Revisiting long-term prognostic factors of biliary atresia: A 20-year experience with 81 patients from a single center

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ABSTRACT

Background/Aims: The present study aimed at investigating the long-term outcomes and prognostic factors of patients with biliary atresia (BA) diagnosed and followed at a single center.

Materials and Methods: Patients with BA treated during 1994-2014 at a large-volume pediatric tertiary referral center were reviewed retrospectively with regard to demographic, clinical, laboratory, and diagnostic characteristics for identifying the prognostic factors and long-term clinical outcomes.

Results: Overall, 81 patients (49 males, 32 females) were included. Mean age at diagnosis was 73.1±4.7 (median: 64) days. Of the patients included, 78 patients (96%) underwent a portoenterostomy procedure. Mean age at operation was 76.8±4.7 (median: 72) days. The surgical success rate was 64.8%. A younger age (either at diagnosis or surgery) was the only determinant of surgical success. The 2-, 5-, and 10-year overall survival (OS) rates, including all patients with or without liver transplantation, were 75%, 73%, and 71% respectively, whereas the 2-, 5-, and 10-year survival rates with native liver (SNL) were 69%, 61%, and 57%, respectively. Mean follow-up duration was 9.4±7.5 years. Successful surgery, presence of fibrosis and/or cirrhosis on the liver pathology, and prothrombin time [international normalized ratio (INR)] at presentation were independent prognostic factors for both OS and SNL.

Conclusion: A younger age at diagnosis is strongly associated with surgical success in BA. Surgical success, the prothrombin time (INR) at presentation, and liver pathology are independent prognostic factors affecting the long-term outcomes in patients with BA. Therefore, timely diagnosis and early referral to experienced surgical centers are crucial for optimal management and favorable long-term results in BA.

Keywords: Biliary atresia, portoenterostomy, prognostic factors, follow-up, outcomes, survival

INTRODUCTION

Biliary atresia (BA) is the most common cause of neonatal cholestasis and liver transplantation in childhood and is characterized by the obstruction or discontinuity of intra- and extrahepatic bile ducts, leading to chronic cholestasis, progressive liver damage, fibrosis, and biliary cirrhosis. The incidence of BA is reported as 1:8000-1:18000 live births in the USA and European countries whereas 1:2400 for the far Eastern countries. BA is fatal if left untreated (1). Since the introduction of Kasai hepatoportoenterostomy (HPE) in 1959, the survival rates have improved. However, despite successful surgery, a majority of patients with BA will eventually require liver transplantation (2,3).

Several authors have studied the long-term outcomes and prognostic factors in patients with BA. A majority of recent studies have focused on improved outcomes with early diagnosis and younger age at surgery (4-11), whereas some other studies have reported conflicting results showing no significant effect of age at the time of Kasai HPE (12-15). Liver histology, a less studied prognostic factor, seems to be as important as the age at the time of Kasai HPE in predicting both short- and long-term outcomes (16,17). Several potential factors, such as laboratory parameters, have also been implicated in the prognosis, but it is unknown whether these factors provide additional prognostic value for patients with BA. The aim of the present study was to re-evaluate the predictive and prognostic factors influencing surgical success and long-term clinical outcomes in a retrospective cohort of patients with BA diagnosed, treated, and followed at a single large-volume academic children's hospital in Turkey.

MATERIALS AND METHODS

Ethics approval and study design

The present study was approved by the Institutional Ethics Committee for Clinical Research and complied

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with the principles of Helsinki Declaration. The medical records of 87 consecutive patients diagnosed with a definitively with BA, treated, and followed at largevolume pediatric tertiary referral center between 1994 and 2014 were retrospectively reviewed.

Inclusion and exclusion criteria

Patients were included if (1) the diagnosis of BA was confirmed through radiological, operative, and pathological investigations; (2) patients were treated (except for liver transplantation) and followed up at our institute for at least 3 months after the operation; and (3) medical records were available. Patients were excluded if (1) other neonatal cholestasis etiologies were not excluded; (2) an HPE surgery was performed at another center; and (3) medical records were insufficient.

