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Trends and clinical characteristics of pediatric acute pancreatitis patients in Japan: A comparison with adult cases based on a national administrative inpatient database

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ABSTRACT

Background: /Objectives: Pediatric acute pancreatitis (AP) is not as rare as previously thought, and an increased incidence thereof has been reported. We aimed to clarify the trends and clinical characteristics of pediatric AP in Japan.

Methods: We utilized the Japanese Diagnosis Procedure Combination inpatient database for patients admitted between April 2012 and March 2021, and extracted the data of patients whose principal diagnosis was AP (ICD-10 code K85) or in whom AP accounted for most of the medical expenses. Patients were classified into pediatric (≤18 years) and adult (age >18 years) groups.

Results: We included 3941 AP cases in pediatrics and 212,776 in adults. AP cases accounted for 0.08 % of all admissions in pediatrics and 0.33 % in adults, with upward trends during the study period. The proportion of AP patients among all admissions was increased with advancing age in pediatrics. Compared to adults, pediatric AP patients had a smaller proportion of severe cases (22.9 % vs. 28.7 %; $P < 0.001$), fewer interventions for late complications (0.2 % vs. 1.3 %; $P < 0.001$), shorter hospital stays (mean 16.6 days vs. 18.0 days; $P = 0.001$), lower overall mortality (0.7 % vs. 2.9 %; $P < 0.001$), and lower mortality in severe cases (1.3 % vs. 5.6 %; $P < 0.001$). Pediatric cases were more frequently transferred from other institutions and treated at academic hospitals than adults (both $P < 0.001$).

Conclusions: There was an upward trend in the proportion of AP among all admissions in pediatrics, with a lower risk of complications and mortality than adult cases.

1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas and one of the common gastrointestinal diseases [1–3]. Most patients with AP have mild disease courses; however, approximately 20 % of the patients develop severe diseases, complicated with pancreatic necrosis and multiple organ failure, which may be fatal [1–3]. AP is no longer rare in children, and increased incidence of pediatric AP has been reported since the late 1990s [4–8]. More recent studies, however, have shown that the incidence is stable [9,10], particularly among privately insured children in the United States between 2007 and 2014, ranging from 6.2 to 7.1 cases per 100,000 persons [9]. Stabilized incidence of pediatric AP was also reported between 2010 and 2015 at the Cincinnati Children's Hospital Medical Center [10]. In Japan, however, the nationwide epidemiological survey of AP in 2016 showed that cases with patients under the age of 20 accounted for only 1.0 % of all AP cases [11]. Most studies on this topic in Japan were case-series in a single center [12,13].

The clinical characteristics of the pediatric AP patients might be different from those of adult patients [14]. Two common causes of AP in adults are alcohol and gallstones [1–3]; the former cause is virtually absent in pediatric cases, where bile or obstructive factors,

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Abbreviations usedare

AP	acute pancreatitis
CCI	Charlson comorbidity index
CP	chronic pancreatitis
CT	computed tomography
DPC	diagnosis procedure combination
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICU	intensive care unit
LOS	length of hospital stay
SD	standard deviation

drugs, and systemic diseases are common [4–6]. As opposed to adult cases, only a small portion of pediatric patients might develop severe complications such as multiorgan dysfunction and pancreatic necrosis [4–6]. Overall mortality might be lower in children, and many pediatric patients die from underlying diseases instead of pancreatitis alone. Additionally, a meta-analysis of 48 studies revealed geographical differences in the etiology and case-fatality rate of AP cases [15]. The main cause in Asia was gallstones; however, this was found to be idiopathic in Europe and North America. The case-fatality rate was 6.2 % in Europe, but 2.4 % in Asia [15]. Therefore, population/region-specific information is important for the improved characterization of AP in children.

We aimed to clarify the recent trends and clinical characteristics of pediatric AP, especially in comparison with adult cases, in Japan, through analysis of the Japanese Diagnosis Procedure Combination (DPC) inpatient database.

2. Methods

2.1. DPC database

We used the DPC inpatient database, which contains discharge abstracts and administrative claims data for acute inpatient care from approximately 1000 hospitals including all academic hospitals across Japan [16–18]. It covers approximately 50 % of acute-care inpatients in Japan. This database includes age, sex, main diagnoses coded with the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and daily procedures using the Japanese medical procedure codes, daily drug administrations, admission, and discharge status for each hospitalization. Information after discharge is not available. The improved mortality of AP after the revision of the Japanese guidelines for the management of AP has already been shown using this database [19].

