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Long-Term Follow-Up and Outcome of Pediatric Acute Pancreatitis: A Multicenter Study

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What is already known on this topic?

- *The incidence of acute pancreatitis (AP) is increasing in developed countries.*
- *The progression of AP to acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) is still not well documented in children.*

What this study adds on this topic?

- *The number of hospitalization due to pancreatitis in children increases in developing countries.*
- *In long-term follow-up, the progression rate of AP to ARP was 30.9%, ARP to CP was 27.4%.*
- *Widespread use of second-line investigations in patients having a risk factor for developing ARP/CP decreased the rate of idiopathic cases.*

ABSTRACT

Objective: Over the past decades, the incidence of acute pancreatitis is increasing, but the progression of acute recurrent pancreatitis and chronic pancreatitis is still not well documented in children. The aim of this multicenter study is to delineate the changes that occur in a certain time period in the course of childhood pancreatitis.

Materials and Methods: The data of consecutive patients hospitalized with acute pancreatitis between 2010 and 2017 in 4 different pediatric gastroenterology units were reviewed. The clinical characteristics of the disease were defined.

Results: A total of 165 patients (55.2% female) were included. Over the years, the rate of acute pancreatitis admissions increased while the duration of hospitalization decreased ($P < .05$). Nearly two-thirds of the patients with acute pancreatitis resolved spontaneously, 30.9% and 4.3% of the cases developed acute recurrent pancreatitis and chronic pancreatitis, respectively. Furthermore, 27.4% patients with acute recurrent pancreatitis progressed to chronic pancreatitis, and eventually, 12.7% of cases developed chronic pancreatitis within 3-4 years. Local complications developed in 13.3% of the patients with pancreatitis in this cohort.

Conclusion: The result of this study confirmed the increased incidence of acute pancreatitis in recent years. Conversely, the length of hospital stay decreased over the years. Patients with pancreaticobiliary abnormalities or genetic risk factors had a higher rate of progression to acute recurrent pancreatitis or chronic pancreatitis. Therefore, genetic testing and radiological imaging should be considered early in the follow-up of patients with acute pancreatitis having risk factors for progression to acute recurrent pancreatitis/chronic pancreatitis.

Keywords: Children, pancreatitis, etiology, disease

INTRODUCTION

Acute pancreatitis (AP) is a reversible systemic inflammatory process and characterized by abdominal pain, elevated serum amylase and/or lipase, and typical findings on abdominal radiological imaging. Recent studies have estimated that the annual incidence of pediatric AP has been approaching to that of adults.[1,2] Most children with AP have a single episode that resolves without complications, but a subset develops acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP). Recent studies have suggested that 20%–40% of the patients with AP progress to ARP; however, data regarding the progression of pediatric pancreatitis to CP are limited.[3] The major etiologic factors for AP are gallstones and alcohol consumption

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in adults, while the etiologies are more diverse in children such as pancreaticobiliary abnormalities/gallstones, medications, systemic diseases, trauma, and viral infections depending on the age of the patient.[1] The course and complications, as well as the etiology of pancreatitis, differ in children.[4]

In recent years, there are many reports particularly from different geographical areas pertaining to increased incidence of pancreatitis in children.[2,3,5,6] Furthermore, it has recently been documented that the incidence and hospitalization rate due to pancreatitis has increased during the last decade.[7] The aim of this multicenter study was to assess the frequency of pediatric pancreatitis and to evaluate the etiological factors and clinical course of pancreatitis over the years.

MATERIALS AND METHODS

Data Source and Selection of Cases

A total of 165 pediatric patients who had their first episode of AP and were hospitalized in 4 different pediatric gastroenterology centers between 2010 and 2017 were retrospectively analyzed. The diagnoses of AP, ARP, and CP were done according to the criteria defined by the INternational Study group of Pediatric Pancreatitis: In Search for a CuRE (INSPPIRE).[8] Acute pancreatitis was diagnosed if any 2 of the following 3 criteria were met: abdominal pain compatible with AP, serum amylase, and/or lipase value 3 times or greater the upper limits of normal and radiologic findings of AP. Acute recurrent pancreatitis was defined as the return of lipase and/or amylase levels to normal levels between episodes in a patient with 2 or more AP episodes. In a patient with typical abdominal pain, a diagnosis of CP was made in the presence of characteristic radiological imaging or pancreatic insufficiency (endocrine and/or exocrine) findings.[8] Patient records regarding demographic features, etiology, comorbid conditions, radiological imaging, clinical course, and length of hospital stay (LOS) were compiled from patient files.

