Clinical characteristics of acute pancreatitis in children: a single-center experience in Western China

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Abstract

Background: The diagnosis of pediatric pancreatitis has been increasing over the last 20 years. We aimed to compare the clinical characteristics for pediatric acute pancreatitis (AP) with adult AP, and investigate the risk factor for acute recurrent pancreatitis (ARP) in children.

Method: From June 2013 to June 2019, a total of 130 pediatric patients with AP at the inpatient database were enrolled. Univariate analysis and multivariate Cox regression analysis were performed to identify the risk factors for ARP in children.

Result: Major etiologic factors in 130 patients were biliary (31.5%), idiopathic (28.5%), trauma (16.2%). There was a significant difference in the constituent ratio of etiology between pediatric patients and adult patients (p<0.001). Compared with the adult patients, the pediatric patients had significantly lower severity (p=0.012) and occurrence rate of pancreatic necrosis (p=0.02). During the follow-up time (34.2±20.8 months), 19 children (14.6%) developed into ARP. Multivariate Cox regression analysis showed that female (p=0.025; OR=3.632; 95% confidence interval (CI) 1.179-11.188), hyperlipidemia (p=0.022; OR=3.480; 95% CI 1.201-10.085), pancreatic necrosis (p=0.001; OR=8.815; 95% CI 2.446-31.774) were the independent risk factors of ARP. The risk of recurrence was significantly different in each etiology group. Hyperlipidemic AP had the highest risk of recurrence over time, while viral and drug-induced AP had the lowest risk of recurrence (p=0.035).

Conclusion: Biliary and idiopathic disease were the major etiologies of AP in children. Compared to adults, children tend to have milder disease conditions and a better prognosis. Female, hyperlipidemia, and first AP attack with pancreatic necrosis were associated with the increased risk of ARP.

Background

Acute pancreatitis (AP) is an inflammatory reaction that causes the digestion, edema, bleeding, and necrosis of pancreatic tissue after activation of various trypsin enzymes in pancreatic tissue, caused by a variety of etiologies [1]. Clinically, it is characterized by acute epigastric pain, vomiting, and elevated pancreatic amylase. It has been reported that the incidence of AP in children has increased in the past 20 years [2, 3]. At present, AP is more common in children over five years old, with an incidence of 3/100 000, but its severity is similar in children of all ages [3, 4]. The overall case fatality rate is less than 5% [2, 5]. Compared with adults, there are significant differences in the incidence, etiology, clinical manifestation, and prognosis of AP in children [6]. Therefore, the purpose of this study was to analyze the demographic characteristics, etiology, clinical manifestations, and prognosis of AP, compare to adult AP, and to investigate the risk factors for acute recurrent pancreatitis (ARP) in children in southwest China.

Methods

Patients
We collected data retrospectively on 130 children with AP from June 2013 to June 2019 at the inpatient database. The diagnostic criteria for pediatric AP were in accordance with the guidelines of the International Pediatric Pancreatitis Study Group, the European Pancreatic Club, and the Hungarian Pancreatic Group [2, 7, 8]. Pediatric AP can be recognized in patients less than 18 years old, when two of the following three criteria are fulfilled: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values $\geq$ 3 times the upper limits of normal, (3) imaging findings consistent with AP. The clinical classification of AP includes: mild acute pancreatitis (MAP), characterized by the absence of organ failure and local or systemic complications; moderately-severe acute pancreatitis (MSAP), characterized by transient organ failure (< 48 h), or accompanied by local or systemic complications; severe acute pancreatitis (SAP), characterized by persistent organ failure (> 48 h). In addition, acute recurrent pancreatitis (ARP) is characterized by: (1) at least two distinct episodes of AP, irrespective of the specific time interval between AP episodes, with complete normalization of serum pancreatic enzyme levels before the subsequent episode of AP is diagnosed, along with complete resolution of pain symptoms, (2) there was absence of changes of chronic pancreatitis on noninvasive imaging [8]. We enrolled 130 adult patients with AP from the medical record database as the control group using the random number table method. The criteria for adult AP were in accordance with the Atlanta International consensus 2012 [9].