Data collection

Of the 87 patients, 81 met the inclusion criteria. Six patients were excluded due to a Kasai HPE done at another hospital (n=4) and insufficient medical data (n=2). Data were collected on demographic, clinical, laboratory, and diagnostic characteristics of these patients; prognostic factors and long-term follow-up results of these patients were investigated. The laboratory results of bilirubin (total and conjugated), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), protein, albumin levels, and prothrombin time [international normalized ratio (INR)] as well as abdominal ultrasonography (US) findings at the initial presentation were recorded.

All but three patients underwent an HPE procedure within a median of 7 days following the initial diagnosis based on clinical, laboratory, and radiological investigations. Between 1994 and 1998, the Sawaguchi HPE was the preferred surgical technique (n=6), whereas all the patients treated after 1998 (n=72) underwent a Kasai HPE. Liver biopsy results were available for 78 patients who underwent a surgery and for other 3 patients who underwent a percutaneous biopsy only. The three patients did not undergo an HPE operation due to an already established liver failure and severe complications associated with very late presentation (two patients >200 days, one patient 110 days old). Two patients died during hospital stay, and the third patient was referred to another center for liver transplantation.

The histopathological diagnosis of BA was established based on cholestasis, ductular proliferation, inflammation, and portal fibrosis/cirrhosis (18). The surgical success was defined as the clearance of jaundice and resolution of alcoholic stools within 3 months after the HPE. A surgical mortality was defined as death within 30 days after the operation. Complications were identified as cholangitis, liver failure, portal hypertension, gastroesophageal varices, ascites, hypersplenism, hepatopulmonary syndrome, failure to thrive, and malignancy recorded at any time during the follow-up. Cholangitis was established by the typical clinical symptoms and signs of infection in the presence of laboratory and imaging studies suggestive of infection and biliary obstruction. Patients were grouped according to age at the time of diagnosis (group 1: ≤60 days, group 2: 61-90 days, and group 3: >90 days).

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences version 21.0 (IBM Corp.; Armonk, NY, USA) Data were presented as mean±standard deviation or median (range) wherever appropriate. Student's t-test was performed to detect the differences between the means of two independent groups, whereas one-way ANOVA was used for comparing the means of more groups for continuous variables. Chisquare tests were used for categorical data. Predictors of surgical success were assessed using the logistic regression model. The rates of (1) survival with native liver (SNL), which starts at birth and ends either at death or at liver transplantation, and (2) overall survival (OS), which starts at birth and ends at death, were calculated. Survival analyses were performed by using the Kaplan-Meier method and compared using the log rank test. Univariate analysis of categorical prognostic factors was performed using the Kaplan-Meier method and a log rank test, whereas a Cox proportional hazards model was used for continuous variables. Variables with $p<0.1$ in the univariate analysis and those deemed clinically important were introduced into the multivariate model. Multivariate regression analysis using the Cox model (Backward:Wald method) helped identify independent prognostic factors. A p value <0.05 was considered statistically significant, whereas p value ranging 0.05-0.1 was considered to represent a trend toward significance.

RESULTS

Baseline characteristics of the patients

A total of 81 (49 males, 60.5%) patients were enrolled in the study. Thirteen patients (10.5%) had other associated congenital anomalies, such as cardiac anomalies in nine patients, intestinal malrotation in three, situs inversus in two, and polysplenia in one patient. Demographic,

Table 1. Baseline patient characteristics (n=81)