2.2. Study population

We extracted data of patients admitted between April 1st, 2012 and March 31st, 2021 whose principal diagnosis was AP (ICD-10 diagnostic code K85) or in which AP accounted for most of the medical expenses. Although patients with recurrent AP could be included, we could not distinguish these patients from those with a single episode of AP because such information is not recorded in the DPC database. The extracted patients were classified into two groups according to age at admission: pediatric group (age $\leq$18 years) and adult group (age >18 years). We further stratified pediatric AP patients into three groups [aged 1–6 (preschool), aged 7–12 (primary education), and aged 13–18 (secondary education)] based on the Japanese education system. We used the Charlson comorbidity index (CCI) to categorize comorbidities [20].

We examined the comorbidities present on admission and complications arising after admission. If chronic pancreatitis (CP) was recorded as a comorbidity present at the time of admission, we regarded the patients as those with acute exacerbation of CP (acute-on-CP). We calculated the proportion of AP among all admissions, with all hospital admissions as the denominator and the number of AP cases as the numerator, and presented the number of AP per 100,000 admissions. We identified the procedures according to the following procedure codes: 140029850 for continuous hemodiafiltration; 140054710, tube feeding with elemental diet; 150362410, endoscopic ultrasound-guided fistuloplasty (representing endoscopic ultrasound-guided transluminal drainage); 150347510, percutaneous abscess drainage; and 150348210 and 150277310 for AP-related surgery. We determined the severity of AP according to the Japanese Ministry of Health, Labor and Welfare criteria (Supplementary Table 1) [21], where severity of AP is determined independently by nine prognostic scores and computed tomography (CT) grade. Severe AP is defined if $\geq$ 3 positive prognostic factors or CT grade $\geq$2 was fulfilled. Other cases were defined as mild AP. Because the severe AP patients fulfilling the prognostic factors had higher mortality than those fulfilling the CT grade [11], we have differentiated the AP severity according to the fulfillment of prognostic factors and/or the CT grade.

2.3. Statistical analysis

All statistical analyses were performed using JMP 15 software (SAS Institute Inc., Cary, NC). Continuous variables are presented as means and standard deviation and compared using an analysis of variance and Welch's *t*-test. Categorical variables are presented using numbers and percentages and compared using the Pearson's chi-square test or Fisher's exact test. We utilized the Cochrane-Armitage test for trend analysis. A one-sided (for trend analyses) or two-sided (for other analyses) *P*-value <0.05 was considered statistically significant.

2.4. Ethics

We performed this study in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (article number: 2021-1-029). Written informed consent was waived due to the anonymous nature of the data.

3. Results

3.1. Overview of pediatric AP patients

We identified a total of 216,717 patients (140,568 males and 76,149 females) with AP, including 3941 (1.8 %) and 212,776 (98.2 %) patients in the pediatric and adult groups, respectively. In subsequent analyses, we excluded the patients aged 0 because routine hospital delivery comprises a significant proportion of entries [7]. The number of pediatric patients with AP ranged from 380 (107 per 100,000 admissions) in 2020 to 499 (93 per 100,000 admissions) in 2014 (Table 1). In adults, the number of AP patients ranged from 19,936 (302 per 100,000 admissions) in 2012 to 25,892 (335 per 100,000 admissions) in 2016. AP cases accounted for 0.08 % of all admissions (85 per 100,000 admissions) aged between 1 and 18 years in pediatrics and 0.33 % (331 per 100,000 admissions) in adults across all years, with upward trends during the study period ($P < 0.0001$ for both) (Fig. 1). In pediatrics, the proportion of AP among all admissions was increased with advancing age ($P < 0.001$) (Fig. 2). We also examined the age distribution of the AP patients in

Table 1
Proportions of AP among all admissions in pediatrics and adults stratified by year.

Year	AP/all admissions, n (per 100,000 admissions)		
	All	Pediatrics[a]	Adults
2012	20,331/7,118,837 (286)	395/519,103 (76)	19,936/6,599,734 (302)
2013	21,957/7,091,520 (310)	412/499,623 (83)	21,545/6,591,897 (327)
2014	24,765/7,840,619 (316)	499/537,167 (93)	24,266/7,303,452 (332)
2015	24,870/7,990,156 (311)	464/555,459 (84)	24,406/7,434,697 (328)
2016	26,375/8,315,281 (317)	483/575,713 (84)	25,892/7,739,568 (335)
2017	26,105/8,042,148 (325)	458/548,488 (84)	25,647/7,493,660 (342)
2018	24,902/8,013,585 (311)	402/544,452 (74)	24,500/7,469,133 (328)
2019	23,665/7,565,913 (313)	436/501,757 (87)	23,229/7,064,156 (329)
2020	23,735/6,942,203 (342)	380/354,433 (107)	23,355/6,587,770 (355)
Total	216,717/68,920,262 (314)	3929/4,636,195 (85)	212,776/64,284,067 (331)

AP, acute pancreatitis.
[a] excluding the patients aged 0.

