

# Clinical Outcome of Children with Progressive Familial Intrahepatic Cholestasis: A Cohort Study

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**Received:** 02 December, 2024, Manuscript No. AAJCP-24-153912; **Editor assigned:** 05 December, 2024, Pre QC No. AAJCP-24-153912 (PQ); **Reviewed:** 19 December, 2024, QC No. AAJCP-24-153912; **Revised:** 26 December, 2024, Manuscript No. AAJCP-24-153912 (R); **Published:** 03 January, 2025, DOI:10.35841/0971-9032.29.01.2408-2422.

## Abstract

**Background:** Progressive Familial Intrahepatic Cholestasis (PFIC) is a rare genetic liver disorder characterized by cholestasis and progressive liver damage, often leading to cirrhosis and liver transplantation. Understanding the clinical course and outcomes of PFIC is important for improving management techniques, particularly in resource-limited settings like Iran.

This study aimed to assess the clinical outcomes and survival rates of children with PFIC in Iran, emphasizing the importance of early diagnosis and liver transplantation.

**Methods:** This cohort study is part of the Shiraz Pediatric Liver Cirrhosis Cohort Study (SPLCCS), initiated in 2018. Data were collected on demographic characteristics, clinical features and laboratory findings. Cox regression analysis was employed to identify risk factors for mortality.

**Results:** Out of 100 PFIC cases, 35% of the children died, with younger age at diagnosis and higher Pediatric End-Stage Liver Disease (PELD) scores associated with increased mortality risk. Liver Transplantation (LTx) was performed in 50% of the cohort, with survival rates of 74%, 70% and 66% at 12 months, 24 months and 60 months, respectively, post-transplant. Higher White Blood Cells (WBC), Aspartate Aminotransferase (AST) and direct bilirubin levels were also significant predictors of mortality.

**Conclusions:** Early diagnosis and liver transplantation are important for improving survival in children with PFIC. High PELD scores, WBC, AST and bilirubin levels are associated with increased mortality risk, emphasizing the need for early intervention and regular monitoring.

## Key words:

Survival, Pediatrics, Progressive Familial Intrahepatic Cholestasis, Cohort study

## Abbreviations

Progressive Familial Intrahepatic Cholestasis (PFIC), Shiraz Pediatric Liver Cirrhosis Cohort Study (SPLCCS), Pediatric End-Stage Liver Disease (PELD), Liver Transplantation (LTx), White Blood Cell (WBC), Aspartate Aminotransferase (AST), Standard Deviation (SD), Statistical Package for Social Science (SPSS), Red Blood Cell (RBC), Hemoglobin (Hb), Alanine Aminotransferase (ALT), Gamma-Glutamyl Transferase (GGT), Alkaline phosphatase (ALP), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized Ratio (INR), Hazard Ratio (HR), Partial External Biliary Diversion (PEBD), Total Internal Biliary Diversion (TIBD), Live Donor Liver Transplantation (LDLT), Partial Internal Biliary Diversion (PIBD), Model for End-Stage Liver Disease (MELD)

Accepted on 03<sup>rd</sup> January, 2025

## Background

Progressive Familial Intrahepatic Cholestasis (PFIC) is a rare congenital disorder with several subtypes, all of which are autosomal recessive in nature. These subtypes involve various genes, characterized by liver dysfunction and cholestasis and typically progress to liver cirrhosis, necessitating Liver

Transplantation (LTx). However, it's essential to recognize that despite transplantation, patients may still experience ongoing complications associated with the disorder [1,2].

PFIC poses a significant burden on affected individuals and their families due to its potentially life-threatening complications. This highly impacts patient's quality of life and

imposes substantial economic and emotional burdens on caregivers as well [3-5].

Given the complexity and variability of PFIC subtypes, there remains a need for more comprehensive studies to improve diagnostic approaches and better treatment options. Further research endeavors are essential not only to better understand the pathophysiology of PFIC, but also to develop targeted therapies that can lessen the symptoms, reduce disease progression and ultimately improve outcomes for affected individuals [6,7].