Demographic and clinical characteristics	
Age at presentation (days)	
Mean±SD	73.1±42.5
Median (range)	64 (15-261)
Male:Female	1.53 (49:32)
Term at birth, n (%)	79 (98)
Consanguinity, n (%)	19 (24)
Symptoms at presentation	n (%)
Prolonged jaundice	81 (100)
Alcoholic stool	77 (95)
Dark urine	68 (84)
Abdominal distension	10 (12)
Vomiting and feeding difficulties	9 (11)
Bleeding	5 (6)
Findings on physical examination	
Jaundice only	29 (36)
Jaundice+hepatomegaly	17 (21)
Jaundice+hepatosplenomegaly	35 (43)
Laboratory findings	Mean±SD
Total bilirubin (mg/dL)	12.3±5.5
Conjugated bilirubin (mg/dL)	8.7±3.9
ALT (IU/L)	140±100
AST (IU/L)	232±154
ALP (IU/L)	1206±1069
GGT (IU/L)	763±695
Albumin (g/dL)	3.9±0.5
Protein (g/dL)	6.0±0.7
PT (INR)	1.37±0.71
Radiological and histopathological findings	n (%)
US Findings:	81 (100)
-Contracted or invisible gall bladder	60 (74)
-Rudimentary or hipoplasic gall bladder	10 (12)
-Normal bile ducts	9 (11)
-Hepato/splenomegaly	28 (34)
-Polysplenia	2 (2.5)
-Situs inversus	2 (2.5)
-Ascites	2 (2.5)
Scintigraphy:	64 (79)
-No excretion	64 (79)
Biopsy:	79 (97)
-Compatible with BA	62 (77)
-BA + fibrosis and/or cirrhosis	16 (20)

ALP: alkaline phosphatase; ALT: alanine amino transaminase; AST: aspartate amino transaminase; BA: biliary atresia; GGT: gamma-glutamyl transferase; PT: prothrombin time; SD: standard deviation; US: ultrasonography; INR: international normalized ratio

clinical, laboratory, and radiological details at presentation are shown in Table 1. The median age at diagnosis was 64 days (range: 15-261 days). Prolonged jaundice, alcoholic stool, and dark urine were the leading symptoms at presentation seen in >80% patients. Jaundice was present in all patients and hepatomegaly in more than twothird of patients. The mean total bilirubin level was 12.3±5.5 mg/dL (range: 3.6-37.1); the conjugated bilirubin level was 8.7±3.9 mg/dL (range: 2.7-24.3); and the prothrombin time (INR) was 1.37±0.71 (range: 0.88-5.65). The comparison of baseline laboratory results among age groups did not reveal a difference except for the GGT values (Table 2). Abdominal ultrasound (US) was the firstline imaging technique in all patients. The most frequently reported finding in the US was invisible and/or contracted gallbladder (74%). In 11% of the cases, the bile ducts were reported to be normal. The diagnosis was confirmed in all patients by intraoperative cholangiography and/or liver histopathological evaluation.

Surgical management and postoperative follow-up

Overall, 78 patients (96.3%) were operated: 6 patients (7.7%) with Sawaguchi portocutaneostomy (1994-1998) and 72 patients (92.3%) with Kasai HPE (since 1998). The surgical mortality rate was 5.1% (n=2 due to bleeding, n=2 due to nosocomial infections). All patients had histopathologic features consistent with BA, whereas 16 patients (19.8%) had accompanying fibrosis and/or cirrhosis secondary to BA.

Surgery was performed at a median age of 72 days (range: 19-270 days; mean: 76.8±4.7 days). The median duration between diagnosis and surgery was 7 days (range: 1-111 days). The surgical success rate was 64.8%. Postoperatively, all patients received coadjuvant therapy, such as choleretics (ursodeoxycholic acid 10 mg/kg/day for 4 weeks), antibiotics (sulperazone, ornidazole, and amikacin were started before operation and continued for 1 week postoperatively, followed by trimethoprim sulfamethoxazole for 1 week), and corticosteroids (methylprednisolone 2 mg/kg/day for 2 weeks, then tapered for a total of 4 weeks) along with nutritional support.