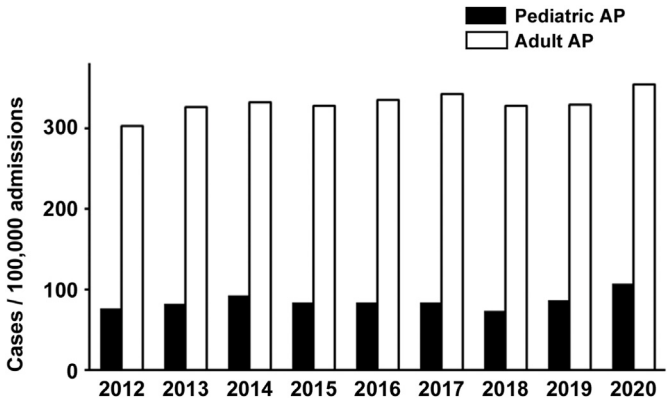

Fig. 1. Trends of the proportion of AP patients among all admissions during the study period.
We calculated the proportion of AP among all admissions in pediatrics and adults during the study period, with all hospital admissions as the denominator and the number of AP cases as the numerator. We presented the number of AP cases per 100,000 admissions.

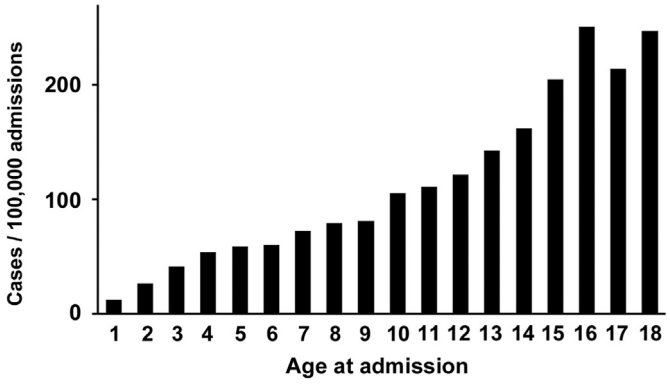

Fig. 2. Age distribution of the patients with pediatric AP.
We calculated the proportion of AP among all admissions according to the age at admission in pediatrics, with all hospital admissions as the denominator and the number of AP cases as the numerator. We presented the number of AP cases per 100,000 admissions.

adults. The absolute number of the AP patients was increased until the 70s, but decreased thereafter (Supplementary Fig. 1A). The proportion of AP among all admissions was increased until the 40s, but decreased thereafter (Supplementary Fig. 1B)

We stratified pediatric AP patients into three groups according to the age of AP admission: aged 1–6, 7–12, and 13–18 (Table 2). Proportions of AP among 100,000 admissions were 34.8 in the patients aged 1–6, 93.2 in those aged 7–12, and 205 in those aged 13–18. The proportion of AP among all admissions was increased with advancing age ($P < 0.001$). Males accounted for nearly 70 % of patients in the group aged 13–18, whereas fewer than 50 % of patients were males in the younger groups. Although the proportion of severe cases was not different, there were more cases fulfilling the prognostic score criteria in the younger groups (1–6, 28.2 %; 7–12, 18.8 %; 13–18, 11.8 %). The proportions of transferred cases and those who underwent admission to the intensive care unit (ICU) was the greatest and mortality was the highest in the preschool group.

Five percent of the pediatric patients with AP were transferred from other institutions. These patients were younger, more frequently suffered from severe AP, and required ICU admission and were treated at academic hospitals more often than the cases who were directly admitted (Table 3). Length of hospital stay (LOS) was longer and mortality was higher than the cases with direct admission.