Data Collection
In order to analysis of the clinical characteristics of AP in children of different ages, patients were divided into two groups: a low age cohort (2–9 years old) and a high age cohort (10–17 years old). Basic information on these patients was collected, including age, sex, etiologies, clinical symptoms, laboratory indexes (blood amylase, lipase, triglyceride (TG), C-reactive protein (CRP), blood glucose, serum calcium), complications, and treatment outcome. We compared the characteristics between the recurrence and the non-recurrence group, and analyzed the risk factors associated with ARP in children. We also compared the clinical characteristics between children with AP and adults with AP. 130 children had telephone follow-up for at least 3 months.

Statistical analysis
The data were analyzed using SPSS software version 25.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were described by mean $\pm$ standard deviation or median (range) and classified variables by percentages. Comparison of non-normally distributed data and hierarchical data groups used the Mann–Whitney U test. The chi-squared test and Fisher’s exact probability test were employed to complete the univariate analysis. The chi-squared test for trend was used for unidirectional ordered classification, and Goodman–Kruskal gamma analysis was used for variables with bidirectional ordered classification. Factors with $p < 0.05$ were entered into a multivariate Cox regression analysis to determine adjusted odds ratios (Ors). A Cox proportional hazards model was used to analyze etiology groups and time to ARP for the whole sample. $P < 0.05$ was considered statistically significant for analyses.

Results
Baseline characteristics

Major etiologic factors in 130 patients were biliary (31.5%) (including 29 cases of bile duct stones, 8 cases of congenital biliary dilatation, 4 cases of biliary tapeworm), idiopathic (28.5%), trauma (16.2%), viral infection (10%), hyperlipidemia (9.3%) (TG > 11.30 mmol/L in 12 children), and drug-induced (4.6%) (including 5 children were taking dexamethasone and 1 child with leukemia was receiving chemotherapy with Cytarabine). There was a significant difference in the etiological constituent ratio between children and adults (p < 0.001): cases in children were mainly biliary and idiopathic, and those in adults were mainly hyperlipidemic and biliary. The severity of AP in the children was milder than that in the adult group (p = 0.012), and the rate of pancreatic necrosis in the children was lower than that in the adult group (p = 0.02). (Table 1)
Table 1
Clinical characteristics of acute pancreatitis in children and adults.

| Variables                        | Pediatric (n = 130) | Adult (n = 130) | P-value |
|----------------------------------|---------------------|-----------------|---------|
| Onset to admission time (days)   | 1.7 (0.9 ~ 4)       | 1 (0.3 ~ 3)     | 0.075<sup>a</sup> |
| Age, years                       | 11.2 ± 4.2          | 46.2 ± 13.7     | < 0.001<sup>a</sup> |
| Sex, Male, n%                    | 72 (55.4%)          | 84 (64.6%)      | 0.129<sup>b</sup> |
| Etiology, n%                     |                     |                 | < 0.001<sup>c</sup> |
| Biliary                          | 41 (31.5%)          | 43 (33.1%)      | 0.791<sup>b</sup> |
| Idiopathic                       | 37 (28.5%)          | 6 (4.6%)        | < 0.001<sup>b</sup> |
| Trauma                           | 21 (16.2%)          | 0 (0%)          | < 0.001<sup>b</sup> |
| Hyperlipidemic                   | 12 (9.2%)           | 44 (33.8%)      | < 0.001<sup>b</sup> |
| Viral infection                  | 13 (10%)            | 0 (0%)          | < 0.001<sup>b</sup> |
| Drug-induced                     | 6 (4.6%)            | 0 (0%)          | 0.029<sup>c</sup> |
| Alcoholic                        | 0 (0%)              | 12 (9.2%)       | < 0.001<sup>b</sup> |
| Multiple etiologies*             | 0 (0%)              | 20 (15.4%)      | < 0.001<sup>b</sup> |
| Other**                          | 0 (0%)              | 5 (3.9%)        | 0.060<sup>c</sup> |
| Severity, n%                     |                     |                 |         |
| MAP                              | 96 (73.8%)          | 78 (60%)        |         |
| MASP                             | 30 (23.1%)          | 41 (31.5%)      | 0.012<sup>a</sup> |
| SAP                              | 4 (3.1%)            | 11 (8.5%)       |         |
| Blood amylase(U/L)               | 534.8 (226.4 ~ 1131.1) | 314.5 (198.9 ~ 768.3) | 0.018<sup>a</sup> |
| Blood lipase(U/L)                | 361.2 (167.5 ~ 1055.2) | 257.1 (110.5 ~ 777.0) | 0.061<sup>a</sup> |