LABORATORY AND RADIOLOGICAL INVESTIGATION

The laboratory tests at admission including white blood cell count, C reactive protein, amylase (normal <200 U/L), and lipase (normal <60 U/L) were retrieved. Patient records were also evaluated for initial radiological investigations. The underlying etiology of the patient having recurrent or CP was further assessed for autoimmune pancreatitis, genetic mutations [cystic fibrosis transmembrane regulator (CFTR) gene, serine protease inhibitor (SPINK1) gene, and cationic trypsinogen (PRSS1) gene], and anatomic abnormalities such as pancreas divisum (PD), stricture or scarring of the pancreatic duct, choledochal cyst. At admission, all of the patients with AP were already examined by ultrasonography. Acute pancreatitis patients having a history of gallstone and the ones with ARP were undergone magnetic resonance cholangiopancreatography (MRCP) in order to delineate the structural abnormalities of the pancreaticobiliary tract.

Clinical Course of the Patients

All children were analyzed whether they had another attack of pancreatitis during the follow-up period. Accordingly, patients who had other attacks or the signs of CP were divided into subgroups: namely ARP and CP. The time of the progression from the first-documented AP attack to ARP or CP was determined retrospectively. The study group was also analyzed for the complications and the surgical procedures patients underwent at the admission and during the follow-up period. The study protocol was approved by the ethics committee of Marmara University.

Statistical Analysis

The data were analyzed with computer software program, the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median (minimum or maximum) or mean ± standard deviation (SD), and categorical variables are presented as numbers or percentages. The normality of the continuous data was tested by Kolmogorov–Smirnov test and Q–Q plots. Continuous variables are presented as median (minimum or maximum) or mean ± SD, and categorical variables are presented as numbers or percentages. The normality of the continuous data was tested by Kolmogorov–Smirnov test and Q–Q plots. Continuous variables in 2 independent groups were analyzed using the Student's *t*-test (when the data followed normal distribution) or Mann–Whitney *U*-test (when the data were asymmetrical), while χ^2 or Fisher's exact test was used for the analysis of categorical variables used for the comparison of groups where appropriate. Kruskal–Wallis test was used to compare the means of 3 or more groups where appropriate. Cumulative incidence of relapse and CP were calculated by using the Kaplan–Meier method, and the period from the first attack of AP to the date of the second attack (i.e., recurrent pancreatitis) and the development of clinical/radiological manifestations of CP were calculated. The calculated *P*-values of less than .05 indicated statistical significance.

RESULTS

Characteristics of Patients

A cohort of 165 children who had the diagnosis of AP between 2010 and 2017 were evaluated in this study. The mean duration of the follow-up was 2.6 ± 1.8 years, ranging between 3 and 82 months. The mean age of the patients at onset was 9.6 ± 4.5 years, and 55.2% of them were female. The number of patients diagnosed with pancreatitis has increased over the years (Figure 1A). In this cohort of pediatric pancreatitis, the most common etiologies were biliary obstruction secondary to gallstone in 20% (33 patients), drugs in 9.1% (valproic acid in 5, azathioprine in 4, phenobarbital in 3, and L-asparaginase in 3), and pancreaticobiliary abnormalities (4 PD, 4 choledochal cyst) in 4.8% of the patients. The etiology could not be identified in 39.4% of the cases. The etiologic distribution of patients with pancreatitis is shown in Figure 2A and 2B.

Clinical Aspect

At presentation, the median serum amylase level was 760 U/L (range: 56-3870 U/L) and median serum lipase level was 1080 U/L (range: 82-8476 U/L). The median LOS was 8 days, ranging from 3 to 92 days. There was a decrease in the LOS over the years (Figure 1B). All cases received analgesics and intravenous fluids, and they were kept nil per os (NPO) on the first day of admission. In this cohort of patients with AP, the median duration of NPO was 59 hours (range: 12-600 hours).

