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Original Article

Increasing Diagnosis Rates and the Changing Etiology in Childhood Pancreatitis; Ten Years of a Single-Center Experience in Turkey

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ABSTRACT

Aim: In this study, we aimed to evaluate the etiological, clinical, and laboratory characteristics of children with pancreatitis and the changes in these data over the years.

Materials and Methods: Children hospitalized with a diagnosis of pancreatitis between January, 2011 and January, 2021 were evaluated retrospectively. The etiology, demographic characteristics, laboratory findings, and changes over the years were analyzed.

Results: A total of 111 cases were enrolled, 72 (64.9%) in the acute pancreatitis (AP) group and 39 (35.1%) in the acute recurrent pancreatitis and chronic pancreatitis (ARP/CP) group. The most common causes of AP were idiopathic (27.8%), cholelithiasis (26.4%), and infections (8.4%). In ARP/CP assessments, idiopathic (35.9%), trauma (15.4%), and drugs (10.3%) were the most frequent etiologies. During the first five-year period, only 14 patients were diagnosed with pancreatitis, but in the second five years, 97 patients were diagnosed with pancreatitis. In both periods, the most frequent diagnosis was idiopathic pancreatitis (42.9% and 28.9%, respectively). While trauma (14.3%) and infections (14.3%) were the most common etiologies in the first five years, cholelithiasis (20.6%) and drugs (9.3%) were the most common in the second five years.

Conclusion: There was a significant increase between the first and the second five-year periods in pancreatitis-related hospitalizations. The most common cause of pancreatitis in all groups was still unknown. The cholelithiasis ratio increased from 7.1% to 20.6% in the second five-year period. Additionally, drugs played a bigger role in pancreatitis at a high rate of 9.3% over the years. Additionally, it was seen that the administration of octreotide treatment decreased over the years.

Keywords: Pancreatitis, etiology, child

Introduction

Over the last few years, pancreatitis has been increasingly diagnosed in children. Reports from different centers have shown that the incidence of childhood acute pancreatitis (AP) increased in the range of 0.78 to 13.2 annually per 100,000 children (1-5). Additionally, the incidence of pediatric chronic pancreatitis (CP) was 0.5-2 annually per 100,000 children and the prevalence was 6 cases per 100,000 children (6-8).

Pancreatitis is a clinical diagnosis based on a combination of history, physical examination, laboratory tests, and

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radiological findings. Thus, a significant increase in awareness plays a key role in the rise of pancreatitis incidence. As well as increased awareness among physicians, easily accessible serum amylase and lipase measurement and facilitated access to experienced radiologists undoubtedly provide for a rapid and accurate diagnosis of pancreatitis in children. Additionally, the definition of pancreatitis in children became clearer after the international pediatric pancreatitis working group (INSPPIRE) report, which has contributed to the increase in the number of patients diagnosed with pancreatitis (9,10). One study examined the changing frequency of AP across pediatric ages and characterized etiologies by age (11). As far as we know, this was the first report investigating and comparing the etiology, laboratory, and treatment modalities of pancreatitis in children over the years and it revealed an increase in pediatric pancreatitis referrals to tertiary care centers.

This study aimed to determine the trends of pediatric pancreatitis during the last decade at a tertiary care university-affiliated children's hospital and we hypothesized that the rate of pancreatitis in childhood increased over time.

Materials and Methods

This retrospective study was performed for all hospitalized children and adolescents (<18 years of age) diagnosed with pancreatitis at our institution between January, 2011 and January, 2021.

The patients' data were obtained from the electronic medical records of the hospital retrospectively and the analysis was limited to inpatient encounters and the first encounter with those patients with more than one admission for pancreatitis. Those patients whose data was unavailable or missing were excluded. The patients were categorized into two groups according to the international study group on pediatric pancreatitis: in search for a cure INSPPIRE; the AP group, and the acute recurrent pancreatitis (ARP) or CP (ARP/CP) group (10). All diagnoses were manually confirmed by a review of symptoms and signs at admission, along with laboratory, and imaging findings. The patients were evaluated in terms of their age, sex, body mass index (BMI) status by using Centers for Disease Control and Prevention criteria for pediatric-specific BMI percentiles, clinical findings, laboratory test results, radiologic findings, treatments, treatment responses, etiology of pancreatitis (as documented by the treating physicians), comorbidities and surgical procedures (12).