Sex, jaundice beginning time, presence of bleeding or abdominal distension at initial presentation, physical investigation findings (jaundice only or jaundice and hepatomegaly or jaundice and hepatosplenomegaly), consanguinity of parents, laboratory results, and liver histopathology had no significant effect on surgical success. The only predictor of surgical success was the age both at diagnosis (odds ratio [OR]: 0.982, 95% confidence

Table 2. Baseline laboratory values according to age groups

	≤60 days (n=34)	61-90 days (n=30)	>90 days (n=17)	p
Total bilirubin (mg/dL)	11.2±4.1 (3.6-21.6)	12.9±4.9 (5.3-24.3)	13.3±8.3 (6.0-37.1)	0.312
Conjugated Bilirubin (mg/dL)	7.9±3.7 (2.7-18.6)	9.3±3.3 (4.6-17.9)	9.4±5.2 (4.0-24.3)	0.289
ALT (IU/L)	119±93 (14-441)	157±103 (36-526)	152±108 (43-387)	0.270
AST (IU/L)	193±137 (11-625)	250±173 (92-982)	281±139 (98-609)	0.118
ALP (IU/L)	1059±1219 (105-6693)	1425±1079 (375-4617)	1113±633 (370-2289)	0.367
GGT (IU/L)	575±480 (80-2034)	1033±809 (193-2978)	681±741 (32-3028)	0.030
Protein (g/dL)	5.9±0.8 (4.3-8.2)	5.8±0.5 (4.9-7.0)	6.2±0.9 (4.7-7.9)	0.191
Albumin (g/dL)	4.0±0.5 (2.0-5.0)	3.8±0.4 (3.1-4.5)	3.8±0.5 (3-4.8)	0.298
PT (INR)	1.29±0.58 (0.92-3.82)	1.48±0.93 (0.88-5.65)	1.36±0.46 (0.96-2.97)	0.552

ALP: alkaline phosphatase; ALT: alanine amino transaminase; AST: aspartate amino transaminase; GGT: gamma-glutamyl transferase; SD: standard deviation; PT: prothrombin time; INR: international normalized ratio

Table 3. SNL and OS

	2-year	5-year	10-year	p
Survival with native liver (all)	69%	61%	57%	
Successful surgery	87%	79%	76%	<0.001
Unsuccessful surgery	49%	32%	22%	
Overall survival (all)	75%	73%	71%	
Successful surgery	89%	89%	86%	0.009
Unsuccessful surgery	65%	58%	58%	

SNL: survival with native liver; OS: overall survival

Table 4. Effects of categorical variables on SNL and OS (Log rank)

	Survival with native liver			Overall survival		
Variable	Patients (n)	Mean±SE survival (month)*	p	Patients (n)	Mean±SE survival (month)*	p
Age at admission						
≤60 days	34	173±20	0.049	34	243±17	0.019
>60 days	47	123±21		47	158±21	
Age at surgery						
≤70 days	35	197±23	0.005	35	244±16	0.008
>70 days	43	107±19		43	148±19	
Fibrosis ± cirrhosis						
Present	16	46±28	<0.001	16	96±36	<0.001
Absent	63	170±15		63	232±15	
Surgery success#						
Successful	46	204±17	<0.001	46	241±14	0.002
Unsuccessful	25	43±13		25	102±21	

*Represents automatic calculated expected survival
#Among 78 operated patients, 71 were appropriate for surgical success evaluation
SNL: survival with native liver; OS: overall survival; SE: standard error

Table 5. Effects of continuous variables on survival (Cox regression)