During the follow-up period, a total of 247 acute episodes of pancreatitis were diagnosed. Of 165 patients with AP, 107

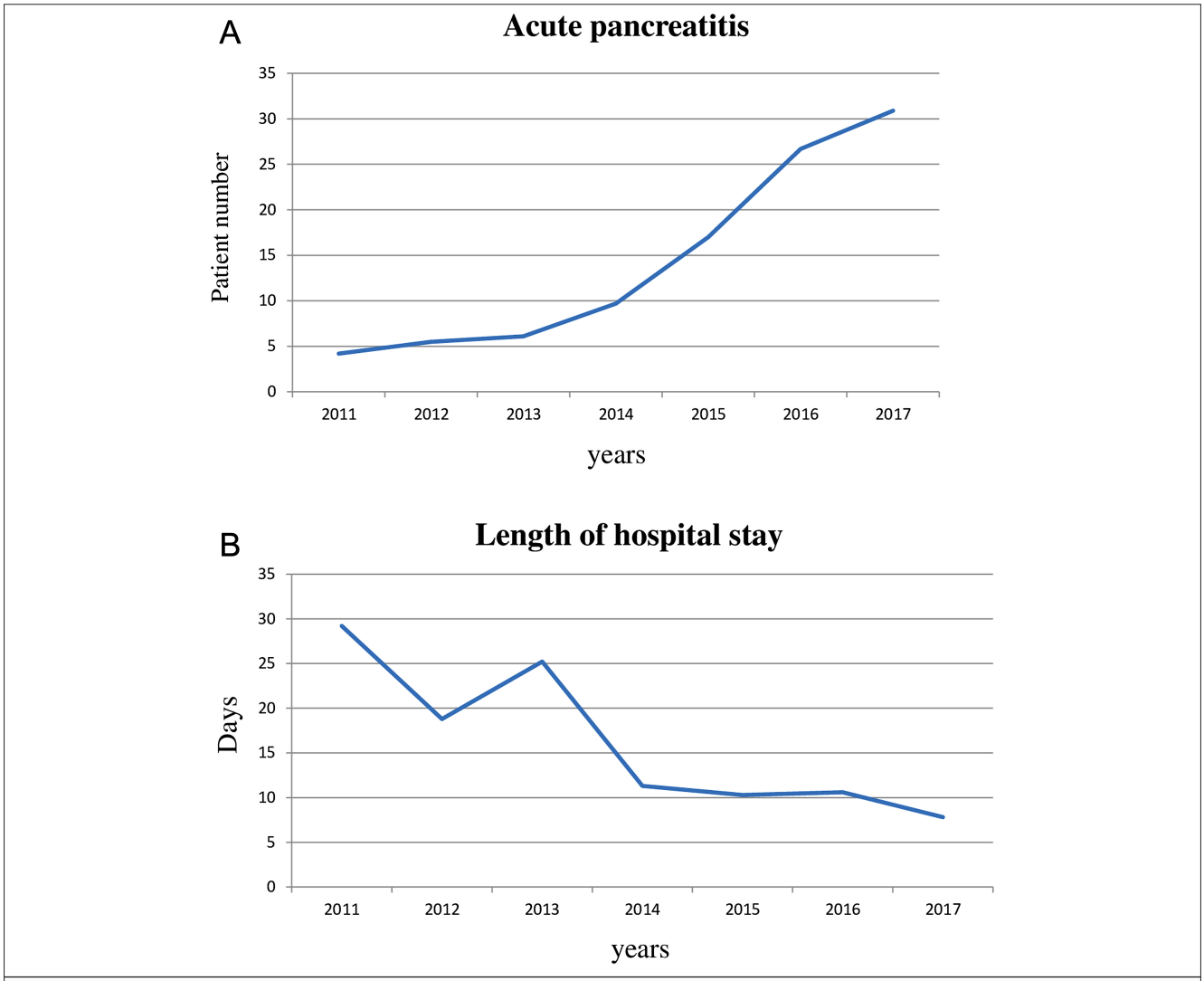

Figure 1. (A) The rate of acute pancreatitis over the years. (B) The change in length of hospital stay over the years in patients with acute pancreatitis.

(64.8%) improved during follow-up, ARP developed in 51 (30.9%) patients, and CP developed in 7 (4.3%) patients over the years (Figure 3). In this population, 14 of 51 (27.4%) patients with ARP progressed to CP within 3.3 ±1.2 years, and overall, 21 of 165 (12.7%) patients with AP developed CP. In the Kaplan–Meier analysis, it has been found that 20% of the patients with AP developed a second attack within 20 months, and CP developed in 17% of patients with AP within 50 months (Figure 4).