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval no: 2021/19-01, date: 09.12.2021).

Statistical Analysis

The data were assessed using descriptive statistics, including the numbers, percentages distributions, median, means, and standard deviations. Outcomes of interest were compared by the χ^2 test for categorical data. Student's t-test and Mann-Whitney U tests were used to compare continuous data which were distributed normally and non-normally, respectively. The total number of hospitalized patients was determined each year starting in 2011 and the incidence of pancreatitis among hospitalized patients was calculated annually. The data was evaluated via Statistical Package for the Social Sciences (SPSS) 20 (IBM SPSS Statistics for Windows, Version 20.0, released 2011; IBM Corp., Armonk, NY, USA). All p-values were 2-tailed, and $p<0.05$ was considered significant.

Results

There were 111 patients admitted for pancreatitis between 2011 and 2021. The median age at diagnosis was 11.0 years (1.0-17.0 years) and 54% of patients were male. The study group consisted of 111 children with 72 (64.9%) AP, 27 (24.3%) ARP, and 12 (10.8%) CP. Only one of the 12 CP cases was female, and the ratio of male to female patients was statistically significant in the CP group ($p=0.012$). Two patients from the CP group had a family history of pancreatitis but none of the AP or ARP cases had any family history. The demographic and clinical features of the patients are shown in Table I and the laboratory findings of the AP and ARP/CP groups are shown in Table II.

The most common causes of pancreatitis were idiopathic (27.8%), cholelithiasis (26.4%), and infections (8.4%) in the AP group. In the ARP/CP group, idiopathic (35.9%), trauma (15.4%), and drugs (10.3%) were detected most frequently (Table III). The rate of gallstones was higher in the AP group compared to the ARP/CP group (26.4% vs 5.1%, $p=0.006$). Two patients (1.8%) presented with pancreatitis and were diagnosed with primary pancreatic cancer, both with a negative family history of pancreatic cancer. The first one was a 15-year-old female with AP presentation of pancreatic neuroendocrine tumors, and the other was a 15-year-old male with CP presentation of an isolated pancreatic desmoid tumor.

The number of cases increased progressively from 14 to 97 between the first and the second five-year periods and

there was a significant increase (p<0.001) in pancreatitis-related hospitalizations over the years (Figure 1).

The demographic and clinical characteristics according to the first and the second five years are shown in Table IV. There was no statistical difference between these two periods in terms of laboratory test results, except for glucose (Table V). The median serum glucose levels were detected at 81.5 (6-221) mg/dL in the first five-year period, while it was higher in the second 101 (67-614) mg/dL (p=0.038).

The most common etiologies in the first five years were idiopathic (42.9%), trauma (14.3%), and infections (14.3%), while idiopathic (28.9%), cholelithiasis (20.6%), and drugs

Table I. Demographic and clinical features of the patients with pancreatitis

	Acute pancreatitis (n=72)	**Acute recurrent/Chronic pancreatitis (n=39)**	**p-value**
Gender (M/F) n (%)	38 (52.8)/34 (47.2)	22 (56.4)/17 (43.6)	0.714
Age (year) Median (min-max)	11 (1-17)	13 (1-17)	0.250
Clinical symptoms at admission n (%)	Abdominal pain 57 (79.1) Vomiting 11 (15.3) Fever 1 (1.4) Weight loss 3 (4.2)	Abdominal pain 31 (79.4) Vomiting 6 (15.4) Fever 1 (2.6) Weight loss 1 (2.6)	0.945
Weight status at admission n (%)*	Underweight 5 (6.9) Normal weight 47 (65.3) Overweight 4 (5.6) Obese 16 (22.2)	Underweight 4 (10.3) Normal weight 29 (74.3) Overweight 3 (7.7) Obese 3 (7.7)	0.300
Family history n (%)	0	2 (5.9)	NS

*According to BMI percentile
BMI: Body mass index, min-max: Minimum-maximum, M/F: Male/Female, NS: Not significant