The exclusive hub for pediatric LTx within Iran can be found in Shiraz. Consequently, children and adolescents suffering from cirrhosis are directed to this facility from all corners of the country for transplant assessments. This unique resource creates an opportunity for researchers to conduct comprehensive studies on cirrhotic conditions in the pediatric population. The establishment of the Shiraz Pediatric Liver Cirrhosis Cohort Study (SPLCCS) aims to evaluate cirrhotic children, monitor the progression of their illness and observe the effectiveness of various treatments over time. Furthermore, the substantial sample size and consistent patient follow-up procedures offer an ideal environment for conducting longitudinal investigations [8]. The objective of SPLCCS was to conduct a prospective assessment of the natural progression of chronic liver disease in children, identifying factors influencing complications and mortality rates among those referred to the Shiraz Liver Transplant Center. This current report, based on SPLCCS data, delves into the demographic landscape of the PFIC subgroup. By shedding light upon the characteristics of PFIC in Iran, we aimed to contribute to the vast understanding of this rare but debilitating condition and further facilitate targeted approaches to its prevention and management.

**Methods**

The SPLCCS initiative commenced in September 2018 after obtaining approval from the ethics committee at Shiraz University of Medical Sciences (IR.SUMS.REC.1398.142). Prior to participation, written consent was secured from the parents or legal guardians of the participants. Operating as an open cohort study, enrollment remains ongoing to date.

All children in SPLCCS, who were diagnosed with PFIC since 2018, were eligible to be included in the current prospective cohort study. Then, those who were misdiagnosed and children with insufficient or incomplete medical data were excluded.

Patient’s demographic information, parents’ information, prenatal and neonatal history including associated congenital malformations and transplantation, in addition to surgical history, post-operation events and complications were taken into consideration. Furthermore, patients’ laboratory data, histopathological findings and radiologic findings were collected. However, unreliable evidence was not regarded. Patient’s follow-ups if available were extracted from the Shiraz Pediatric Cirrhosis database (IR.SUMS.REC.1399.530). Further information on children who underwent liver transplantation, such as the outcome of transplantation was also fetched from Abu-Ali Sina Hospital's HIS system.

The protocol of this study approved by Shiraz Ethic Committee (IR.SUMS.REC.1403.091)

**Statistical methods:** Quantitative data were reported as Mean ± Standard Deviation (SD) and qualitative data as number (%) respectively. Independent t-test and if the data are not normal, the Mann-Whitney U test was used to compare quantitative variables. Chi-square test or Fisher's exact test was also used to compare qualitative variables between living and dead children. In multivariate analysis, a multiple Cox regression model was used. The forward method was used to enter the variables into the model and variables whose significance was less than 5% were entered into the model. The software used was Statistical Package for Social Science (SPSS) version 16. All the tests were done two-sided and at the level of 5%.

**Results**

A total of 100 cases of PFIC were found in the Shiraz Pediatric Liver Cirrhosis Cohort Study (SPLCCS). The mean age of enrollment is 47.51 ± 46.22 months. 52 (52 %) of children were male, 70 (70 %) were issues of consanguine parents. Among the latter group, 50 (50%) children’s parents were cousins.

Eventually, 35 (35%) children were death (Table 1). The overall survival and survival after liver transplanted were presented in Figure 1 and Figure 2 respectively. According to Figure 1, survival rate after 12 months, 24 months and 60 months were 77%, 66% and 60% respectively and according to Figure 2, survival rate after 12 months, 24 months and 60 months after transplant were 74%, 70% and 66% respectively.

A comparison of two groups of dead and alive based on demographic characteristics and basic information is given in Table 2. According to these results, the age of enrollment in the study and the age of diagnosis in children who died were significantly lower (p<0.05). The PLED score was significantly higher in dead children (p=0.021).

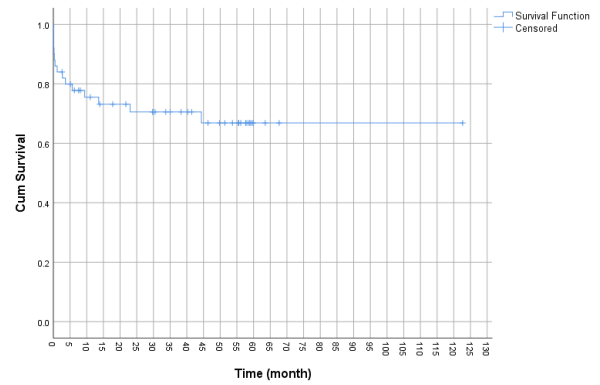
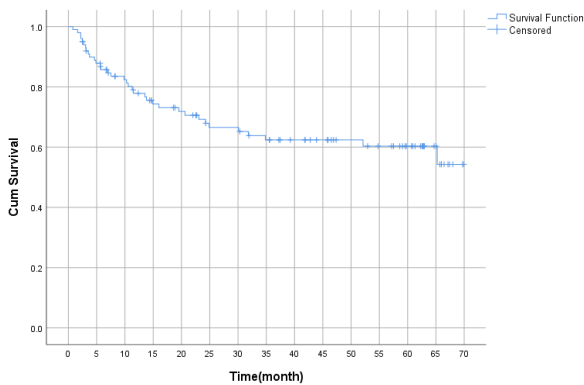
**Table 1.** Demographic and Baseline Data of Children with Progressive Familial Intrahepatic Cholestasis.