<sup>a</sup> Mann-Whitney U test.  
<sup>b</sup> Chi-square test.  
<sup>c</sup> Fisher's exact test.

MAP: Mild acute pancreatitis  
MASP: Moderately-severe acute pancreatitis  
SAP: Severe acute pancreatitis

*At least two etiologies of biliary, hyperlipidemic, alcoholic

**Two patients of pregnancy, two patients of surgery, one patient of tumor
### Variables

|                         | Pediatric (n = 130) | Adult (n = 130) | P-value |
|-------------------------|---------------------|-----------------|---------|
| C-reactive protein (mg/L) | 18 (3.4 ~ 74.4)    | 18.4 (5.7 ~ 99) | 0.144\(^a\) |
| Pancreas necrosis, n%    | 5 (3.8%)            | 15 (11.5%)      | 0.020\(^b\) |
| Pancreatic pseudocyst, n% | 14 (10.8%)         | 10 (7.7%)       | 0.391\(^b\) |
| ICU admission, n%        | 4 (3.1%)            | 11 (8.5%)       | 0.063\(^b\) |
| Cholecystectomy, n%      | 8 (6.2%)            | 14 (10.8%)      | 0.181\(^b\) |
| Hospital stay (days)     | 11 (7.8 ~ 19)       | 10 (6 ~ 15)     | 0.058\(^a\) |
| Death, n%                | 0 (0%)              | 1 (0.7%)        | 1.000\(^c\) |

\(^a\) Mann-Whitney U test. \(^b\) Chi-square test. \(^c\) Fisher's exact test.

MAP: Mild acute pancreatitis MASP: Moderately-severe acute pancreatitis
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*At least two etiologies of biliary, hyperlipidemic, alcoholic

**Two patients of pregnancy, two patients of surgery, one patient of tumor

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**Clinical characteristics based on age**

AP was more likely to occur in older age groups of children. However, the severity of the disease was independent of the increase in age, and there was no significant difference in etiology, sex and the constituent ratio of complications among different age groups. Viral infectious pancreatitis was more likely to occur in young children (p = 0.03). (Table 2)
Table 2
Patient demographics and hospital characteristics by age groups.

| Variables                | Aged 2 ~ 9 (n = 43) | Aged 10 ~ 17 (n = 87) | P-value |
|--------------------------|---------------------|-----------------------|---------|
| **Etiology, n%**         |                     |                       |         |
| Biliary                  | 10 (24.4%)          | 31 (75.6%)            | 0.153b  |
| Idiopathic               | 15 (40.5%)          | 22 (59.5%)            | 0.254b  |
| Trauma                   | 9 (42.9%)           | 12 (57.1%)            | 0.298b  |
| Hyperlipidemic           | 1 (8.3%)            | 11 (91.7%)            | 0.103c  |
| Viral infection          | 8 (61.5%)           | 5 (38.5)              | 0.030c  |
| Drug-induced             | 0 (0%)              | 6 (100%)              | 0.177c  |
| **Sex, n%**              |                     |                       |         |
| Male                     | 21 (29.2%)          | 51 (70.8%)            | 0.291b  |
| Female                   | 22 (37.9%)          | 36 (62.1%)            |         |
| **Severity, n%**         |                     |                       |         |
| MAP                      | 34 (35.4%)          | 62 (64.6%)            |         |
| MSAP                     | 9 (30%)             | 21 (70%)              | 0.260d  |
| SAP                      | 0 (0%)              | 4 (100%)              |         |
| **Complication, n%**     |                     |                       |         |
| Yes                      | 9 (26.5%)           | 25 (73.5%)            | 0.341b  |
| No                       | 34 (35.4%)          | 62 (64.6%)            |         |

b Chi-square test. c Fisher’s exact test. d Goodman-Kruskal Gamma analysis

MAP: Mild acute pancreatitis MASP: Moderately-severe acute pancreatitis
SAP: Severe acute pancreatitis

