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RETRACTED: Peg-Asparaginase-Associated Pancreatitis in Chemotherapy-Treated Pediatric Patients: A 5-Year Retrospective Study

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Background: Asparaginase-associated pancreatitis (AAP) is one of the most common complications occurring in patients with asparaginase-treated acute lymphoblastic leukemia (ALL). Peg-asparaginase (peg-asp), a chemically recombined asparaginase with lower hyposensitivity and better patient tolerance, is now approved as the first line asparaginase formulation in ALL chemotherapy regimens. Due to the differences in pharmacokinetic characteristics and administration procedure between l-asp and peg-asp, this study aimed to investigate the clinical manifestations of peg-asp-associated pancreatitis.

Method: Patients with peg-asp-associated pancreatitis diagnosed within a 5-year period (July 2014 to July 2019) were identified and retrospectively studied. The clinical manifestations, laboratory findings, and imaging results of patients with AAP were analyzed. AAP patients were further classified into mild/moderate and severe groups based on criteria used in previous studies. Clinical outcomes were compared between groups.

Results: A total of 38 patients were enrolled in this study. The underlying disease included ALL (n=35) and lymphoma (n=3). The majority of patients developed AAP during the first phase, called remission induction (n=26, 68.4%), after a median of 2 peg-asp doses (range: 1–11). The DVLP regimen (n=23) is the most common peg-asp regimen used in AAP patients. Abdominal pain occurred after a median of 14.5 days (range: 1–50) from the last peg-asp administration, accompanied by abdominal distension (n=14), nausea (n=17), vomiting (n=21), and fever (n=19). Serum amylase elevation was reported in all AAP patients, of whom 65.8% (n=25) exhibited an elevation in the level of this enzyme three times the upper normal level, fulfilling the Atlanta criteria. The level of serum lipase (median days of elevation=23 days, range: 4–75) was significantly elevated compared with that of serum amylase (median days of elevation=9 days, range: 2–71) and persisted at a markedly high level after the level of serum amylase returned to normal. Common local complications included abdominal ascites (n=10) and peripancreatic fluid collection (n=8).

Approximately 42.1% (n=16) of patients with severe AAP experienced systemic complications (septic shock or hypovolemic shock) or severe local complications (pseudocyst), among whom 5 failed to recover. Approximately 84.8% (n=28/33) of the remaining patients resumed chemotherapy; among them, peg-asp formulation in 30.3% (n=10/33) of these patients was adjusted, while asparaginase treatment in 39.4% (n=13/33) was permanently discontinued. Five patients experienced an AAP relapse in later stages of asparaginase treatment. Comparison between mild/moderate and severe AAP patients showed a statistically significant difference in the number of pediatric intensive care unit stays (p=0.047), survival rate (p=0.009), AAP prognosis (p=0.047), and impacts on chemotherapy (p=0.024), revealing a better clinical outcome in mild/moderate AAP patients.

Conclusion: Early recognition and management of AAP is essential in reversing the severity of AAP. The existing AAP criteria had a low strength in determining the severity of pediatric AAP. A well-defined AAP definition could help distinguish patients with high anticipated risk for redeveloping AAP and ALL relapse, in order to prevent unnecessary withdrawal of asparaginase. Our study could serve as a basis for conducting future large cohort studies and for establishing an accurate definition of pediatric AAP.

Keywords: asparaginase, pegaspargase, pancreatitis, childhood leukemia, retrospective study

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INTRODUCTION

Asparaginase is an essential chemoagent used in combination with chemotherapy for ALL, especially in the early remission induction stage. By catalyzing the hydrolysis of extracellular asparagine, thus depleting the level of plasma asparagine necessary for the growth of leukemic lymphoblasts in vitro, asparaginase could inhibit leukemic lymphoblast protein synthesis and subsequently induce apoptosis while not posing any hematological toxicity (1). This will help achieve remission and induce the anti-leukemic effect of post-chemotherapy agents (2). A previous study showed that an asparaginase-included regimen could achieve a significantly higher event-free survival rate (71% vs 31%) (3). A recent study has proven that those who completed the asparaginase regimen had a higher 5-year event-free survival rate (90%) compared with those who were unable to tolerate toxicity and forced to discontinue the treatment (73%) (4).

However, repeated administration and hypersensitivity to *Escherichia coli*-derived asparaginase led to various undesired clinical events, which could either delay or suspend chemotherapy (2). To combat this high immunogenicity while maintaining an effective asparaginase activity, a chemically recombinant form of asparaginase was developed. Peg-asparaginase (peg-asp) has a polyethylene glycol molecule conjugated to its *E. coli*-derived L-asparaginase (l-asp), which could alter its immunogenic property, preventing hypersensitivity and unfavorable immune response (5). With a longer half-life and better patient tolerance, peg-asp is now approved as a first-line asparaginase formulation in ALL chemotherapy regimens (6–8). Others recommend peg-asp as an alternative treatment for ALL patients who are hypersensitive to native asparaginase (9). This treatment is also effective in patients with other malignant diseases and tumors such as lymphoma and myelosarcoma (10).