3.2. Pediatric versus adult AP patients

We compared the clinical characteristics between the pediatric and adult AP patients. The mean age at AP admission was 11.5 years in the pediatric group and 62.6 years in the adult group (Table 4). The proportion of male patients was smaller in the pediatric group than that in the adult group; the male-to-female ratio was 1.41 in the pediatric group and 1.86 in the adult group ($P < 0.001$). Pediatric patients with a CCI $\geq$3 were rare and accounted for only 0.6 % of cases, whereas these patients accounted for 7.5 % of all cases in adults. Similarly, comorbidities present on admission and complications arising after admission such as CP, diabetes mellitus, pancreatic cancer, and cholelithiasis were less frequent but congenital anomalies of the pancreas such as pancreatic divisum and pancreaticobiliary maljunction was more frequent in the pediatric group than the adult group (Supplementary Table 2).

The proportion of patients who were treated at academic hospitals and those who were referred from other institutions was greater in the pediatric group than in the adult group (both $P < 0.001$). Pediatric cases underwent admission to ICU and intervention for local complications less frequently and had shorter LOS than adult cases. Mortality was lower in pediatric cases than that in adult cases (0.7 % vs. 2.9 %; $P < 0.001$), and was similar between male and female in pediatric cases (0.7 % for males vs. 0.6 % for females, $P = 0.48$). Mortality was higher in males compares to female in adults (2.6 % for males vs. 3.4 % for females, $P < 0.001$). CT

Table 2
Clinical characteristics of the AP patients according to the age at admission.

	1–6 years old (n = 912)	7–12 years old (n = 928)	13–18 years old (n = 2089)	*P* value
AP/all admissions, n (per 100,000 admissions)	912/2,623,170 (34.8)	928/995,640 (93.2)	2,089/1,017,385 (205)	<0.001
Sex, male, n (%)	412 (45.8)	462 (49.8)	1426 (68.3)	<0.001
Age at AP onset, mean (SD)	3.7 (1.6)	9.6 (1.7)	15.9 (1.6)	<0.001
CCI				0.22
0	793 (86.9)	770 (82.9)	1772 (84.8)	
1-2	114 (12.5)	151 (16.3)	304 (14.6)	
3>	5 (0.6)	7 (0.8)	13 (0.6)	
Severe AP, n (%)	110/515 (21.4)	117/557 (21.0)	374/1561 (24.0)	0.24
Severe due to prognostic factor only	14/110 (12.7)	8/117 (6.8)	15/374 (4.0)	0.004
Severe due to CT grade only	79/110 (71.8)	95/117 (81.2)	328/374 (87.7)	<0.001
Severe due to both prognostic factor and CT grade	17/110 (15.5)	14/117 (12.0)	31/374 (8.3)	0.076
Cases transferred from other institutions, n (%)	65 (7.1)	57 (6.1)	75 (3.6)	<0.001
ICU admission, n (%)	48 (5.3)	42 (4.5)	66 (3.2)	0.013
Mortality[a]				
All AP	14/912 (1.5)	8/928 (0.9)	4/2089 (0.2)	<0.001
Mild AP	2/405 (0.5)	0/440 (0.0)	0/1187 (0.0)	0.018
Severe AP	4/110 (3.6)	4/117 (3.4)	0/374 (0.0)	0.001

[a] Because AP severity was not recorded in all cases, the total number of cases was not equal to the sum of mild and severe cases. AP, acute pancreatitis; CCI, Charlson comorbidity index; CT, computed tomography; ICU, intensive care unit; SD, standard deviation.

Table 3
Comparison of the characteristics of the pediatric AP patients stratified by the admission route.

	Direct (n = 3743)	Transferred (n = 198)	*P* value
Sex, male, n (%)	2199 (58.8)	110 (55.6)	0.37
Age at admission, mean (SD)	11.6 (5.3)	9.8 (5.4)	<0.001
CCI, n (%)			0.79
0	3179 (84.9)	168 (84.9)	
1-2	541 (14.5)	28 (14.1)	
>3	23 (0.6)	2 (1.0)	
Severe AP[a], n (%)	543 (21.7)	61 (46.2)	<0.001
Admission to ICU, n (%)	126 (3.4)	31 (15.7)	<0.001
Hospital type, academic, n (%)	648 (17.3)	83 (41.9)	<0.001
Mortality, n (%)	22 (0.6)	4 (2.0)	0.039
LOS, days, mean (SD)	15.9 (25.9)	29.1 (45.4)	<0.001

[a] Information about the severity was recorded in 2506 directly admitted and 132 transferred patients. AP, acute pancreatitis; CCI, Charlson comorbidity index; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

Table 4
Comparison of clinical characteristics between pediatric and adult patients with AP.