	SNL			OS		
Variable	HR	95% CI	p	HR	95% CI	p
Age at admission (day)	1.008	1.001-1.015	0.019	1.008	1.000-1.016	0.058
Age at surgery (day)	1.007	0.9991.014	0.075	1.006	0.997-1.014	0.180
ALT (IU/L)	1.001	0.997-1.004	0.711	1.003	1.000-1.006	0.079
AST (IU/L)	0.999	0.997-1.002	0.613	1.001	0.998-1.003	0.662
ALP (IU/L)	1.000	1.000-1.000	0.509	1.000	1.000-1.001	0.027
GGT (IU/L)	1.000	1.000-1.001	0.364	1.000	1.0001.001	0.251
Total bilirubin (mg/dL)	1.048	0.986-1.113	0.129	1.042	0.975-1.113	0.222
Conjugated bilirubin (mg/dL)	1.069	0.982-1.164	0.124	1.050	0.957-1.152	0.304
Albumin (mg/dL)	0.782	0.319-1.915	0.590	0.542	0.194-1.512	0.242
Protein (mg/dL)	1.609	1.033-2.506	0.035	1.559	0.924-2.630	0.096
PT (INR)	1.519	1.089-2.119	0.014	1.478	1.009-2.163	0.045

ALP: alkaline phosphatase; ALT: Alanine amino transaminase; AST: aspartate amino transaminase; CI: confidence interval; GGT: gamma-glutamyl transferase; HR: hazard ratio; SNL: survival with native liver; OS: overall survival; PT: prothrombin time; INR: international normalized ratio

Table 6. Independent prognostic factors affecting survival with native liver (Multivariate regression analysis)

		SNL			OS	
Variable	HR	95% CI	p	HR	95% CI	p
Surgical success Successful vs. unsuccessful	0.114	0.044-0.291	<0.001	0.186	0.060-0.580	0.004
Fibrosis ± cirrhosis on liver biopsy Present vs. absent	5.174	1.985-13.490	0.001	4.313	1.492-12.471	0.007
PT (INR) (for every one unit increase)	2.158	1.348-3.453	0.001	2.135	1.188-3.834	0.011

CI: confidence interval; HR: hazard ratio; SNL: survival with native liver; OS: overall survival

interval [CI]: 0.965-1.000, p=0.046) and surgery (OR: 0.984, 95% CI: 0.969-0.999, p=0.038). Patients younger than 60 days at diagnosis had significantly better surgical results compared to those older than 60 days at diagnosis (surgical success: 78.1% vs. 53.8%, respectively; p=0.046). The mean age at surgery was significantly lower in patients who had a successful surgery (69.5±29 vs. 91.8±50.1 days, p=0.021), but we were unable to identify a clear cut-off value for age at surgery although there was a trend toward significance, with 60 days as a cut-off limit for age at surgery (p=0.076).

Long-term follow-up: complications and outcomes

The mean follow-up duration was 9.4±7.5 years ranging 0.2-21.4 years. Sixteen (19.7%) patients were lost to follow-up. Of the remaining 65 patients, 13 (22.8%) never had complications, 10 (17.5%) had liver transplantation, 20 (24.6%) had at least one complication, and 22 (38.6%) died. The mean age at diagnosis differed between three groups (without complications, with complications, death; p=0.002). The mean age at diagnosis was significantly lower in the no complication group compared to the death group (40.9±3.5 days vs. 84.9±9.3 days, p=0.001).

Cholangitis was encountered in 33% (n=19) of patients in the first 2 postoperative years. Of these, five had repeated episodes (2-4 times).

Living-related liver transplantation (LT) was performed on 10 patients (M:F=7:3) ranging in age from 0.8 to 14.2 years. These patients received LT over a median duration of 2.6 years after diagnosis. All the transplantreceiving patients had undergone a previous Kasai operation except for one patient having had a Sawaguchi operation previously. No *de novo* LT was performed to date. The indications for LT included surgery failure and progress to liver cirrhosis with complications.

Eight patients (6.5%) were followed up over 10 years. Among these patients, one had LT but others were alive with their native livers. Four patients had at least one of the following complications: portal hypertension, gastroesophageal varices, hypersplenism, and hepatopulmonary

syndrome, and one patient (with a follow-up duration of 21.4 years) developed cholangioblastic hepatoblastoma in addition to having all of the above-mentioned complications and underwent chemo- and radioembolization as deemed inoperable, whereas two patients are still complication free.