Adverse events had always been a major concern during the period of chemotherapy. Events such as hyperinsulinemia, hypertriglyceridemia, hypoproteinemia, and coagulation disorders have been reported during asparaginase administration (11). No significant difference was observed in the types of adverse events between l-asp and peg-asp formulation (9). Asparaginase-associated pancreatitis (AAP) is one of the most common adverse events. The onset of severe AAP would require permanent withdrawal of asparaginase from the patient's chemotherapy regimen, which affected the remission rate and resulted in a poor treatment outcome (6). Studies regarding pediatric peg-asp-associated pancreatitis are limited. Due to the differences in pharmacokinetic characteristics and administration procedure between l-asp and peg-asp, it is important to evaluate the clinical profile of peg-asp-associated pancreatitis.

This study aimed to study the clinical profile of peg-asp-associated pancreatitis in pediatric patients. A 5-year retrospective study was conducted in a pediatric center. All baseline characteristics, underlying disease profile, laboratory findings, and radiographic results were analyzed. The clinical manifestations of patients with peg-asp-associated pancreatitis

Abbreviations: AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; CT, computed tomography; Dex, dexamethasone; DNR, daunomycin; DVLP, daunomycin (D), vincristine (V), peg-asparaginase (L), prednisolone (P); ERCP, endoscopic retrograde cholangiopancreatography; HR, high risk; HSCT, hematopoietic stem cell transplant; IR, intermediate risk; l-asp, L-asparaginase; LR, low risk; MRD, minimal residue disease; peg-asp, peg-asparaginase; PICU, pediatric intensive care unit; PH+, Philadelphia chromosome-positive; UNL, upper normal level; VCR, vincristine.

were summarized and the patients were classified into mild/moderate and severe groups. The clinical outcomes were compared between the two groups.

MATERIALS AND METHODS

Study Participants and Definitions

All clinical diagnosis and treatment procedures were carried out in Shanghai Children's Medical Center, affiliated hospital of Shanghai Jiao Tong University School of Medicine, department of hematology or pediatric intensive care unit. Once the underlying disease diagnosis and risk stratification was confirmed, the patients were enrolled in the study following the standardized nationwide protocol. Acute lymphoblastic leukemia (ALL) was diagnosed and treated according to the CCCG-ALL 2015 protocol, while lymphoma (both Hodgkin's and non-Hodgkin's lymphoma) patients were diagnosed and treated following the CCCG-LBL-2016 protocol. Our study was approved by the ethics committee of the hospital, and a written informed consent was obtained from the patients' parents or guardians.

Peg-asp was a preferential formulation as it only requires a few injections, has lower immunogenicity, and has better patient tolerance. All recipients were tested for hypersensitivity to asparaginase before administration, and asparaginase was administered to patients with no prior exposure to l-asp. Peg-asp was administered at a standard dose of 2,000 U/m^2 via intramuscular injection. In prospective treatment, a half-dose of Erwinia asparaginase was administered to the mild/moderate AAP group, while the administration of asparaginase was permanently discontinued in the severe AAP group (6).

ALL risk stratification was based on patients' cytogenetic profile and baseline WBC counts. The risk group was modified according to the patient's remission status, which was referred to as minimal residue disease (MRD). Patients with a precursor B-cell phenotype and who had one of the following features were classified as the low-risk (LR) group: age >1 years, baseline WBC count ≤50×10^9/L, chromosomes >50, and presence of TEL-AML1 gene. Treated patients with an MRD of >1% on Day 19 were classified as the intermediate-risk group (IR). The other IR groups were Philadelphia chromosome-positive (PH+), T-cell phenotype, hypodiploidy (<44 chromosomes), and LR MLL-r ALL patients (indicated as WBC<300×10^9/L and age >6 months). Patients with a high-risk (HR) MLL-r phenotype or a MRD of >1% on Day 46 were classified as the HR group. Lymphoma was either classified as stage III (tumors in the lymph node areas on both sides of the diaphragm) or stage IV (CNS or bone marrow involvement) according to the invasiveness of the neoplasm.

The diagnosis of pancreatitis was made based on the Atlanta classification (12), which requires the fulfillment of any two of the following criteria: (1) typical abdominal pain associated with pancreatitis (persistent, radiating back pain), (2) level of serum amylase or lipase is three times higher than the upper normal level (UNL), and (3) typical signs of pancreatitis on imaging (either ultrasound or computed tomography [CT] scan).

AAP was referred to as onset of pancreatitis associated with a previous treatment of asparaginase-included chemotherapy. The clinical diagnosis of AAP was based on the patient's symptoms (abdominal pain associated with nausea and vomiting) and previous medications, concurrently supported by an elevation in the levels of serum amylase and imaging evidences. Patients with pancreatitis related to trauma, biliary duct obstruction, or hyperlipidemia were excluded from this study. Patients with abnormal pancreatic imaging prior to peg-asp administration were also excluded. Patients' medical records were carefully assessed. For severity classification, AAP patients were further classified into mild/moderate (severe pain, vomiting, and medical intervention required) and severe AAP group (life-threatening incidents or urgent intervention required) according to the classification criteria used in a previous study (13).