**Treatment**

130 patients were mainly treated with conservative medicine and clinical outcomes were good, of which 123 patients were cured and discharged, 7 patients were improved or discharged for further treatment, 8 patients were treated with cholecystectomy, 14 patients had pancreatic pseudocysts, 10 patients of which healed after medical treatment, 4 patients underwent pseudocyst drainage, none died.
Risk factors for ARP

Of the 130 children with AP, 19 (14.6%) progressed to ARP during the study period. The median interval from AP to ARP was seven months (interquartile range (IQR): 3–14), and the median age at development of ARP was 12 years (IQR: 8–14). The recurrence rate increased with an increase in disease severity (p = 0.034). Female sex (p = 0.001), hyperlipidemia (p = 0.016), and the presence of pancreatic necrosis during the first AP attack (p = 0.022) were significantly correlated with ARP. (Table 3)
Table 3
Characteristics of patients in Recurrence and Non-recurrence groups.

| Variables                | Recurrence group | Non-recurrence group | P-value |
|--------------------------|------------------|----------------------|---------|
|                          | n = 19           | n = 111              |         |
| Age, years               | 11.2 ± 4.2       | 11.3 ± 4.2           | 0.926<sup>a</sup> |
| Sex, n%                  |                  |                      |         |
| Male                     | 4 (5.6%)         | 68 (94.4%)           | 0.001<sup>b</sup> |
| Female                   | 15 (25.9%)       | 43 (74.1%)           |         |
| Etiology n%              |                  |                      |         |
| Biliary                  | 5 (12.2%)        | 36 (87.8%)           | 0.804<sup>b</sup> |
| Idiopathic               | 6 (16.2%)        | 31 (83.8%)           | 0.745<sup>b</sup> |
| Trauma                   | 3 (14.3%)        | 18 (85.7%)           | 0.963<sup>b</sup> |
| Hyperlipidemic           | 5 (41.7%)        | 7 (58.3%)            | 0.016<sup>c</sup> |
| Viral infection          | 0 (0%)           | 13 (100%)            | 0.116<sup>b</sup> |
| Drug-induced             | 0 (0%)           | 6 (100%)             | 0.299<sup>b</sup> |
| Severity n%              |                  |                      |         |
| MAP                      | 11 (11.5%)       | 85 (88.5%)           |         |
| MASP                     | 6 (20%)          | 24 (80%)             | 0.034<sup>e</sup> |
| SAP                      | 2 (50%)          | 2 (50%)              |         |
| Complication n%          |                  |                      |         |
| Pancreas necrosis        | 3 (60%)          | 2 (40%)              | 0.022<sup>c</sup> |
| Pancreatic pseudocyst    | 2 (14.3%)        | 12 (85.7%)           | 1.000<sup>c</sup> |

<sup>a</sup> Mann-Whitney U test.  <sup>b</sup> Chi-square test.  <sup>c</sup> Fisher's exact test.  <sup>e</sup> Trend Chi-squared test

MAP: Mild acute pancreatitis  MASP: Moderately-severe acute pancreatitis  SAP: Severe acute pancreatitis

Multivariate Cox regression analysis showed that female sex (p = 0.025; OR = 3.632; 95%CI 1.179−11.188), hyperlipidemia (p = 0.022; OR = 3.480; 95%CI 1.201−10.085), and pancreatic necrosis (p = 0.001;
OR = 8.815; 95% CI 2.446–31.774) were the independent factors influencing ARP. (Table 4)

| Variable              | Univariate analysis | Multivariate analysis |
|-----------------------|---------------------|-----------------------|
|                       | OR (95% CI)         | P-value               |
| Sex, Female           | 4.626 (1.535–13.941)| 0.007                 |
| hyperlipidemic        | 4.505 (1.619–12.537)| 0.004                 |
| Pancreas necrosis     | 8.288 (2.380–28.865)| 0.001                 |