Table II. Laboratory findings of patients with pancreatitis

	Acute pancreatitis (n=72)	**Acute recurrent/ Chronic pancreatitis (n=39)**	**p-value**
Amylase (IU/L) Median (min-max)	613 (67-8,517)	743 (95-2,199)	0.576
Lipase (IU/L) Median (min-max)	588 (25-5,670)	518 (21-4,640)	0.619
Alanine aminotransferase (IU/L) Median (min-max)	28 (7-788)	15.5 (6-475)	0.076
Aspartate aminotransferase (IU/L) Median (min-max)	35 (14-1,020)	23.5 (14-471)	0.022
Gamma-glutamyl transferase (IU/L) Median (min-max)	33 (2.8-788)	15 (6-238)	0.312
Alkaline phosphatase (IU/L) Median (min-max)	168 (8.4-388)	206.5 (72-449)	0.885
Blood glucose (mg/dL) Median (min-max)	102 (70-236)	94 (5-186)	0.191
Plasma creatinine (mg/dL) Median (min-max)	0.6 (0.4-1.0)	0.7 (0.3-1)	0.280
Calcium (mg/dL) Median (min-max)	9.7 (7.6-11.4)	9.5 (7.6-10.3)	0.837
C-reactive protein (mg/L) Median (min-max)	0.9 (0.02-23)	0.47 (0.05-6.6)	0.077
White blood cell count (/mm³) mean ± SD	11,989±6,085	9,728±3,637	0.017
Hematocrit (%) Median (min-max)	38.2 (5.3-45.4)	39.2 (29.9-44.4)	0.259
Platelet count (×10⁹/L) mean ± SD	358,500±3,866	286,480±1,370	0.264

min-max: Minimum-maximum, SD: Standard deviation

Table III. Etiology of pancreatitis			
	Acute pancreatitis frequency (n=72), n (%)	**Acute recurrent/Chronic pancreatitis frequency (n=39), n (%)**	**p-value**
Idiopathic	20 (27.8)	14 (35.9)	0.150
Gallstone	19 (26.4)	2 (5.1)	
Infections **Influenza** ***Salmonella*** **Coronavirus** **Mumps** ***Pneumococcal pneumonia*** **Tuberculosis**	6 (8.3) 2 (2.8) 1 (1.4) 1 (1.4) 1 (1.4) 1 (1.4) -	2 (5.1) - 1 (2.6) - - - 1 (2.6)	
Trauma	3 (4.2)	6 (15.4)	
Drug-related **Asparaginase** **Methylprednisolone** **Mercaptopurine** **Sodium valproate** **Colchicine overdose**	5 (6.9) 2 (2.8) 1 (1.4) - 1 (1.4) 1 (1.4)	4 (10.3) 2 (5.1) 1 (2.6) 1 (2.6) - -	
Hereditary ***SPINK1* gene positive** ***PRSS1* gene positive** ***CFTR* gene positive**	5 (6.9) 1 (1.4) 1 (1.4) 3 (4.2)	1 (2.6) - - 1 (2.6)	
Anatomic anomalies **Pancreas divisum** **Choledochal cyst**	3 (4.2) - 3 (4.2)	3 (7.7) 1 (2.6) 2 (5.1)	
Hypertriglyceridemia	4 (5.5)	2 (5.1)	
Autoimmune pancreatitis	2 (2.8)	-	
Duodenal bezoar	1 (1.4)	-	
Systemic disease **Familial Mediterranean Fever** **Type 1 diabetes mellitus** **Celiac disease** **Ulcerative colitis**	4 (5.5) - 1 (1.4) 1 (1.4) 2 (2.8)	3 (7.7) 1 (2.6) 1 (2.6) - 1 (2.6)	
Tumor	-	2 (5.1)	
PRSS1: Cationic trypsinogen gene, *SPINK1: Pancreatic secretory trypsin inhibitor* gene, *CFTR: Cystic fibrosis transmembrane conductance regulator* gene			