Data Collection

The cytogenetics profile of patients was determined once the underlying disease was diagnosed. The karyotype and immunophenotype were determined using the cytometric bead array system, while the targeted gene mutation was detected by performing a fluorescence in situ hybridization assay. All peg-asp-treated hospitalized patients underwent routine blood sample collection for laboratory testing to monitor for peg-asp-related adverse events. For emergency patients admitted in the hospital, a laboratory test was performed within 2 hours of in-patient admission. Ultrasound was used for screening and diagnosis of AAP, while contrast CT was used to confirm the severity of pancreatitis and local complications. For patients who were highly suspected of having AAP but inflammatory edema was not detected by ultrasound, contrast-enhanced CT or MRI were performed to further obtain imaging evidence. For patients with persistent pancreatic enzyme elevation and progressing clinical symptoms, MRI was performed to evaluate for the presence of severe complications.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 19.0. Continuous data such as days were presented as median and range. Measurement data were presented as mean and range. Enumeration data were expressed as frequency and rate (%). The differences in the recorded values between the mild/moderate group and severe AAP group were tested for significance using the Fisher's exact test. A two-sided p value of <0.05 was considered significant.

Chemotherapy Protocol

The CCCG-ALL 2015 protocol was designed and adapted to Chinese pediatric patients based on the 10-year multicenter clinical experiences. This protocol is widely used in more than 20 provinces (including Hong Kong). In the CCCG-ALL 2015 protocol, all newly diagnosed patients received the DVLP regimen in the first remission induction stage, of among the ALL risk groups. Peg-asp was administered on Days 6 and 26 concurrently with daunomycin (D), prednisolone (P), and vincristine (V) for 3–4 weeks. For the IR or HR groups, an

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additional dose of peg-asp was administered on Day 50, concurrently with CAT+VCR regimen (cyclophosphamide, cytarabine, mercaptopurine, and vincristine). During the second remission stage, a combination of dexamethasone (Dex), daunomycin (DNR) (for LR group)/cytarabine (Ara-C) (for IR and HR groups), vincristine (VCR), and peg-asp was used. For HR patients who failed to achieve remission and were preprocessing for a hematopoietic stem cell transplant (HSCT) procedure, a DAEL regimen (daunomycin, cytarabine, etoposide, and peg-asp) was administered after the consolidation stage. In the CCCG-LBL-2016 protocol, patients received peg-asp as part of the DVLP regimen during the first remission and a HR regimen (together with Dex, cytarabine, and etoposide) during the consolidation stage. A prospective chemotherapy was provided after peg-asp was successfully administered and the dose was adjusted according to the protocols. The appropriate dose of other chemotherapeutic agents was provided according to the aforementioned protocols.

RESULTS

Patients' Characteristics

Between July 2014 and July 2019, 965 patients were administered with peg-asp, and 40 hospitalized patients were diagnosed with pancreatitis during asparaginase treatment. Two patients with hyperlipidemia and abnormal pancreatic imaging before peg-asp administration were excluded. The remaining 38 patients met the AAP criteria and were eligible for this study. The incidence of AAP was 3.94% (38/965). The female to male ratio was 1:2.17 (12 women and 26 men), and the mean age was 8.52 years (range: 1.3–16.1) (**Table 1**).

With regard to the underlying disease and chemotherapy cycle, 92% (n=35) of the patients were diagnosed with ALL, in whom 21 had ALL in the first stage of induction, 10 had ALL in the second stage of induction, 3 had ALL in the relapse stage, and 1 had ALL while preparing for HSCT. All relapse patients underwent the induction stage. Among the 35 ALL patients, 1 had mixed lineage leukemia and the other had CML-BC. The remaining patients were diagnosed with lymphoma, of whom 2 had Hodgkin's lymphoma (HL) in the induction stage and 1 had non-Hodgkin's lymphoma (NHL) in the consolidation stage. The B-cell immunophenotype (n=29) was more prevalent than the T-cell phenotype (n=9), which is an IR ALL subtype. The targeted gene fusion was only detected in 26.3% (n=10) of the patients, while the other patients had more than one fusion gene. Fusion genes include TEL-AML1 (n=4), PH+/BCR-ABL (n=4), TCF3/PBX1 (n=3), and 11q23 (referring to MLL-r) (n=1). Approximately 80% (n=9) of these patients were classified as the IR group (**Table 1**).

The ALL IR group comprised 60.5% (n=23) of patients in our study. Approximately 18.4% (n=7) and 13.2% (n=5) of the patients comprised the HR and low-risk (LR) groups, respectively. The IR and HR groups received the same combination of chemotherapeutic agents recommended in the CCCG-ALL-2015 protocol. For lymphoma, two patients were diagnosed with stage III, while one was diagnosed with stage IV (**Table 1**).

TABLE 1 | Baseline and underlying disease characteristics.