Prognostic factors of survival

The 2-, 5-, and 10-year OS rates, including all patients with or without LT, were 75%, 73%, and 71%, respectively, whereas the 2-, 5-, and 10-year SNL was 69%, 61%, and 57%, respectively (Table 3). Sex, jaundice beginning time, and physical examination findings (jaundice only or jaundice and hepatomegaly or jaundice and hepatosplenomegaly) had no significant effect on OS or SNL.

The univariate analysis revealed that the age at diagnosis younger than 60 days (p=0.049 for SNL and p=0.019 for OS), age at operation younger than 70 days (p=0.005 for SNL and p=0.008 for OS), and successful surgery (p<0.001 for SNL and p<0.001 for OS) were good prognostic factors, whereas the presence of fibrosis and/or cirrhosis on the liver pathology indicated poor prognosis (p<0.001 for SNL and p=0.002 for OS). Every one-day delay in diagnosis was associated with a 1% increase in mortality (hazard ration [HR]: 1.008; 95% CI: 1.001-1.015; p=0.019), whereas every 0.1 unit increase in the prothrombin time (INR) raised the risk of mortality by 5% (HR: 1.519; 95% CI: 1.089-2.119; p=0.014).

Successful surgery (p<0.001 for SNL and p=0.004 for OS), presence of fibrosis and/or cirrhosis on the liver pathology (p=0.001 for SNL and 0.007 for OS), and the prothrombin time (INR) at presentation (p=0.001 for SNL and p=0.011 for OS) were identified as independent prognostic factors for both SNL and OS (Table 4, 5, 6).

DISCUSSION

This was a retrospective study investigating the long-term follow-up results of patients with BA from a large-volume academic pediatric hospital in Turkey. We showed that the initial prothrombin time, liver histology, and successful portoenterostomy were independent prognostic factors for both OS and SNL in patients with BA. In contrast, the only predictor of surgical success was found to be age, both at diagnosis and surgery. Taken together, our results affirm the importance of early diagnosis and treatment in patients with BA.

The postoperative clearance of jaundice, which indicates achievement of bile drainage, is considered a strong predictor of success for portoenterostomy. Most authors have recommended referring the patient for LT evaluation if persistent jaundice or elevated serum bilirubin are present at 3 months after portoenterostomy (7,19,20). Therefore, in the present study, surgical success was defined as the clearance of jaundice (serum bilirubin <2 mg/dL) 3 months after portoenterostomy. The surgical success rate was 64.8% in our study. Likewise, various studies have reported that the clearance of jaundice can be achieved with portoenterostomy in approximately 50%-60% of children (21,22). Surgical success is closely related to SNL. The 4-year SNL was reported to be around 50%, whereas the 5-year SNL was reported to be 37%-49% from various European countries (5,6,22). Successful surgery also increases the OS of patients with BA and postpones LT (23). In accordance with literature, we demonstrated that successful portoenterostomy resulted in improved SNL and OS in patients with BA independently from other factors.

A younger age at diagnosis and surgery were significantly associated with better surgical results in our study in accordance with most studies, which have demonstrated better outcomes with younger age at operation (24,25). In our cohort, mean age at diagnosis was 73.1±4.7 days (median: 64 days), and mean age at operation was 76.8±4.7 days (median: 72 days), which are considered delayed according to the widely shared opinion that success in achieving bile drainage is better if portoenterostomy is performed before the age of 60 days. Indeed, we also showed that patients younger than 60 days at diagnosis had significantly better surgical results when compared with those older than 60 days at diagnosis. Mean age at surgery was significantly lower in patients whose surgery was successful; however, we were unable to identify a clear cut-off value for age at surgery although there was a trend toward significance with 60 days as a cut-off limit for age at surgery. These results stress the importance of early diagnosis and timely surgical intervention to construct a new bile drainage system for patients with BA. Although we did not include age as a covariate in multivariate models of survival due to its strong correlation with surgical success, it is apparent that the age at operation indirectly affects both SNL and OS in the long-term by determining success of portoenterostomy.