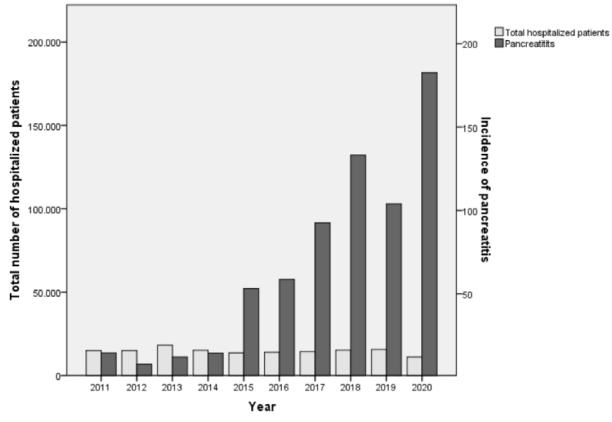

Figure 1. Incidence of pancreatitis among hospitalized patients. The 5-year incidence significantly increased in 2016-2020 compared to 2011-2015 (110.32/100,000 vs. 18.30/100,000; p<0.001; OR: 6.02, 95% CI 3.41-10.65)
OR: Odds ratio, CI: Confidence interval

Table IV. Demographic and clinical features of patients with pancreatitis over the years

	2011-2015 (n=14), n (%)	2016-2020 (n=97), n (%)	p-value
Gender (M/F)	10 (71.4)/4 (28.6)	50 (51.5)/47 (48.5)	0.163
Age (year) Median (min-max)	10.5 (1-16)	12 (1-17)	0.127
Clinical symptoms at admission	Abdominal pain 10 (71.4) Vomiting 4 (28.6) Fever - Weight loss -	Abdominal pain 78 (80.4) Vomiting 13 (13.4) Fever 2 (2.1) Weight loss 4 (4.1)	0.945
Nutritional status at admission	Underweight - Normal weight 13 (92.9) Overweight - Obese 1 (7.1)	Underweight 9 (9.3) Normal weight 63 (65.9) Overweight 7 (7.2) Obese 18 (18.6)	0.248
Family history	0	2 (2.1)	NS

min-max: Minimum-maximum, M/F: Male/Female, NS: Not significant

Table V. Laboratory features of patients with pancreatitis over the years

	2011-2015 (n=14), n (%)	2016-2020 (n=97), n (%)	p-value
Amylase (IU/L) Median (min-max)	405 (65-2294)	603 (11-8517)	0.653
Lipase (IU/L) Median (min-max)	970 (35-3270)	582 (21-5670)	0.506
Alanine aminotransferase (IU/L) Median (min-max)	46 (7-695)	22 (6-788)	0.577
Aspartate aminotransferase (IU/L) Median (min-max)	65 (18-542)	28 (8-1020)	0.139
Gamma-glutamyl transferase (IU/L) Median (min-max)	47 (4-831)	22 (2-811)	0.580
Alkaline phosphatase (IU/L) Median (min-max)	167 (104-399)	174 (8-594)	0.879
Blood glucose (mg/dL) Median (min-max)	81 (6-221)	101 (67-614)	0.038
Plasma creatinine (mg/dL) Median (min-max)	0.6 (0.3-0.8)	0.6 (0.3-1)	0.273
Plasma calcium (mg/dL) Median (min-max)	9.5 (7.6-10.3)	9.3 (7.6-9.7)	0.851
C-reactive protein (mg/L) Median (min-max)	0.4 (0.20-14.3)	0.5 (0.02-23)	0.653
White blood cell count (/mm^3) mean ± SD	12,356±7,712	11,025±5,104	0.452
Hematocrit (%) Median (min-max)	40.3 (29.9-48.3)	38.2 (5.3-48.4)	0.269
Platelet count (×10^9/L) mean ± SD	350,166±1,797	330,288±3,350	0.841