	All patients (n = 38)
Baseline and underlying disease characteristics	
Age, years	8.52(3.98)
Gender	
Male	26(68.4%)
Female	12(31.6%)
Underlying disease	
ALL	33(86.9%)
HL	2(5.3%)
NHL	1(2.6%)
CML-BC	1(2.6%)
Mixed lineage leukemia	1(2.6%)
Baseline WBC counts, 10^9/L	
<50	27(71.1%)
50–299	8(21%)
>300	3(7.9%)
Immunophenotype	
B cell	29(76.3%)
T cell	9(23.7%)
Fusion gene detected	
TEL-AML1	4(10.5%)
PH+/BCR-ABL	4(10.5%)
TCF3/PBX1	3(7.9%)
11q23	1(2.6%)
Not yet defined	4(10.5%)
No aberrations	24(63.2%)
Risk group	
Low risk (LR)	5(13.2%)
Intermediate risk (IR)	23(60.5%)
High risk (HR)	7(18.4%)
Stage III (lymphoma)	2(5.3%)
Stage IV (lymphoma)	1(2.6%)
Chemotherapy in cycle	
First induction	26(68.4%)
Second induction	10(26.3%)
Consolidation	1(2.6%)
Preprocessing for HSCT	1(2.6%)
Chemotherapy in regimen	
DVLP	23(60.5%)
CAT+VCR+PEG (IR/HR)	3(7.9%)
Dex+Ara-C+VCR+PEG(+6mp) (IR/HR)	8(21.1%)
Dex+DNR+VCR+PEG (LR)	2(5.3%)
DNR+Ara-C+vp-16+PEG (DAEL)	1(2.6%)
Dex+Ara-C+vp-16+PEG	1(2.6%)
AAP severity	
Mild/moderate	22(57.9%)
Severe	16(42.1%)
Clinical outcome	
Alive in remission	28(84.8%)
Alive in AAP relapse	5(15.2%)
Dead	5(13.2%)

Enumeration data is presented in n(%) while age is presented in mean(standard deviation). n/N% is calculated with N=38. ALL, acute lymphoblastic leukemia; HL, Hopkin's lymphoma; NHL, Non-Hopkin's lymphoma; CML-BC, Chronic myeloid leukemia blast crisis; CAT, cyclophosphamide (C), cytarabine (A), mercaptopurine (T); DVLP, daunomycin (D), vincristine (V) peg-asparaginase (L), prednisolone (P); VCR, Vincristine; DNR, Daunomycin; Ara-c, cytarabine; Dex, Dexamethasone; 6mp, Mercaptopurine; vp-16, Etoposide; PEG, Peg-asparaginase; HSCT, Hematopoietic stem cell transplant; PH+, Philadelphia chromosome positive.

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With regard to the chemotherapy regimen, 26 (68.4%) patients underwent the first stage of induction. Approximately 60% (n=23) of the patients received DVLP regimen, while 7.9% (n=3) received a combination of CAT, VCR, and peg-asp. One patient received DAEL while preprocessing for HSCT. Among the 10 patients who underwent the second induction, 2 received a low-risk regimen (Dex+DNR+VCR+peg-asp), 3 received an IR/HR regimen (Dex+Ara-C+VCR+peg-asp), and 5 received mercaptopurine (6MP) as additional regimen. Only one patient (NHL) received a peg-asp regimen in the consolidation stage (**Table 1**). The other pancreatitis-related HR medications were glucocorticoids (n=10), mercaptopurine (n=8), cytarabine (n=15) as part of the combined chemotherapy, furosemide (n=5) for prevention of fluid overload, and sulfamethoxazole (n=10) as prophylaxis against *Pneumocystis carinii* infection.

Asparaginase-Associated Pancreatitis

Clinical Manifestation

Pancreatitis-related symptoms occurred after a median of 14.5 days (range: 1–50) from the last peg-asp administration. The median administration doses of peg-asp before AAP onset was 2 doses (range: 1–11), in which the majority of AAP cases occurred during the first stage of induction (n=26, 68.4%), when the patients had their initial exposure to peg-asp (**Table 2**).

Abdominal pain was the most common symptom reported in all AAP patients, manifested as localized (n=21) or diffused (n=16) abdominal pain. The duration of abdominal pain was diverse and could last for as long as 41 days. Among all patients, four experienced hypovolemic shock during the onset of AAP. The other common associated symptoms included abdominal distension (n=14), nausea (n=17), vomiting (n=21), fever (n=19), diarrhea (n=4), and gastrointestinal bleeding (n=4) (**Table 2**).

Approximately 52% (n=20) of the patients developed local complications. The short-term complications were abdominal ascites (n=10), peri-pancreatic fluid collection (n=8), intestinal obstruction (n=3), and pancreatic pseudocyst (n=3). The long-term complications were chronic pancreatitis (n=4) and obstruction of the main pancreatic duct (n=3). Three patients required endoscopic retrograde cholangiopancreatography (ERCP) for bile duct stent placement, while two required drainage of ascites. Meanwhile, the most common systemic complications were septic shock (n=8), hypovolemic shock (n=6), hypoproteinemia (n=9), hepatic insufficiency (n=6), pneumonia (n=6), coagulation disorder (n=4), and DIC (n=4) (**Table 2**).