	Pediatric group (n = 3941)	Adult group (n = 212,776)	*P* value
Age at AP admission, mean (SD)	11.5 (5.3)	62.6 (17.8)	<0.001
Sex, male, n (%)	2309 (58.6)	138,259 (65.0)	<0.001
CCI, n (%)			<0.001
0	3347 (85.0)	115,010 (54.0)	
1-2	569 (14.4)	81,846 (38.5)	
3>	25 (0.6)	15,920 (7.5)	
Severity, n (%)[a]			<0.001
Mild AP	2034 (77.1)	116,177 (71.3)	
Severe AP	604 (22.9)	46,841 (28.7)	
Admission to ICU, n (%)	157 (4.0)	13,251 (6.2)	<0.001
Hospital type, academic, n (%)	731 (18.6)	16,787 (7.9)	<0.001
Cases transferred from other institutions, n (%)	198 (5.0)	8251 (3.9)	<0.001
Intervention for local complications, n (%)	8 (0.2)	2818 (1.3)	<0.001
LOS, days, mean (SD)	16.6 (27.3)	18.0 (24.2)	0.001
In-hospital death, n (mortality, %)	26 (0.7)	6151 (2.9)	<0.001
Male, n (%)	17/2309 (0.7)	3604/138,259 (2.6)	<0.001
Female, n (%)	9/1632 (0.6)	2547/74,517 (3.4)	<0.001

[a] Because AP severity was not recorded in all cases, the total number of cases was not equal to the sum of mild and severe cases. AP, acute pancreatitis; CCI, Charlson comorbidity index; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

was performed in 2793 (70.9 %) pediatric patients, within 2 days of admission in 2474 (62.8 %) whereas it was performed in 195,960 (92.1 %) adult patients, within 2 days of admission in 182,240 (85.7 %) (**Supplementary Table 3**). CT including contrast-enhanced one was more frequently performed in adult patients than that in pediatric patients ($P < 0.001$). Magnetic resonance imaging was performed in 1560 (39.6 %) pediatric and 66,995 (31.5 %) adult patients, but only in 354 (9.0 %) pediatric and 22,399 (10.5 %) adult patients within 2 days of admission.

Information about AP severity according to the Japanese

severity criteria was available in 2638 (1635 males and 1003 females) pediatric and 163,018 (107,018 males and 56,000 females) adult AP cases (**Table 5**). Because AP severity was not recorded in all cases, the total number of cases was not equal to the sum of mild and severe cases. In total, 604 (22.9 %; 372 males and 232 females) pediatric and 46,841 (28.7 %; 30,829 males and 16,012 females) adult cases were classified as severe, less frequently in pediatrics than in adults ($P < 0.001$). Pediatric severe AP patients underwent admission to ICU and were transferred from other institutions more frequently than those with mild AP (**Supplementary Table 4**). LOS was longer and mortality was higher in pediatrics with severe AP than those with mild AP.

The proportion of severe cases fulfilling both of the prognostic score and the CT grade criteria was smaller in the pediatric group than in the adult group (**Table 5**). In all the AP cases, the proportion of patients treated at academic hospitals ($P < 0.001$) and those transferred from other institutions ($P = 0.003$) was greater in the pediatric group than in the adult group. Pediatric cases underwent admission to ICU and intervention for local complications less frequently and had shorter LOS than adult cases. Mortality was lower in pediatric severe cases than in adult cases (1.3 % vs. 5.6 %; $P < 0.001$).

We compared the clinical characteristics of the patients who had CP on admission, which we regarded as those with acute-on-CP (**Supplementary Table 5**). Proportion of the patients with acute-on-CP among AP was smaller in pediatrics than that in adults ($P < 0.001$). Among the 123 pediatric patients with acute-on-CP, 17 were aged 1–6, 28 aged 7–12, and 78 aged 13–18. Although the proportion of severe cases was not different between pediatric and adult cases, it was smaller compared to AP overall both in pediatrics (13.0 % vs. 22.9 %; $P = 0.04$) and adults (19.8 % vs. 28.7 %; $P < 0.001$). Mortality was not different between pediatric and adult cases and none of the pediatric patients with acute-on-CP died.