In patients with AP, biliary obstruction and pancreaticobiliary anatomic abnormalities were the most common etiologies in 25.2% (27/107) of children, and almost 85.2% (23 out of 27) of them had gallstone as a predisposing factor. Likewise, pancreaticobiliary abnormalities and biliary obstruction (cholelithiasis, choledocholithiasis, PD, and choledochal cyst) were the most common etiologies (29.8%) in children with ARP, and almost 82% of those had cholelithiasis. In CP group, genetic mutations were the most common etiology (28.5%), and CFTR was the most common genetic mutation (19%) detected.

All of the patients with CP had specific cross-sectional MRCP findings (namely, calcifications, pancreatic duct changes, parenchymal signal changes, glandular atrophy), which were compatible with CP. The etiologic distribution in AP, ARP, and CP groups is shown in Figure 2B. There was no significant difference between the groups in terms of age at presentation, gender, LOS, and duration of NPO at admission. The comparison of general characteristics and clinical features of AP, ARP, and CP was depicted in Table 1.

At admission, all of the patients underwent a radiographic evaluation (ultrasound or computed tomography) to establish the diagnosis of pancreatitis. All patients with ARP/CP underwent an MRCP to evaluate the pancreaticobiliary system. Thus, a total of 76 (46%) children with pancreatitis were examined by MRCP. A pancreaticobiliary malformation, namely choledochal cyst (n = 4) and PD (n = 4) was diagnosed in 8 patients.

Nearly 80% of patients with ARP and CP could be evaluated for at least 1 genetic mutation predisposing to pancreatitis (i.e., CFTR, SPINK1, PRSS). Cystic fibrosis transmembrane regulator mutations were the most frequently investigated genetic analysis and were performed in 46 patients with ARP/CP. Serine protease inhibitor and PRSS mutations were performed in 18 and

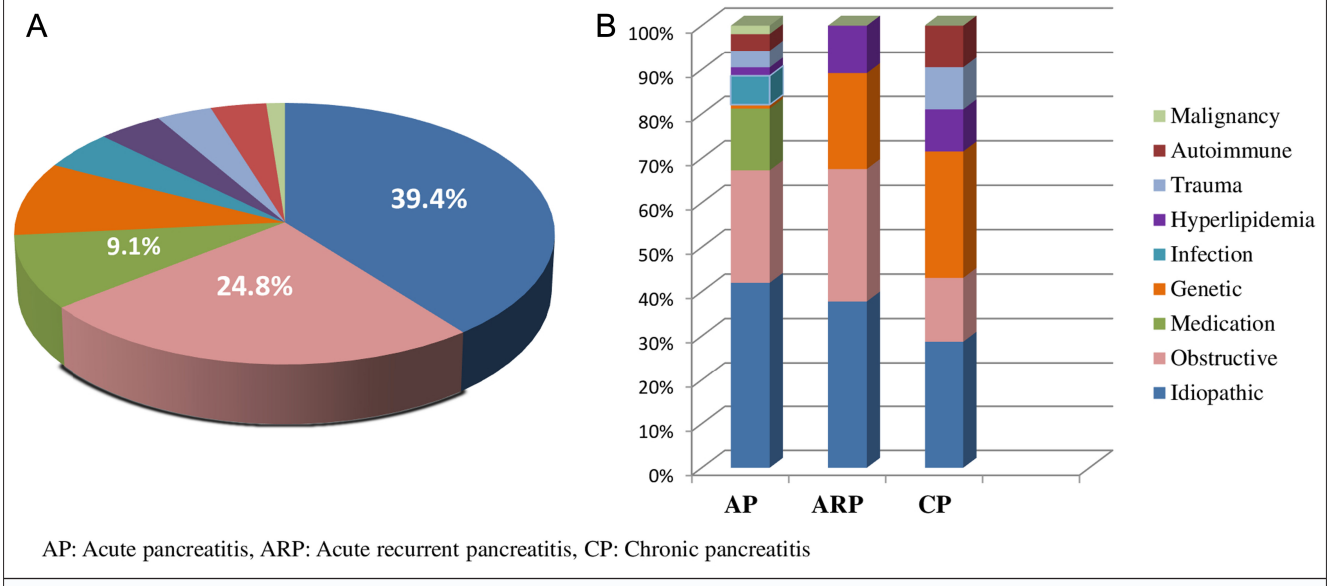

Figure 2. (A) Etiological distribution of all patients with pancreatitis in the study cohort. (B) Etiological distribution of the patients in acute pancreatitis, acute recurrent pancreatitis, and chronic pancreatitis.