Pancreatic Enzymes and Imaging Results

Elevation of serum amylase was reported in all AAP patients. Approximately 65.8% of patients (n=25) experienced an elevation three times higher than the UNL within 48 hours of onset. Serum amylase reached the peak value within a median of 3.5 days (range: 1–37 days), with a mean peak value of 466 U/L (range: 50–1,702 U/L). The level of serum amylase returned to normal within 8 days (range: 1–70 days). However, the serum amylase level in four patients did not return to normal due to unfavorable clinical outcomes. All patients experienced an elevation in serum lipase levels three times higher than the UNL, with a mean peak value of 2,982 U/L (range: 899–4,545 U/L) (**Table 3**). The level of serum lipase was significantly elevated compared with that of serum amylase and persisted at a markedly high level (median days of elevation=24 days, range: 4–75) after the level of serum amylase normalized (median days of elevation=9 days, range: 2–56). In sporadic cases, the lipase level remained extraordinarily high (>2,000 U/L) for months until normalization.

In our study, either or both abdominal ultrasound and contrast CT scan were performed in each patient. The detection rates were 78.4% (n=29/37) and 71% (n=22/31), respectively (**Table 3**). The overall imaging detection rate was 89.5% (n=34/38). The remaining four patients were diagnosed based on their clinical symptoms and elevation of serum amylase (**Table 2**). Both imaging methods provided an acceptable detection efficacy. The ultrasound could be applied at earlier clinical settings and performed at bedside. Hence, it is more

TABLE 2 | Clinical manifestations of AAP patients.

	All patients (n = 38)
Clinical manifestation of AAP	
Abdominal pain as onset symptoms	37(97.3%)
Localized	21(55.3%)
Diffused	16(42%)
Clinical symptoms	
Abdominal pain	37(97.3%)
Abdominal distension	14(36.8%)
Nausea	17(44.7%)
Vomiting	21(55.3%)
Diarrhea	4(10.5%)
Fever	19(50%)
Gastric-intestinal bleeding	4(10.5%)
Diagnosis related	
Pancreatic enzymes>3 times UNL	24(63.2%)
Diagnosed by imaging evidences	34(89.5%)
Diagnosed by enzymes elevation	4(10.5%)
Local complication	
Abdominal ascites	10(26.3%)
Peri-pancreatic fluid	8(21.1%)
Chronic pancreatitis	4(10.5%)
Pseudocyst	3(7.9%)
Disruption of main pancreatic duct	3(7.9%)
Intestinal obstruction	3(7.9%)
Systemic complication	
Septic shock	8(21.1%)
Hypovolemic shock	6(15.8%)
Hypoproteinemia	9(23.7%)
Hepatic insufficiency	6(15.8%)
Pneumonia	6(15.8%)
Coagulation disorder (except DIC)	4(10.5%)
DIC	4(10.5%)
Renal insufficiency	3(7.9%)
Hyperglycemia	1(2.6%)
Duration	
Days from last PEG-ASP to diagnosis	14.5(1–50)
Days from onset to peak amylase level	3.5(1–37)
Days from enzyme elevation to normalization	8(1–70)

Enumeration data is presented in n(%) while continuous data is presented in median (range). n/N% is calculated with N=38. UNL, upper normal limit; PEG-ASP, Peg-asparaginase.

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TABLE 3 | Laboratory and radiographic results of AAP patients.

	All patients (n = 38)
Laboratory and radiographic results	
Serum pancreatic enzyme	
Peak amylase level, U/L	466(50-1702)
<3 times UNL	13(34.2%)
≥3 times UNL	25(65.8%)
Peak lipase level	2982(899–4545)
<3 times UNL	0
≥3 times UNL	38(100%)
Liver enzyme	
Alanine aminotransferase, U/L	113.25 (9–587)
<69	20(52.6%)
70-138	6(15.8%)
>139	12(31.6%)
Aspartate aminotransferase, U/L	34.9(13–1185)
<46	15(39.5%)
47-92	9(23.7%)
>93	14(36.8%)
Other test results	
Total bilirubin, μmol/L	16.3(11–106.5)
Prothrombin time, s	13.6(6.8–45.3)
Activated partial thromboplastin time, s	74.2(21–180)
Fibrinogen, g/L	1.32(0.29–3.89)
Creatine, μmol/L	33.8(13–167)
Blood urea nitrogen, mmol/L	6.7(1.5–22.8)
Radiographic detected cases	
Ultrasound (N=37)	29(78.4%)
Contrast CT (N=31)	22(71%)

Results were collected at diagnosis of AAP and were continuously monitored. Enumeration data is presented in n(%) while measurement data is presented in mean (range). n/N% is calculated with N=38. Only radiographic detected cases with a corresponding N stated in the table. Upper normal level (UNL) of amylase and lipase are 110U/L and 300 U/L respectively. CT, computed tomography.

preferentially used in critical conditions. The direct ultrasound findings included enlargement, edema, and echo heterogeneity of the pancreas. Contrast-enhanced CT scan had a higher sensitivity in detecting abdominal effusion and less disturbed by intestinal gas, which is a better tool for assessing the severity of AAP. The status of hepatic and renal functions should be assessed prior to the injection of contrast medium.

AAP Severity

With regard to the AAP severity, 57.9% (n=22) of the patients had had mild/moderate AAP, while 42.1% (n=16) had severe AAP (**Table 1**). In severe AAP group, 14 patients experienced systemic complication such as septic shock (n=8) and hypovolemic shock (n=6), accompanied with organ dysfunction within 48 hours of onset. The remaining two patients had severe local complications (pseudocyst) and required percutaneous puncture drainage. The clinical outcomes and prognosis were individually analyzed according to AAP severity and are mentioned below.

