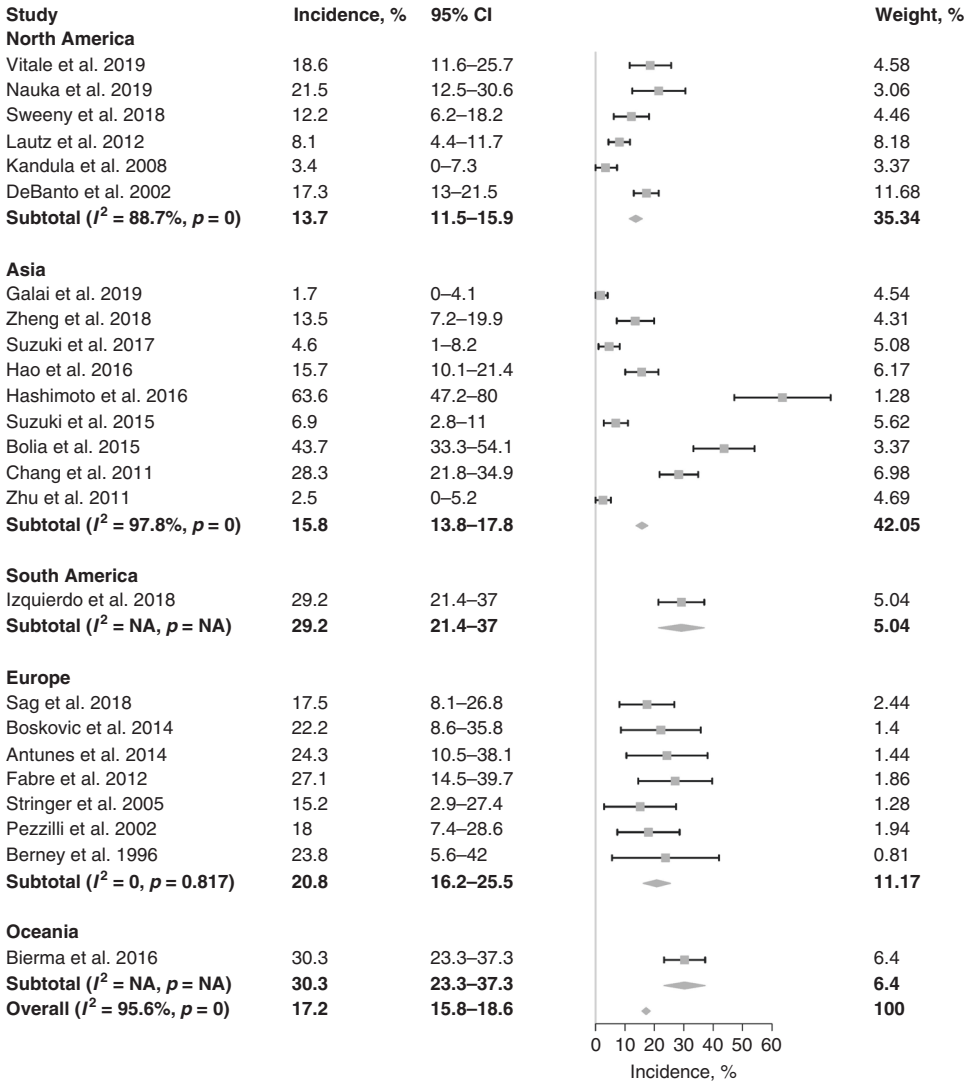

Fig. 5 Forest plot of severe acute pancreatitis rates of pediatric AP in different regions. They had similar prevalence of pediatric SAP 13.7% (95% CI, 11.5 to 15.9), 15.8% (95% CI, 13.8 to 17.8), 29.2% (95% CI, 21.4 to 37), 20.8% (95% CI, 16.2 to 25.5), 30.3% (95% CI, 23.3 to 37.3) in North America, Asia, South America, Europe, and Oceania, respectively.

may easily lead to SAP.[61] The analysis of the etiology found that Oceania (30.3%) and South American (29.2%) were idiopathic and metabolic, respectively.

The CFR of pediatric AP in various regions was various. The reason may be that the etiology of pediatric AP varied in different regions. Studies have found that the mortality rate of alcoholic pancreatitis was as high as 30.6%, which was a known cause of high mortality.[58] In this study, the two regions with etiology data for alcoholic pancreatitis were North American and Europe. Their CFRs ranked second and third in five continents, respectively.

The focus of treatment of pediatric AP also included prevention of recurrence.[65] This study found that the incidence rates of pediatric RAP in North American, Asia, and Europe were 15.3, 13.1, and 13.8%, respectively. Studies on adults found that age was one of the factors associated with rapid progression to RAP during the initial AP attack. However, this study found that there was no correlation between age and pediatric RAP through regression analysis. Some studies reported that genetic mutations (such as PRSS1, SPINK1, CFTR, etc.) were closely related to pediatric RAP.[20,66] Therefore, carrying out genetic testing related to RAP in regions with high genetic mutations was vital for the diagnosis and prediction of RAP in children.

There were several limitations that were largely associated with factors in the primary data. First, the heterogeneity between studies was still existing unexplained by the variables examined, which caused major uncertainty around the predicted estimates, may be partly from an issue inherent to AP epidemiology. Second, there was insufficient data for subgroup analyses. Meta-regression analyses were performed to find the potential heterogeneity. Studies differed widely in design, number of patients, and the size of the geographic area covered. Because of the limitations of the included research data, it failed to conduct sex- and gender-based analysis in this meta-analysis, which may result in sex and gender bias.[67] Third, small-study effects examined by publication bias may overestimate the effect sizes. Thus, these findings should be read with caution during the interpretation of meta-analyses. Fourth, the longer period ranged (1976–2017) may vary in the AP of diagnosis, and the larger varied sample (11–2127) made a difference to the result. Period ranged and sample sizes could bring instability to the result. Despite these limitations, this meta-analysis offered a comprehensive overview of the prevalence of AP.

In conclusion, the etiology composition of pediatric AP in different regions is various. The epidemiology of recurrence, case

fatality, and severity of pediatric AP was varied in diverse regions, which may be related to different etiological factors, but not to the age of children. It would be helpful if physicians pay attention to the etiology of pediatric AP for the preliminary assessment, diagnosis, prediction of relapse, and appropriate treatment at a later stage, with the goal of reducing mortality. Meanwhile, it would be meaningful to clarify the differences in the etiology of pediatric AP in different regions to help health decision-makers understand the epidemiology of the disease in their respective regions and to provide a basis for the implementation of local pediatric AP health policy.

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AUTHOR CONTRIBUTIONS

Conceptualization: T.J. Acquisition of data: all authors. Analysis and interpretation of data: G.T., L.Z. Writing—original draft: G.T. Critical revision of the manuscript for important intellectual content: T.J. Formal analysis: G.T., Q.Z. Funding acquisition: Q.Z., T.J. Methodology: Q.Z. Supervision: T.J.

ADDITIONAL INFORMATION

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Patient consent: Because this is a meta-analysis, patient consent was not required.

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