11 patients with ARP/CP, respectively. Sixteen out of 46 tested for CFTR gene mutation were positive (5 homozygous and 11 heterozygous). Out of 2 of those 5 patients, who were homozygous for CFTR mutation were already being followed up in the pediatric CF center in our university hospital. The remaining 3 patients with homozygous CFTR mutation were diagnosed with CF after being hospitalized with an acute episode of pancreatitis. In this cohort, 15 patients were heterozygous for the genetic mutations predisposing to pancreatitis, namely 11 were heterozygous for CFTR, 2 were heterozygous for SPINK1 and 2 were heterozygous for PRSS1 mutations.

At admission, 33 children with pancreatitis had cholelithiasis or choledocholithiasis as predisposing factor, and 16 out of 33 (48.5%) patients with gallstone pancreatitis underwent cholecystectomy while an endoscopic retrograde cholangiopancreatography (ERCP) was performed for the extraction of the gallstones in 8 out of 33 patients. Those who underwent therapeutic ERCP for extraction of gallstones did not experience any other episodes of pancreatitis.

Complications

Local complications were noted in 22 (21%) patients with pancreatitis in this cohort: pseudocysts in 10, pancreatic necrosis in 6, and pancreatic ascites in 6 patients. Three patients had both pancreatic necrosis and pseudocyst, 2 out of 3 patients underwent pancreatic resection. Seven patients had only pseudocyst, and 2 out of 7 patients underwent pancreatic resection or cystogastrostomy in order to alleviate the compression symptoms. Three patients had only pancreatic necrosis, and one of them underwent pancreatic resection because of intractable pain. Pancreaticoduodenectomy was performed in 2 patients, one of them developed pancreatic necrosis and pseudocyst secondary to abdominal trauma, and the other had

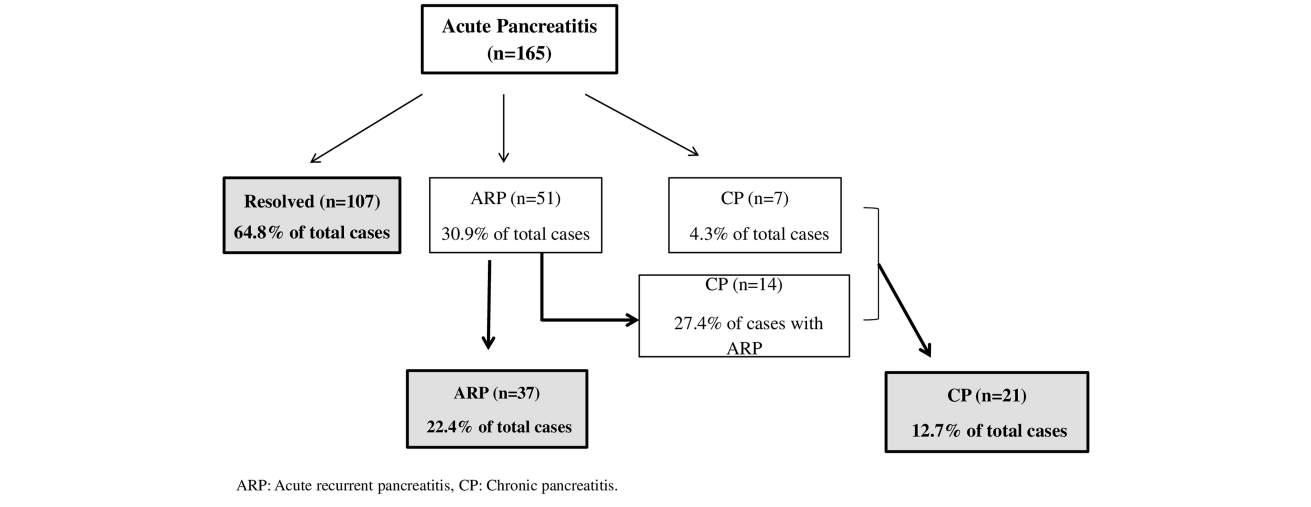

Figure 3. Follow-up course of the acute pancreatitis cohort.