Treatment and Clinical Outcomes

The pancreatitis major treatment measures included fasting, nutritional support (total parenteral nutrition or nasojejunal tube feeding), intravenous fluid resuscitation, and pancreatic secretion inhibition. According to the CCCG-ALL 2015 protocol, the patients were advised to temporarily suspend asparaginase once diagnosed with AAP and received pancreatic secretion inhibitors as major treatment. Somatostatin or its synthetic analog, octreotide, was widely used for inhibiting both pancreatic exocrine and endocrine secretion. In some cases, ulinastatin, a protease inhibitor, was administered to stabilize the pancreatic enzymatic activity in order to alleviate local tissue inflammation. Minor treatment measures included antibiotics against infection, proton pump inhibitors (i.e., omeprazole) for inhibition of gastric acid secretion, and CRRT for alleviating systemic inflammation and removal of toxic substances. All major measures were provided once diagnosis was confirmed. Octreotide was administered at a dose of 0.1 mg, 1–3 times/day (i.d.), while ulinastatin was administered at a dose of 100,000 U, 1–3 times/day (i.v.). For those patients who recovered and required asparaginase-included therapy, a nasojejunal tube was routinely placed in advance for future enteral nutrition needs. Complications such as obstruction of the main pancreatic duct and pancreatolithiasis were resolved by performing an ERCP, while pseudocyst, peri-pancreatic fluid, and abdominal ascites were resolved by performing a percutaneous puncture drainage.

With regard to the clinical outcome, 42.1% (n=16) of the patients experienced severe conditions and were immediately transferred to the pediatric intensive care unit (PICU) in order to receive advanced supportive care. Among all patients, four died due to severe sepsis and multi-organ failure, while one experienced severe infection and eventually developed septic shock. In the review of medical history, all patients developed severe infection due to myelosuppression and were administered with antibiotics accordingly. Some patients had persistent fever and were unresponsive to asparaginase; the infectious state might have possessed an extra risk of developing severe AAP. After appropriate medication and measures were provided, 86.8% (n=33) of the AAP patients survived, and no case fatality was observed in the mild/moderate AAP group.

The median length of PICU stay was 6 days (range: 2–20 days). With regard to the impact of chemotherapy, 76.3% (n=28/33) of the patients ultimately recovered and resumed ALL chemotherapy, while 15% (n=5/33) experienced relapse of AAP. Most of the AAP patients who recovered received a half dose of L-asp with octreotide for prophylaxis in the proceeding chemotherapy. Some relapse patients experienced AAP recurrence (≥2 times) due to the inappropriate re-challenging with asparaginase. One patient was re-challenged with asparaginase after temporary suspension for two courses. This patient experienced subsequent severe AAP and was irresponsive to routine pancreatitis treatment. Another patient repeatedly experienced AAP when the asparaginase therapy was resumed (administered with one-half dose of l-asp). Asparaginase administration was still not discontinued in this patient despite the recurrence of AAP. All AAP relapse patients experienced severe local complications during the initial onset of AAP. The obstruction of pancreatic duct, substantial ascites, and pancreatic pseudocyst were confirmed respectively and were tracked throughout the disease course. The peg-asp dose was adjusted

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in 30.3% (n=10) of the patients, while asparaginase was permanently withdrawn from the chemotherapy regimen in 39.4% (n=13) of the patients (**Table 4**).

Comparison between mild/moderate and severe AAP patients showed a statistically significant difference in the number of PICU stay (p=0.047), survival rate (p=0.009), AAP prognosis (p=0.047), and impacts on chemotherapy (p=0.024). Mild/moderate AAP was associated with shorter PICU stay, higher survival rate, higher remission rate, and lower risk of permanent withdrawal of asparaginase treatment. Overall, the mild/moderate AAP group showed better overall clinical outcome (**Table 4**). The presence of local complication (p=0.008) was significantly observed in relapse cases and was statistically different from that in non-relapse cases. This can serve as a potential risk factor and remain to be confirmed in a larger cohort.

Case Analysis

In occult cases, the AAP symptoms could be concealed by the side effect of chemotherapy or underlying disease. One 12-year-old boy with ALL relapse experienced exacerbation a day after peg-asp administration, manifested as continuous vomiting and hematemesis without any local abdominal signs. The levels of serum amylase were elevated at the onset of AAP but only reached the peak value a week later. He was admitted to the PICU 2 weeks later due to refractory hypovolemic shock and received advanced supportive care. The patient then developed severe pneumonia and gastroenteritis due to myelosuppression and gradually progressed to septic shock. He did not recover and died 2 weeks after hospitalization. Another patient experienced left lumbar pain with pain radiating to the back 16 days after peg-asp administration. He later underwent ERCP and was diagnosed with duodenum hyperplasia and pancreatolithiasis. Both patients had non-typical episodes due to a comorbidity and their primary disease. The management of AAP should not be focused on treating the local symptoms. The systematic symptoms and accompanying disease must also be taken into consideration. Most of these patients have long histories of hospitalization, multi-drug medications, or malnutrition. They were at higher risk for developing infection, which could delay AAP remission. Hence, a systemic evaluation of potential complications was of utmost importance.