We were also interested in studying the etiology or risk factors associated with the first AP occurrence and their effect on progression to ARP over time for the whole sample. We compared patients with biliary, idiopathic, traumatic, hyperlipidemic, viral, and drug-induced AP. We found that hyperlipidemic AP had the highest risk of recurrence over time, while viral and drug-induced AP had the lowest risk of recurrence (p = 0.035). (Fig. 1)

**Discussion**

It has been reported [10–12] that the incidence of AP in children has shown an upward trend in recent years. The incidence rate in children in the United Kingdom was about 0.78/100 000 [13], while in the United States, this figure was 3–13/100 000 [3]. In this study, the clinical characteristics of AP in children in southwest China were analyzed and summarized. As far as we know, this is the first report in English on the clinical features of AP in children from China.

The etiology of AP in children is significantly different from that in adults. In previous studies, Poddar et al. [14] studied 320 children with AP from India and found that trauma (21%) and biliary tract disease (10%) were the most common causes of AP in children. Park et al. [15] found that the biliary tract (36.2%) and drugs (25.6%) were the leading causes of AP in 215 children in the United States. In another study of 115 children in the United States [16], idiopathic (31%) and drug associated (23%) were the main causes. We found that biliary (31.5%), idiopathic (28.5%) and traumatic (16.2%) were the main causes, which was consistent with most studies. In adults, biliary obstruction leading to AP is almost always due to a stone or tumor; however, in children, 30% of cases are caused by biliary silt rather than complete calculus [3, 6]. No study has reported on this difference. In addition, metabolic problems such as hyperlipidemia in children were significantly rarer than in adults. Only 2–7% of children with AP have metabolic causative factors [10, 11]. In this study, 12 cases (9.2%) were caused by hyperlipidemia. In the control group of adults, high fat levels accounted for 33.8%, and the difference was significant. The most exciting finding in our study was that viral infectious pancreatitis was more common in young children and the rate was
significantly different from that in adults. We consider that is was related to the incomplete development of the immune system in young children. The mechanism of AP related to virus infection is not clear at present, although some research has shown that the virus directly invades pancreatic cells [3]. In recent years, with the extensive use of drugs, drug-induced pancreatitis has shown a significant increasing trend, although, overall, it is still constitutes less than 10% of cases [17].

Our study showed that the severity of AP in children was similar in all age groups, which is consistent with a previous report [3], but the disease was less severe than in adults. Possible reasons are: (1) Children were admitted to the hospital earlier than adults because of reduced tolerance, in order to get treatment as soon as possible; (2) In terms of etiological composition, hyperlipidemia and alcoholic pancreatitis account for few cases in children, and some studies have shown that hyperlipidemia and alcohol can easily lead to SAP [18]; (3) In terms of complications, pancreatic necrosis is positively correlated with the severity and prognosis of the disease. Necrotizing pancreatitis is rare in children. According to the literature [19], necrotizing pancreatitis occurs in less than 1% of children with AP. Among the five large sample pediatric cases reported in the United States [20], only 3 of 1014 children with AP had pancreatic necrosis, which was significantly less severe than that of adults. (4) Pediatric biliary AP often results from the formation of silt, so the rate of operation is less than in adults, and there are fewer complications due to biliary diseases.

For AP with specific causes, such as bile duct stones, anatomical abnormalities, bile duct dilatation, etc., it has been suggested that surgery should be performed as soon as possible after the condition is controlled and stable, to prevent recurrence [11, 21]. In the literature [22], the mortality rate of pediatric AP is less than 5%, which is significantly lower than that of adult AP, possibly because: (1) Alcoholic pancreatitis is rare in pediatric cases, and alcoholic pancreatitis is a known cause of high mortality, with a mortality rate as high as 30.6% [23]. (2) With age, adults may lose some critical protective mechanism, which children retain [6]. (3) Adult cases may be associated with severe underlying diseases, while AP in children is rarely associated with multiple problems with organ function. (4) The severity of the disease in children is significantly lower than that in adults, which has also been confirmed in this study.