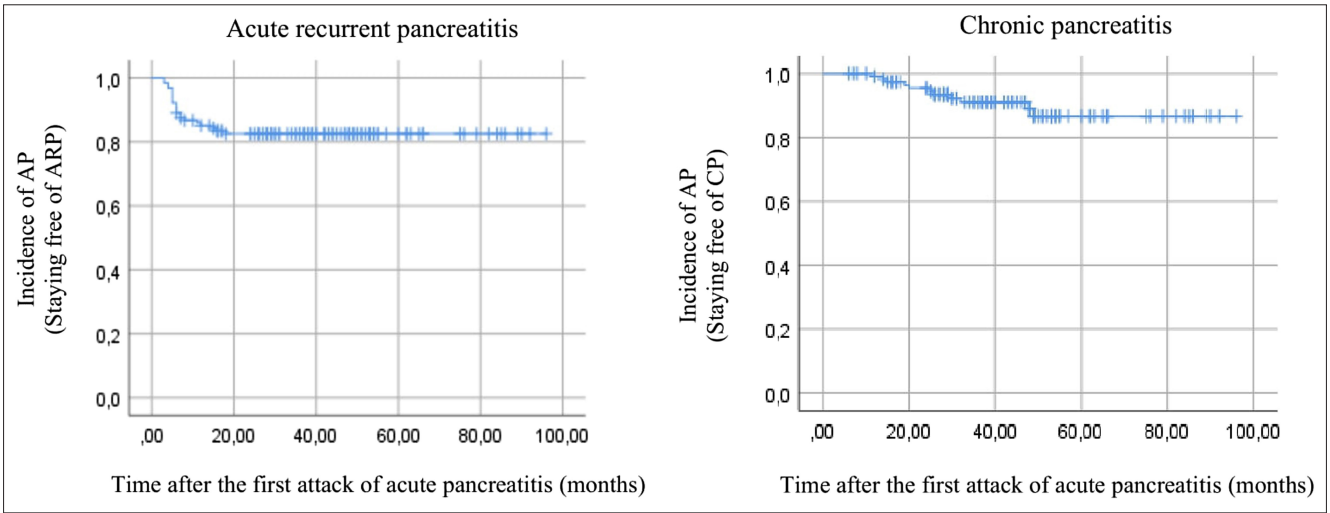

Figure 4. Cumulative incidence of recurrent attack after the first attack (left) and chronic pancreatitis (right) in the study group.

a malignancy. Five children with a pseudocyst, 3 children with pancreatic necrosis were managed conservatively. When the groups were evaluated in terms of local complications, the rate of patients who had pseudocyst was higher in ARP group. The rate of patients who developed pancreatic necrosis and underwent resection was higher in the CP group (Table 1). No mortality was observed in this cohort of patients.

DISCUSSION

This multicenter study, including a total of 165 children with AP, demonstrated an increased number of hospitalizations due to pancreatitis in children, and a decrease in LOS over the years. Nearly 65% of children with AP resolved while 31% of them progressed to ARP during the follow-up period, and the rate of CP was 12.7% in this population. The etiology of pancreatitis was identified in 60.6% of the study population, and this figure was higher among patients with CP.

Over the past few decades, the mean LOS has decreased in children with AP, and in recent studies, this ranges from 15 to 24 days.[3,9,10] Furthermore, clinical studies in adults and children demonstrated that the introduction of early oral feeding was safe and associated with a shorter hospital stay.[11,12] In this study, the average LOS was 11.9 days, and there was a statistically significant decrease in hospital stay over the years. It was likely related to the increased awareness and improvement in the management of pediatric pancreatitis. Besides, the duration of NPO decreased in the second half of the study period compared to the first half.