3.3. Treatments for AP

We subsequently analyzed treatments for AP (**Table 6**). Because AP severity could not be determined in all cases, the number of cases who received the respective treatment was not equal to the sum of that in mild and severe cases. All treatments, except for intervention therapy, were more frequently performed in severe pediatric cases than in mild pediatric cases. In comparison between pediatric and adult AP cases, protease inhibitors and antimicrobial drugs were less frequently administrated in pediatric cases than in adults, even if stratified by AP severity. Continuous hemodiafiltration was rarely performed in pediatric AP cases, whereas nearly 5 % of severe AP cases in adults underwent this treatment. Tube feeding was more frequently performed in pediatric cases than adult cases regardless of the disease severity. The interval between the admission and start of tube feeding was shorter in pediatric cases than that in adult cases ($P = 0.02$). In the cases of severe AP, if stratified by age group, tube feeding was more frequently performed in younger age groups; 30/113 (26.6 %) in the group aged 0–6, 21/117 (18.0 %) in ages 7–12, and 45/374 (12.0 %) in ages 13–18 ($P < 0.001$). Among the patients who received tube feeding, 106/312 (34.0 %) pediatric patients and 2185/9850 (22.2 %) adults started tube feeding within 2 days of admission. The proportion of patients who started tube feeding within 2 days was greater in the pediatric group than that in the adult group ($P < 0.001$).

Few (n = 8) pediatric AP patients underwent interventions for local complications such as walled-off necrosis. Any interventions for local complications were less frequently performed in pediatric AP patients than in adults (0.2 % vs. 1.3 %, $P < 0.001$).

4. Discussion

This study was conducted on large-scale real-world data of nearly 4000 pediatric patients with AP using a national administrative database in Japan. Pediatric AP cases accounted for 0.08 % of all admissions (85 per 100,000 admissions), roughly comparable to 42.7/100,000 admissions reported in a study in the United States [9]. There was an upward trend in the proportion of AP among all admissions with advancing age in pediatrics. This trend is similar to those reported in previous studies from the United States and Taiwan [9,22]. Importantly, previous studies have shown rising trends of pediatric AP in the late 90s and early 2000s, but the number is steady more recently [7–10]. The previously increasing incidence of AP in pediatrics might result from multiple factors including growing awareness, testing, and recognition of pediatric AP, as shown by the increased testing of pancreatic enzymes [4–8]. In this study, the proportion of pediatric AP patients among all admissions showed an upward trend during the study period. Because the number of all admissions was dramatically decreased from 501,757 in 2019 to 354,433 in 2020 mainly due to the COVID-19 pandemic in Japan [23], it is of interest to see whether the upward trend would continue in the era of post-COVID-19.

Compared to adults, pediatric patients had a smaller proportion of severe cases, a smaller proportion of patients who received

Table 5
Comparison of the clinical characteristics between the severe AP patients in the pediatric and adult groups.

	Pediatric group (n = 604)	Adult group (n = 46,841)	*P* value
Sex, male, n (%)	372 (61.6)	30,829 (65.8)	0.03
Age at AP admission, mean (SD)	12.6 (5.2)	62.2 (18.2)	<0.001
CCI, n (%)			<0.001
0	500 (82.8)	25,533 (54.5)	
1-2	99 (16.4)	18,148 (38.7)	
3>	5 (0.8)	3160 (6.8)	
Severe due to prognostic factor only, n (%)	37 (6.1)	5725 (12.2)	<0.001
Severe due to CT grade only, n (%)	504 (83.5)	32,447 (69.3)	<0.001
Severe due to both prognostic factor and CT grade, n (%)	63 (10.4)	8669 (18.5)	<0.001
Cases transferred from other institutions, n (%)	61 (10.1)	3287 (7.0)	0.003
Hospital type, academic, n (%)	117 (19.4)	4496 (9.6)	<0.001
Admission to ICU, n (%)	66 (10.9)	6510 (13.9)	0.036
Intervention for local complications, n (%)	2 (0.3)	1339 (2.9)	<0.001
LOS, days, mean (SD)	20.2 (25.6)	24.5 (29.5)	<0.001
In-hospital death, n (mortality, %)	8 (1.3)	2600 (5.6)	<0.001
Male	4/372(1.1)	1542/30,829 (5.0)	<0.001
Female	4/232 (1.7)	1058/1,6012 (6.6)	0.001

AP, acute pancreatitis; CCI, Charlson comorbidity index; CT, computed tomography; ICU, intensive care unit; LOS, length of hospital stay; SD, standard deviation.

Table 6
Treatments for AP.