min-max: Minimum-maximum, SD: Standard deviation

Table VI. Etiology of pancreatitis over the years

	2011-2015 (n=14), n (%)	2016-2020 (n=97), n (%)	p-value
Idiopathic	6 (42.9)	28 (28.9)	0.810
Gallstone	1 (7.1)	20 (20.6)	
Infections **Influenza** ***Salmonella*** **Coronavirus** **Mumps** ***Pneumococcal pneumonia*** **Tuberculosis**	2 (14.3) 1 (7.1) - - - - 1 (7.1)	6 (6.2) 2 (2.1) 1 (1.0) 1 (1.0) 1 (1.0) 1 (1.0) -	
Trauma	2 (14.3)	7 (7.2)	
Drug-related **Asparaginase** **Methylprednisolone** **Mercaptopurine** **Sodium valproate** **Colchicine overdose**	-	9 (9.3) 4 (4.1) 2 (2.1) 1 (1.0) 1 (1.0) 1 (1.0)	
Hereditary ***SPINK1* gene positive** ***PRSS1* gene positive** ***CFTR* gene positive**	1 (7.1) 1 (7.1)	5 (5.2) 1 (1.0) 1 (1.0) 3 (3.1)	
Anatomic anomalies	-	6 (6.2)	
Hypertriglyceridemia	1 (7.1)	5 (5.2)	
Autoimmune pancreatitis	1 (7.1)	1 (1.0)	
Duodenal bezoar	-	1 (1.0)	
Systemic disease **Familial Mediterranean Fever** **Type 1 diabetes mellitus** **Celiac disease** **Ulcerative colitis**	- - - - -	7 (7.2) 1 (1.0) 2 (2.1) 1 (1.0) 3 (3.1)	
Tumor	-	2 (2.1)	

PRSS1: Cationic trypsinogen gene, *SPINK1: Pancreatic secretory trypsin inhibitor* gene, *CFTR: Cystic fibrosis transmembrane conductance regulator* gene

(9.3%) were most frequently detected in the second five years (Table VI).

The frequency of obesity was found to be 7.1% in the first five-year period, and it increased to 18.6% in the second five-year period. However, this rise was not statistically significant (p=0.248). Only 2 out of the 21 patients with gallstones were obese (9.5%), and no significant difference in the ratio of obesity was found between pancreatitis with gallstones or without gallstones (p=0.517).

There were 21 cases of gallstone pancreatitis in our cohort. The only significant difference in those patients with gallstones was observed with lower serum amylase with a median of 444 (95-1,857) IU/L compared to those without gallstones with a median of 706 (11-8517) IU/L (p=0.017), while all other laboratory data did not differ significantly.

Octreotide treatment was administered to 6 patients (42.9%) in the first five-year period and all these patients responded, while in the second five-year period, 11 patients (11.3%) were given octreotide and 81.8% of these patients were responsive.

Discussion

This study is one of a limited number of studies pointing out changes in pediatric pancreatitis in a tertiary children's hospital. We reported a significant increase in the incidence of pancreatitis among hospitalized children over the last decade at our hospital. Although the reasons for the increase in number of children with pancreatitis are not clearly understood, there are some possible explanations; namely, the clarification of the diagnostic criteria in pediatric pancreatitis, improved clinical awareness and improved access to imaging methods and laboratory facilities.

Another landmark of our study was the significant differences in the incidence and etiology of pancreatitis over the years. In the past decade, the rate of idiopathic cases decreased from 42.9% to 28.9%, but it was still the most frequent etiology in our center. Another pediatric study from Turkey reported similar findings in that the etiologic factors are still unknown in a quarter of patients, followed by systemic diseases in 14.3%, trauma in 11.1%, and cholelithiasis in 9.5% (13). A single-center study from Western China evaluated 130 children with AP and found that biliary tract disease (31.5%) and the idiopathic group (28.5%) were the most frequent etiologies, while a study from India with 320 children diagnosed with AP found that trauma (21%) and biliary tract disease (10%) were the most common causes (3,14).

In the past decade, we found that infections were the third most common cause of AP, but the rate of infections decreased from 14.3% to 6.2% in the second half of the decade. It was thought that the isolation and protection measures applied due to the coronavirus disease 2019 pandemic seen around the world could also have been effective in reducing the transmission of infection. This is still a very high rate when compared to previous pediatric studies with rates of 1.9-3.2% (5,13,15). Higher rates of viral infections were detected in Taiwanese, Chinese and Italian studies with rates of 10-12%, and this shows that etiology may differ according to geographical regions (14,16,17).