The etiological spectrum of pancreatitis in children is more diverse than in the adults. The most common etiologies of AP were either structural/biliary abnormalities or drugs in more than half of the children.[1,2,12] The etiological spectrum has changed in ARP during the last 2 decades with the widespread use of genetic testing, and it has recently been stated that nearly half of the pediatric cases have an underlying genetic mutation, and 30% of the cases have structural/biliary anomalies.[1,13,14] The etiological distributions of AP and ARP in our cohort were similar to the published series.[1,4,7,13-16] While alcohol abuse is a common risk factor for CP in adults, genetic mutations are the major risk factor in pediatric age group, followed by structural/anatomic abnormalities precipitating an obstruction.[1] In

Table 1. Characteristics and Clinical Features of Acute Pancreatitis, Acute Recurrent Pancreatitis, and Chronic Pancreatitis

	Total Cases (n = 165)	AP (n = 107)	ARP (n = 37)	CP (n = 21)	*P*
Mean age (year)	9.6 ± 4.5	10.1 ± 4.6	9.2 ± 4.4	8.1 ± 4.3	.55*
Female (%)	91 (55.2)	56 (53.3)	25 (67.6)	10 (47.7)	.23**
The duration of hospitalization (day)	8 (1-92)	7.5 (1-92)	8 (4-25)	12 (2-60)	.29***,[a]
NPO at admission (hour)	59 (12-600)	56 (12-600)	65.5 (36-265)	74 (24-250)	.4***,[a]
Nasojejunal tube (%)	8 (4.8)	2 (1.9)	3 (8.1)	3 (14.3)	**.023****
Complications					
Pseudocyst (%)	10 (6.1)	3 (2.9)	5 (13.5)	2 (9.5)	**.032****
Pancreatic necrosis (%)	6 (3.6)	2 (1.9)	2 (5.4)	2 (9.5)	.089****
Cholecystectomy (%)	16 (9.7)	9 (8.6)	7 (18.9)	0	.061****
Pancreatic resection (%)	3 (1.8)	0	0	3 (14.3)	**.002****

AP, acute pancreatitis; ARP, acute recurrent pancreatitis; CP, chronic pancreatitis.
*Student's *t*-test, **χ^2, ***Mann–Whitney *U*-test, ****Fisher's exact test, $P < .05$.
[a]Kolmogorov test, $P < .05$.

a small number of studies related to the etiology of CP in children, genetic mutations account for majority of the cases, while nearly 20% of the cases are associated with pancreaticobiliary anomalies.[1,6] Genetic mutations and pancreaticobiliary anomalies were the most common etiologies detected in 38.1% of the pediatric patients with CP in this cohort.

In recent studies, the rate of idiopathic etiology has decreased to 10%-30% in pediatric pancreatitis series.[4,14] In this cohort, however, the rate of idiopathic etiology in all types of pediatric pancreatitis was higher than the literature.[1,17] One of the explanations for this may be due to the fact that it is a multicenter study in which 4 different pediatric gastroenterology centers with different technical facilities (radiologic, genetic, etc.) participated. Taken as a whole, 79% of patients with ARP and CP had genetic testing and 98% had MRCP. Similar to our data, Poddar et al[7] from India reported even higher rates of idiopathic AP and ARP (52.5% and 70%, respectively) due to the shortage of detailed genetic investigations. Comparably, it has been demonstrated that when the second-line investigations including endoscopic ultrasound, MRCP, and genetic testing were performed, the rate of idiopathic pancreatitis reduced from 49% to 21%.[9] As expected, the rate of idiopathic etiology among children with AP (41.9%) was higher than the cases with ARP or CP (37.8% and 28.6%, respectively) in our cohort. The widespread use of the second-line investigations, namely genetic analysis and MRCP in the recurrent and chronic cases, decreased the rate of idiopathic etiology.[15]

In our cohort, nearly one-third of children with AP progressed to ARP during the follow-up period, while one-third of children with ARP progressed to CP within 3.3 years. The overall rate of CP was 12.7% in this population, which was lower than previously reported rates.[16,18] This lower rate of CP might be explained by the shorter duration of the follow-up period in this cohort. In adults, 10% of the patients with the first episode of AP and 36% of the patients with ARP eventually develop CP.[19] In children, 15%-35% of the cases with AP progress to ARP, and 20%-40% of the children with ARP may progress to CP within 2-5 years after the onset of AP.[1,7,16] The rate of CP was nearly 30% in a large cohort of pediatric pancreatitis, reported by Poddar et al.[7] and further 22% of the patients with ARP developed CP in 2-4 years of follow-up.