Some single-center studies have estimated that 10–35% of children with AP develop ARP [24, 25]. These studies showed that mutations of PRSS1, SPINK1, CFTR, and CTRC13 were firmly related to the progression of ARP. During the first attack of AP in children, age, male sex, pancreatic necrosis, and higher Body Mass Index (BMI) have been associated with the progression of ARP. Anatomic abnormalities of the biliary tract, hyperlipidemia, and genetic factors should be evaluated in cases of recurrence [11, 16, 26]. In our study, among the 19 children (14.6%) with ARP, includes a 2-year-old toddler with congenital bile duct dilatation. We found that female sex, hyperlipidemia, and primary AP with pancreatic necrosis were significantly correlated with ARP, and the severity of primary AP was positively correlated with ARP. The relationship between ARP and sex is controversial and perhaps related to the predominance of hyperlipidemia and biliary tract disease in women [27, 28].
Differences in our findings from those of previous studies may have resulted from differences in race, region, and environment. Hyperlipidemia is an apparent cause of AP and ARP in adults [29], but there has been no analysis of a large sample of ARP cases in children. It has been reported in the literature that hypertriglyceridemia occurring secondary to AP may be related to various genetic mutations [30]. From this point of view, our findings coincide with previous research results.

The disadvantage of this study is that it was a single-center study in China. Thus, the findings of this study cannot be generalized. For the 19 patients with ARP, the etiology of recurrence needs to be examined by endoscopic retrograde cholangiopancreatography and genetic analysis, and there is a lack of corresponding genetic and clinical data in this study. In future, multi-center studies with a larger sample and more rational perspective are needed to analyze pediatric pancreatitis in order to facilitate better treatment.

**Conclusion**

Biliary disease and idiopathic cases were the leading causes of AP in children, and, when compared with adults, children tend to have milder disease and a better prognosis. The recurrence rate increased with an increase in disease severity. Female sex, hyperlipidemia, and a first AP attack involving pancreatic necrosis were associated with an increased risk of ARP. Genetic and anatomical factors need to be studied further in children with ARP.

**Abbreviations**

AP Acute Pancreatitis
ARP Acute Recurrent Pancreatitis
BMI Body Mass Index
CRP C-reactive Protein
IQR Interquartile Range
MAP Mild Acute Pancreatitis
MASP Moderately-severe Acute Pancreatitis
SAP Severe Acute Pancreatitis
TG Triglyceride

**Declarations**

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**Authors’ contributions**

Study conception and design: Xiaowei Tang, Yan Peng. Drafting of manuscript: Rui Zhong and Shali Tan. Acquisition of data and critical revision: Huan Xu, Xin Jiang, Yongfeng Yan. Revision of manuscript, and final approval of manuscript: Xiaowei Tang.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Ethics approval and consent to participate**

This study was approved by the Clinical trial Ethics Committee of the affiliated Hospital of Southwest Medical University (batch number: KY2019054). Date:2019/05/04

**Consent to publish**

Not Applicable

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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Figures
Figure 1

Risk of acute recurrent pancreatitis (ARP) by etiology.

Cumulative number of events

| Etiology          | 0  | 20 | 40 | 60 | 80 |
|-------------------|----|----|----|----|----|
| Biliary           | 0  | 0  | 4  | 5  | 5  |
| Drug-induced      | 0  | 0  | 0  | 0  | 0  |
| Hyperlipidemic    | 0  | 0  | 5  | 5  | 5  |
| Idiopathic        | 0  | 0  | 5  | 6  | 6  |
| Trauma            | 0  | 3  | 3  | 3  | 3  |
| Viral infection   | 0  | 0  | 0  | 0  | 0  |