We also investigated the effects of other potential factors on prognosis. The histopathological status of the liver at the time of diagnosis and/or surgery appears to be an important determinant of clinical outcomes, as it relates to the functional status of the liver. In our co-

hort, 19.8% of the patients had fibrosis and/or cirrhosis in addition to the typical findings compatible with BA; the patients had considerably poorer outcomes than those without fibrosis or cirrhosis. The presence of fibrosis and/or cirrhosis on the liver pathology increased the mortality risk by 2.7 times and was found to be an independent prognostic factor. It was an independent prognosticator of SNL as well. Although less studied than age, the impact of liver pathology on outcomes of BA has been shown by some authors. Consistent with our findings, they have demonstrated that the absence of liver fibrosis has a significant influence on SNL outcomes irrespective of age at the time of the Kasai HPE (13,16,17,26-29).

The prothrombin time (INR) is a direct measure of the liver's biosynthetic capacity and therefore reflects the functional status of the liver. Therefore, INR can be deemed as important as the liver pathology in predicting outcomes of patients with BA. Indeed, the prothrombin time at initial presentation was found to be another independent prognostic factor for both SNL and OS according to our findings. To the best of our knowledge, this is the first study demonstrating the influence of the initial prothrombin time on the outcomes of BA. Taken together with liver histology, these findings may reflect the importance of underlying pathological and functional state of liver on BA outcomes.

Several other prognostic factors have been identified to date, including nonmodifiable factors, such as the type of BA, portal pressure at the time of portoenterostomy, BA with a polysplenia syndrome, and improvable factors such as accessibility to LT or experience of the center in the management of patients with BA (3). We did not study the effects of these factors, as data were not available for such variables. We noticed that although we had only two patients with a polysplenia syndrome, they patients had poor outcomes. Additionally, in the univariate analyses, we showed that the initial serum ALP and protein levels were associated with OS and SNL, respectively, which are likely to be incidental findings because the multivariate analysis did not reveal a significant effect.

In the current study the mean follow-up duration was 9.4±7.5 years (range: 0.2-21.4 years). Most patients surviving for more than 3 years experienced major complications due to the underlying liver condition. Eight patients were followed up for over 10 years. Among these patients, two were complicationfree, whereas the rest had chronic complications, such as cholangitis, portal hypertension, variceal bleeding, hypersplenism, hepatopulmonary syndrome, and cholangioblastic hepatoblastoma. Studies have reported 20-year survival rates of 21%-51% in patients with BA with native liver (23,30). In our study, OS and SNL were in line with the previous studies: 5-year OS: 73%, SNL: 61%; 10year OS: 71%, SNL: 57%. In light of both this study and literature, we conclude that it is important to be aware of and look for the long-term complications of patients with BA for better outcomes.

To the best of our knowledge, this is the largest clinical series of patients with BA from Turkey and one of the largest single center series in the world. All patients were diagnosed and treated in the same institution. Data completeness, including laboratory parameters and follow-up results, was satisfactory in most patients. However, one-fifth of the patients were lost to follow-up. Although most patients were treated with Kasai HPE, a small proportion of the patients underwent Sawaguchi operation. LT was carried out in other institutions for most patients. In addition, the study has inherent biases due to the retrospective nature.

In conclusion, these findings lend support and add further dimensions to existing data. Younger age at diagnosis is strongly associated with surgical success, which in turn determines both SNL and OS. The prothrombin time (INR) at presentation and liver pathology are other factors affecting long-term prognosis. These findings suggest that structural and functional impairment of the liver by the time of surgery is the key factor determining the long-term prognosis of patients with BA. Therefore, timely diagnosis and early referral to experienced surgical centers are crucial for optimal management and favorable long-term results in BA.

Ethics Committee Approval: The present study was approved by the Institutional Ethics Committee for Clinical Research and complied with the principles of Helsinki Declaration.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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