There is a strong association between genetic predisposition and progression to ARP/CP; hence, genetic analysis is recommended in children, who have risk factors for developing ARP/CP.[1] It has been shown that specific mutations in the CFTR, SPINK1, and PRSS1 genes pose a predisposition for hereditary pancreatitis that is associated with a higher risk of progression to ARP and CP.[18] In a previous study, CFTR, SPINK1, and PRSS mutations were discovered in 48%, 27%, and 24% of the children with ARP, respectively.[20] Due to the high rate of consanguineous marriages in our country, initially CFTR then SPINK1 and PRSS mutations were sequentially analyzed in order to evaluate the hereditary factors. Prior to 2016, only CFTR genetic mutations were covered by the national health insurance, later SPINK1 and PRSS1 mutations were also included. Therefore, SPINK1 and PRSS1 mutations were examined in a few patients with ARP/CP. In this cohort, at least 1 genetic mutation was analyzed in nearly 80% of the patients with ARP/CP, and 43.5% of which had a predisposing genetic mutation for pancreatitis. This figure is consistent with other, small, single-center studies, reporting that children with ARP/CP have genetic risk factors in 33.6% and 79%, respectively.[13,15, 20,21]

Today, MRCP has gradually replaced diagnostic ERCP in both adults and children.[22,23] Choledochal cyst is the most common anatomic abnormality that is associated with pancreatitis in children, and 35%-53% of the children having choledochal cyst present with AP depending on the type of the cyst.[24] Pancreas divisum is the most common congenital anomaly of the pancreas, and the frequency of this anomaly varies between 4% and 25% in ERCP series.[19,25] Recently, INSPPIRE group has documented that PD was found in 14.6% of children with ARP/CP.[25] In this cohort, pancreatic abnormalities were 13.8% in the patients with ARP/CP. Sludge or gallstones are predisposing factors in 10%-30% of children with AP.[4] In the past years, while it was advised that cholecystectomy should be performed shortly after the recovery or 2 to 4 weeks after the discharge for mild biliary pancreatitis, recently same admission cholecystectomy is advised instead of interval cholecystectomy. Early cholecystectomy in gallstone pancreatitis reduces readmissions and the risk of recurrent pancreatitis.[26-29] In our cohort, 20.2% of patients with pancreatitis had gallstone, and nearly 73% of them underwent cholecystectomy and/or ERCP. Cholecystectomy was performed in 56.3% of the patient 2-4 weeks after the resolution of the first attack. In this cohort, 9 out of 33 patients with bile stone pancreatitis were not operated on index admission due to lack of access to a pediatric surgeon or non-consent of the family at the time.

Pancreatic pseudocyst is one of the most common local complications, has been recorded in 10%-38% of the cases with pediatric pancreatitis.[6,10,30] In our study, pancreatic pseudocyst and pancreatic necrosis were detected in 6% and 4% of patients with pancreatitis, respectively. Nearly 40% of patients with pancreatic necrosis and/or pseudocyst underwent a surgical procedure in our study. Surgical interventions are not common in pediatric pancreatitis.[29] In this cohort, the main indications for surgery were intractable pain, the presence of an infected collection, or obstructive symptoms.

As a conclusion, the incidence of AP has been increasing in children and, there has also been a significant reduction in hospital stay over the years. The most common etiologies were cholelithiasis, drugs, and genetic mutations in this cohort. On the follow-up, nearly one-third of the children with AP progressed to ARP within 2 years, and more than a quarter of all children with ARP progressed to CP within 3.5 years of the follow-up. Two-thirds of all patients with CP were the ones progressing from ARP to CP, therefore the patient with AP should be followed closely after the second attack, and genetic testing and radiological imaging should be considered early in the follow-up of patients with ARP.

Ethics Committee Approval: This study was approved by Ethics Committee of Marmara University, (Approval No: 09.2018.453, Date: 2018).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.V.; Design – E.T., D.E.; Data Collection and/or Processing – B.V., B.S.A., N.A.B., O.K.S., E.P., G.K.; Analysis and/or Interpretation – N.A.B.; Writing Manuscript – B.V., B.S.A., N.A.B., E.T., D.E.; Critical Review – B.S.A., N.A.B., E.T., D.E.

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Declaration of Interests: The authors have no conflict of interest to declare.

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