In fact, not all cases of AAP onset were latent and untypical. One patient experienced persisted abdominal pain at the left hypochondria area. The serum amylase level peaked (973 U/L) 2 days after the onset of symptoms. This patient had repeatedly experienced nausea and vomiting and gradually developed a Grey Turner's sign. Both ultrasound and contrast CT scan showed evidence of pancreatitis.

DISCUSSION

In this study, AAP occurred at a median of 14.5 days (range: 1–50 days) after peg-asp administration, which is in agreement with the reports of previous studies (range: 11–15 days) (14, 15). One previous study reported a longer duration (26 days) between asparaginase administration and AAP (16). This study enrolled a majority of less severe cases (mild symptoms and lower enzyme elevation) and subclinical AAP treated with a higher dose (2,500 IU/m^2) of peg-asp, which might explain the differences at the time of onset.

The manifestations of AAP was closely related to the pharmacokinetic characteristics of peg-asp. The half-life (5.7 days) of peg-asp was relatively longer than that of the other asparaginase formulations (6). The enzymatic activity could last for 18–21 days or more after administering a single dose of peg-asp (17). Thus, peg-asp was administrated at an interval of no less than 20 days during the induction period. Second, the levels of serum asparagine could remain depleted for 26–34 days (18). Imbalance in serum amino acids is associated with pancreatic injury (19); prolonged activity could pose a delayed or sustained toxic effect at certain clinical settings, which is presented as delayed symptoms weeks after administration, leading to an impression of "sudden, severe onset." AAP could be characterized by a delayed onset of abdominal symptoms,

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TABLE 4 | Clinical outcome and prognosis of AAP patients.

	All patients (n = 38)	Mild/Moderate AAP (n = 22)	Severe AAP (n = 16)	p value
Clinical outcome and prognosis				
Patients admitted to PICU	16(42.1%)	6(27.3%)	10(62.5%)	0.047
Days of PICU stay	6(2–20)	5(2–18)	11(3–20)	
Clinical outcome				
Alive	33(86.8%)	22(100%)	11(68.8%)	0.009
Dead/treatment withdrawal	5(13.2%)	0	5(31.3%)	-
AAP prognosis				
Alive in remission	28(84.8%)	19(86.4%)	9(81.8%)	0.047
Alive with AAP relapse	5(15.2%)	1(4.5%)	4(25%)	-
Impact on chemotherapy				
Chemotherapy adjusted	10(30.3%)	8(36.4%)	2(18.2%)	0.024
Asp permanently withdrawn	13(39.4%)	7(31.8%)	6(54.5%)	-
No impact	10(30.3%)	7(31.8%)	3(27.2%)	-

Clinical outcome is determined by the discharged status within AAP course. Severity of AAP is classified according to clinical manifestation. Enumeration data is presented in n(%) while continuous data is presented in median (range). n/N(%) is calculated with N=38. p value is calculated by Fisher's exact test. AAP, Asparaginase associated pancreatitis; Asp, Asparaginase; PICU, Pediatric intensive care unit.

dynamic changes in radiographic evidence, and longer time for serum amylase to normalize.

In our study, AAP is more prevalent in the early induction stage (68.4%); the median number of peg-asp doses administered before the onset of AAP was two doses, which suggested that the episodes of AAP might not be related to the cumulative doses but more related to the individual differences such as genetic predisposition. A previous study on genotype and discovery of AAP-related genetic variant provided insights in investigating the potential risk factor in developing AAP. CPA2, RGS6, and ULK2 were among the AAP-related variants reported in previous studies (20, 21). Further validation by conducting large cohort studies and investigation of its pathophysiological mechanism is required.

As suggested in recent ALL guidelines, severe AAP patients (severe pancreatitis with amylase elevation >3 times the UNL, accompanied with pseudocyst within 48 hours) were not allowed to receive any asparaginase as a prospective chemotherapy regimen (6, 22). This definition is based on the revised Atlanta criteria (2012), which is a classification system for adults. However, preexisting studies had used inconsistent criteria such as CT severity index, CTCAE, NCI-CTC, or Children Cancer Group criteria to classify the severity of pediatric AAP. The reported incidence rate of severe AAP varied from 7% to 66% (23). The propensity difference in etiological factor between children and adult pancreatitis also determined their distinct clinical manifestation. An asparaginase-included therapy is essential in preventing ALL relapse and may improve the event-free survival rate. However, it is necessary to establish a well-defined classification of pediatric AAP. Evidence-based studies and long term follow-up are needed to determine an appropriate AAP definition and practical AAP severity classification.

With regard to the imaging approach used for diagnosis, both ultrasound and contrast CT scan were the preferred screening tools for AAP. For some mild/moderate patients, ultrasound might be unable to detect inflammatory edema or signs of pancreatitis. This has been observed in previous studies (24). Meanwhile, presence of a large amount of abdominal gas and incompliance during procedure (mostly younger children) might impact the results of ultrasound. Thus, an alternative imaging approach should be used to assess for pancreatitis, and contrast-enhanced CT scan was performed in some of these patients. Although both MRI and CT scan showed equal strength in detecting pancreatitis, CT scan is less time consuming and requires less imaging sequence procedure; thus, clinicians could obtain instant imaging results and provide prompt management.