	Pediatric group	Adult group	*P* value
Protease inhibitor, n (%)			
All AP	2695 (68.4)	175,199 (82.3)	<0.001
Mild AP	1428 (70.2)	95,147 (81.9)	<0.001
Severe AP	499 (82.6)	41,244 (88.1)	<0.001
Antimicrobial drugs, n (%)			
All AP	956 (24.3)	74,557 (35.0)	<0.001
Mild AP	386 (19.0)	30,077 (25.9)	<0.001
Severe AP	288 (47.7)	28,492 (60.8)	<0.001
rTM, n (%)			
All AP	76 (1.9)	3715 (1.8)	0.39
Mild AP	12 (0.6)	492 (0.4)	0.25
Severe AP	26 (4.3)	1840 (3.9)	0.64
Tube feeding, n (%)			
All AP	312 (7.9)	9850 (4.6)	<0.001
Mild AP	92 (4.5)	1895 (1.6)	<0.001
Severe AP	96 (15.9)	5872 (12.5)	0.013
Interval between the admission and start of tube feeding, days, mean (SD)	8.2 (19.2)	10.8 (26.8)	0.02
CHDF, n (%)			
All AP	16 (0.4)	3601 (1.7)	<0.001
Mild AP	1 (0.1)	332 (0.3)	0.052
Severe AP	5 (0.8)	2244 (4.8)	<0.001
Any intervention for local complications, n (%)	8 (0.2)	2818 (1.3)	<0.001
EUS-guided fistuloplasty	3 (0.1)	1488 (0.7)	<0.001
Percutaneous drainage	2 (0.1)	1197 (0.6)	<0.001
Surgery	3 (0.1)	461 (0.2)	0.055

We analyzed 3941 pediatric (2034 mild and 604 severe) and 212,776 adult (115,117 mild and 46,841 severe) cases. Because AP severity was not recorded in all cases, the total number of cases was not equal to the sum of mild and severe cases. AP, acute pancreatitis; CHDF, continuous hemodiafiltration; EUS, endoscopic ultrasound; rTM, recombinant human-soluble thrombomodulin; SD, standard deviation.

intervention for late complications, shorter LOS, and lower mortality, overall and in severe cases. Our results agree with previous studies showing that complication risk and mortality are relatively low in pediatric AP compared with adults [4–6]. Although the number of severe cases was smaller, pediatric AP cases, especially in those aged 1–6, were transferred from other institutions and treated at academic hospitals more often than adult cases. Although they are not specific to pediatric AP, the Japanese guidelines for the management of AP state that the patients should be transferred to a facility that can handle the case, if the patient is judged to be severe and the facility cannot handle the case, or if the disease course becomes difficult to handle due to severe illness or complications of infection [24]. AP might be regarded as a difficult disease to manage in pediatrics, even by pediatric gastroenterologists, and institutions where pediatric AP can be properly treated might be still limited in Japan.

Regarding the treatments for AP, protease inhibitors and antimicrobial drugs were less frequently administered in pediatric AP than in adults. In the Japanese guidelines for the management of AP [24], no recommendation is stated for the administration of protease inhibitors because the efficacy thereof to improve the prognosis and the development of complications has not been proven. Prophylactic administration of antibiotics is not recommended for mild AP and no recommendation is stated for severe AP cases [24]. Tube feeding was more frequently performed in pediatric AP, especially in severe cases of patients aged 1–6 years, than in adult AP. This was unexpected, because tube insertion may be considered to be a greater burden in pediatrics than in adults and only 3 % of pediatric cases underwent enteral feeding in a previous study [4]. A significant reduction in infectious complications, multiple organ failure, and mortality was shown in a meta-analysis when enteral nutrition was initiated within 48 h of AP diagnosis [25]. Nevertheless, enteral nutrition is not commonly used as yet, even in severe AP patients, despite the strong recommendation in the Japanese guidelines [24,26]. A quality improvement initiative to increase the proportion of pediatric patients receiving early enteral nutrition has been reported [27]. It would be of interest to see whether early enteral feeding would improve the prognosis of younger pediatric cases with AP.

In a meta-analysis of 48 studies, the case-fatality rate of pediatric AP was 6.2 % in Europe, 4.7 % in North America, and 2.4 % in Asia [15]. Overall mortality in AP was 0.7 % in this study, which appears to be lower than that in the meta-analysis, but was comparable to 0.76 % in 55,012 pediatric (1–20 years of age) AP patients in a study using the Healthcare Cost and Utilization Project Kids' Inpatient Database in the United States [8]. There might be several explanations for low mortality in pediatric AP. First, alcoholic AP, an etiology with higher mortality [28], is virtually absent. Second, comorbidities are less frequent in pediatrics, as shown by the CCI of 0 in the majority of pediatric patients. Third, interventions for local complications, associated with high mortality, were rarely performed. Previous studies have shown that development of multiple organ failure or pancreatic necrosis is rare and accounts for less than 6 % cases in pediatrics [4–6]. Further studies are warranted to clarify whether local complications resolve spontaneously more often in children than in adults. Some protective mechanisms might exist for the smooth recovery of the injured pancreas [4], which requires further investigations.