The high rate of drug-related pancreatitis (9.3%), which was the third most common cause in the second five-year period, may reflect the frequent use of asparaginase at our institution which has a high volume of oncology care. The fact that no drugs were included in the etiology in those cases in the first five years may be related to not sufficiently questioning drugs in their etiology. The third most common reason for the ARP/CP group was surprisingly drugs with a rate of 10.3%. The four (44.4%) out of the total 9 drug-associated ARP/CP patients were asparaginase-related. The reason for this high rate in ARP/CP patients may be the obligatory use of asparaginase in cancer treatment because of its important role in therapy. In the treatment of acute lymphoblastic leukemia, asparaginase is reported to cause pancreatitis in 5.3-7% of children (5,18).

While trauma is among the most common three causes in other studies, in our center, trauma ranks third with 14.3% in the first five-year period and it fell to fifth rank with 7.2% in the second five-year period. An Australian study had a higher number of AP associated with trauma (36%) compared to our study (15). This data was collected from a regional pediatric trauma and a major referral center for pediatric patients and that might explain the differences in results.

In our study, two patients (1.8%) who presented with pancreatitis were diagnosed with primary pancreatic cancer, both with a negative family history of pancreatic cancer. Smoking habits and possibly heavy alcohol use are elevating risks for pancreatic cancer as seen in pancreatitis in adult studies, and still slightly increased risk after CP was not ruled out (19). However, our patients did not have any alcohol or tobacco use in the past. Although pancreatic cancer is a rare disease, in a multicenter study with 246 patients from 10 countries diagnosed with hereditary pancreatitis at an early age (<30 years), a 3% prevalence of pancreatic cancer was found (20). For this reason, cancer should be considered in the diagnosis of childhood pancreatitis.

Gallstone pancreatitis represented a significant part of our cases with 20.6% over the years, consistent with previous reports which have shown that biliary tract disease is one of the top three causes of pancreatitis in children (3,4,14,21). Obstructive factors are more common in children than in adults (22). An increasing incidence of biliary pancreatitis has been reported due to increasing rates of obesity (21). With regards to this, only 9.5% of patients diagnosed with gallstones were obese and no significant differences in terms of obesity were detected in our study. The results of one pediatric study showed that aspartate transaminase (AST) was an independent predictor of biliary pancreatitis (21). There were 21 cases of gallstone pancreatitis in our cohort. The only significant differences in those patients with gallstone pancreatitis were observed with lower amylase, while lipase, AST, and the other laboratory data did not differ. Despite serum amylase levels remaining elevated for a shorter period compared to serum lipase after AP, it is surprising that lipase values did not differ (23,24). As regards laboratory findings, we found that the AST levels were significantly higher in those children with AP.

When comparing the first five years of laboratory data of our cohort with the second five years, blood glucose levels rose significantly over the years. Hyperglycemia and diabetes mellitus can occur with pancreatitis (25). An increase in the incidence of diabetes mellitus and obesity has been demonstrated globally in recent decades (26,27). As is well-known, hyperglycemia is often observed during AP (28). Additionally, hyperglycemia in CP patients is associated with reduced beta cell area (29). In our data, no significant difference in blood glucose levels was found between the AP and ARP/CP groups. Furthermore, blood glucose has

been correlated with complex high clinical and biochemical prognostic scores in some previous studies (30).

Study Limitations

Although the major limitations of our study are its single-center and retrospective design, it is an instructive study in revealing the nature of pancreatitis in children and addressing certain deficiencies in the diagnosis and management of these patients. Also, our study may be helpful as it provides the opportunity to notice changes in pediatric pancreatitis over the last decade.

Conclusion

This study has highlighted that the incidence of childhood pancreatitis has increased during the last decade (2011-2021) in our hospital. Most cases were idiopathic over this period, but the distribution of detectable etiologies and the tendency of octreotide treatment have changed. The risk factors, etiologies, clinical characteristics, and prognoses of many diseases change rapidly over the years. For this reason, dynamic analytical studies such as ours, in which new findings are evaluated and compared with those of previous periods, can play an important role in the literature.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval no: 2021/19-01, date: 09.12.2021).

Informed Consent: Written informed consent was obtained from the patients and their parents.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: S.Ç., G.E., C.B.E., Ç.Ö.E., Ö.B., Concept: S.Ç., Ö.B., Design: S.Ç., Data Collection or Processing: S.Ç., N.P., Analysis or Interpretation: S.Ç., Literature Search: S.Ç., Writing: S.Ç., Ö.B.

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