With regard to the treatment, pancreatic enzyme inhibitors (octreotide or somatostatin) were considered as safe treatment approaches that have been widely used for pancreatitis patients. Most of our study patients received scheduled chemotherapy in wards during the onset of AAP. Chemotherapy-related toxicities were carefully monitored, and appropriate treatments were provided immediately when AAP was suspected. Therefore, pancreatic enzyme inhibitors were administered immediately after diagnosis to prevent the progression to severe AAP. As all patients received the same standardized treatment at a similar timing, we cannot tell whether such medication led to a more rapid recovery.

For relapse patients, the standardized pancreatitis treatment was less effective. Most of the relapse patients showed signs of pancreatitis recurrence on imaging and were later diagnosed with long-term complications such as obstruction of pancreatic duct or chronic pancreatitis. They eventually developed AAP during the re-challenge at a more rapid pace. Standardized treatment was ineffective in such situations; hence, surgical intervention was performed to maintain pancreatic drainage. In some patients, the inappropriate use of asparaginase possibly contributed to the occurrence of relapse. The patients who had mild pancreatitis recurrence was re-challenged with a half dose of asparaginase. Obviously, these patients might be more susceptible to the effects of asparaginase and required further examination to determine the potential risk factors. Nevertheless, all relapse patients achieved complete remission, and none of them died. In summary, clinicians should carefully consider the use of asparaginase in patients with a higher risk of AAP relapse. Our study was unable to include larger samples of relapse patients; hence, it was hard to confirm the potential risk factors. However, all relapse patients experienced several common events: incidence of AAP during initial administration, mild AAP accompanied with long-term complications, history of recurrent pancreatitis, and less responsive to routine pancreatitis treatment. All patients received certain benefits from surgical intervention and AAP prophylaxis. Meanwhile, local complications occurred in all relapse patients with a statistical difference, and they were potential risk factors that require further investigations using a large cohort. To improve the clinical outcome of AAP patients, the management of AAP should be standardized in a more pragmatic manner, and suggested treatments should be explained further to avoid the occurrence of AAP during re-challenge.

Our study reported a higher mortality rate than the previous studies (12% vs 2%) (22). First, all AAP patients had severe systemic symptoms and required intensive supportive care. They previously developed severe infection due to myelosuppression and persistent fever during the period of asparaginase treatment. Moreover, adverse events such as gastrointestinal bleeding, coagulation disorder, pleural effusion, and substantial ascites were widely observed. All of these events posed increasing difficulties in the management of AAP. Therefore, we presumed that these patients were experiencing irreversible multi-organ failure during the course of AAP, which therefore resulted in an increased mortality in our study.

The severity of AAP was not merely determined by ALL status or pancreatitis-related variables but by the genetic predisposition of individuals, which was not reported in our study. Moreover, prophylactic measures, early recognition, and management of AAP were effective in reversing severe conditions. Our medical center serves as a standardized treatment center for childhood hematological disease; thus, the healthcare personnel in this center have high levels of awareness and clinical experiences regarding chemotherapy-related

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toxicities. Most of our patients are admitted in the hospital throughout the course of chemotherapy and could receive intensive supportive care once diagnosed with AAP, thus improving the clinical outcomes of all AAP patients from different risk groups. In an expert guideline for adolescent and adult patients, the panel suggests the use of an AAP grading system based on the dynamic changes found during continuous monitoring and anticipate that HR patients may develop severe AAP (25). We agree with the urgency and importance in establishing such treatment protocol for pediatric patients.

It is important to stress that the complications of AAP were just the integrated outcomes resulting from the use of an asparaginase-included therapy, but not the direct consequences of asparaginase medication alone. The use of concomitant chemotherapeutic agents such as glucocorticoid, cytarabine, and mercaptopurine can potentially cause pancreatitis. Other HR medications were used in certain clinical settings. In addition, the patients' nutritional status and history of asparaginase use should be considered. Long periods of fasting might contribute to the development of cholelithiasis, which is a common etiological factor of pancreatitis. Patients with hypersensitive reaction and history of AAP should also have their dosage adjusted.

The existing AAP criteria had a low strength in determining the severity of pediatric AAP. Hence, a well-defined AAP definition could help distinguish patients with high anticipated risk in redeveloping AAP and ALL relapse, to prevent unnecessary withdrawal of asparaginase. This study had summarized the clinical characteristics of AAP with a peg-asp formulation and provide clinical evidence for future large cohort studies.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

Our study was approved by the Ethics Committee of Shanghai Children's Medical Center (SCMC), affiliated hospital of Shanghai Jiao Tong University School of Medicine, department of hematology or pediatric intensive care unit and written informed consent was obtained from patients' parents or guardians.

AUTHOR CONTRIBUTIONS

(I) Conception and design: B-tN. (II) Administrative support: B-tN and YW. (III) Provision of study materials or patients: Y-yZ and Q-sY. (IV) Collection and assembly of data: Y-yZ and Q-sY. (V) Data analysis and interpretation: Y-yZ, Q-sY, JQ, and B-rL. (VI) Manuscript writing: Y-yZ and B-tN. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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