Among the pediatric AP patients, there were some differences in clinical presentation and management between the youngest group aged 1–6 and the older groups. Mortality was higher, ICU admission was more frequent, and LOS was longer in patients aged 1–6 than pediatric patients thereafter. Although the proportion of severe cases was not different, there were more cases fulfilling the prognostic score criteria in the younger groups (1–6, 28.2 %; 7–12, 18.8 %; 13–18, 11.8 %). In the latest nationwide epidemiological survey in Japan [11], severe AP patients fulfilling the prognostic factors are at high risk for fatal outcome; severe AP patients fulfilling the prognostic scores had higher mortality than those fulfilling the CT grade (12.5 % vs. 5.0 %, $P < 0.001$).

Previous studies have shown that clinical features of AP cases might differ between infants/toddlers and older children [29,30].

Infants and toddlers with AP present with fewer classical symptoms, are more likely to be diagnosed by serum lipase, undergo radiographic evaluation, and have longer LOS. Young age might predict the disease severity in pediatric AP [31]. Among the patients with the first episode of AP, those younger than 6 years old had a risk for moderate to severe diseases with odds ratio of 7.5. As in the case of transfer, ICU admission is discretion of the treating physician, but the general indication is the difficulty to handle in the general ward. Very young persons have lower physiological reserves than healthy adults, often developing complex comorbid medical conditions associated with AP, requiring intensive management for circulatory and respiratory dynamics in ICU, and resulting in higher mortality.

This study has several limitations, mainly due to the constrains of the DPC database. First, the database does not cover all hospitals or specific populations such as a medical insurance program, relies on the accuracy of ICD-10 codes for AP, and is limited to inpatient settings and retrospective in nature. Because we could not determine the true incidence of AP, we calculated the proportion of AP among all admissions instead. The Japanese clinical guidelines recommend the management of AP cases for inpatient treatment should be provided if the diagnosis of AP is made [24]. However, mild AP cases may be treated in outpatient settings [9]. Second, the DPC database does not contain detailed clinical information including laboratory and radiological data, except for the CT grading in the Japanese severity criteria. The interval between symptom onset and admission is not recorded. AP severity was not recorded in all cases, in part due to the fact that contrast-enhanced CT is often avoided especially in pediatric patients. Third, etiologies and risk factors as well as the number of attacks (sentinel AP or recurrent AP) could not be assessed in detail. It is possible that cases with systemic diseases and AP have been missed if their principal diagnosis was not AP or in whom AP did not account for most of the medical expenses. Regarding biliary AP and acute-on CP, we analyzed the patients in which cholelithiasis and CP were recorded as comorbidities present on admission. The frequency of comorbidities might be underestimated because the recording of comorbidities is not mandatory. Fourth, we could not determine whether in-hospital death was associated with AP or was due to underlying systemic diseases. Lastly, severity was not assessed using the internationally accepted criteria, such as the Atlanta criteria; the Japanese severity criteria, which includes parameters such as age $\geq$70 years and is not optimized for the severity assessment of pediatric AP, was used [12]. Although the pediatric Japanese scoring system has been proposed [12], it is not widely used and such information is not available in the DPC database. Despite these limitations, our study clarified the recent trend and current status of pediatric AP in Japan, including less severe disease course, leading to shorter hospital stays, less frequent interventions for local complications, and lower mortality than in adult AP. Further studies are warranted to clarify the long-term prognosis of pediatric AP including the recurrence and transition to CP. Evidence-based guidelines for the management of pediatric pancreatitis have been proposed by the European Pancreatic Club, in collaboration with the Hungarian Pancreatic Study Group [32]. We hope that the information provided by our study will enhance the background of pediatric AP in Japan, leading to improved diagnosis and treatment thereof.

Author contributions

M.I., K.K., K.T., and A.M. designed the study. K.T., K. Fujimori and K. Fushimi retrieved the data from the DPC database. M.I., K.K., S.H., T.T., R.M., T.S., A.S., M.S., K.T., K. Fujimori, and A.M. analyzed the data. M.I. and A.M. drafted the manuscript and A.M. edited the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2023.10.002.

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