Variable	-	Total; n= 100 (%)
Gender	Male	52 (52)
	Female	48 (48)

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Age in enrolment (month)		47.51 ± 46.22 (min: 2.5; max: 206.63)
The interval between the first sign time and the time of diagnosis (month)		5.10 ± 9.28 (min: 0.03; max: 50.76)
Duration of disease before liver transplant (month)		46.10 ± 33.74 (min: 0.56; max: 157.28)
Liver Transplantation		50 (50)
Death after liver transplant		15 (30.0)
Survival after liver transplant (n=50) (month)	Death (n= 15)	6.98 ± 12.23 (median= 1.15)
	Alive (n= 35)	41.77 ± 24.53 (median= 46.35)
Time duration of study (month) (Follow-up time)		31.56 ± 23.80
Issues of consanguine parents	Yes	70 (70)
	No	30 (30)
Type of parent relation	Cousins	50 (50)
	Second relative	20 (20)
	Not relative	30 (30)
First sign/symptom	Jaundice	77 (77)
	Abdominal swelling	7 (7)
	Pruritus	10 (10)
	Unknown	6 (6)
Blood product transfusion		31 (31)
Primary outcome	Alive	65 (65)
	Deceased	35 (35)
Place of death (n=35)	Hospital	30(88.2)
	Home	4 (11.8)
	Massive GI bleeding	2 (5.9)
Cause of death	Hepatic encephalopathy	6 (17.6)
	Liver transplantation surgery complication	2 (5.9)
	SBP	-
	Infection	1 (2.9)
	Unknown	3 (8.8)
	Others	4 (11.8)
	Covid-19	4 (11.8)
	Multiorgan failure	1 (2.9)
	Heart failure	1 (2.9)
	ARDS	6 (17.6)
	Rejection in liver transplant	2 (5.9)
		2 (5.9)
	Ursodeoxycholic acid	90 (90)
	Furosemide/Propranolol/Spirolactone	22 (22)

Medication	Rifampicin	36 (36)
	Supplement	95 (95)
	-	3 (3)
	-	7 (7)
Re-transplantation		22.30 ± 17.49
Diversion surgery	Male	24 (55.8)
Donors' age	Female	19 (44.2)
Donors' gender	Living donor	22 (44.9)
	Deceased donor	27 (55.1)
Donor type	-	-



**Figure 1.** Overall survival (Time to death) in Children with Progressive Familial Intrahepatic Cholestasis.

**Figure 2.** Survival after liver transplant (Time to death) in Children with Progressive Familial Intrahepatic Cholestasis.

**Table 2.** Comparison of demographic characteristics and baseline data of Children with Progressive Familial Intrahepatic Cholestasis in two living and dead groups.

Variables	Alive (n= 65)	Dead (n= 35)	P value	
Age in enrolment, month	57.41 ± 48.83	29.14 ± 34.62	0.003	
Age in first sign, month	11.86 ± 30.37	6.04 ± 10.90	0.169	
Age in diagnostic, month	18.61 ± 33.01	9.42 ± 12.30	0.048	
Gender (male)	32 (49.2)	20 (57.1)	0.45	
Liver transplantation	35 (53.8)	15 (42.9)	0.295	
Diversion surgery	5 (7.7)	2 (5.7)	>0.999	
First sign/symptom	Jaundice	49 (81.7)	0.836	
	Abdominal pain	4 (6.7)		
	Pruritus	7 (11.7)		
Previous Hospital Admissions	57 (95.0)	28 (90.3)	0.394	
Blood Product Transfusion	20 (33.3)	11 (35.5)	0.837	
Complication	Ascites	12 (18.5)	6 (17.1)	0.87
	Pruritus	22 (34.9)	14 (40.0)	0.617

	Hepatoencephalopathy	2 (3.1)	2 (5.7)	0.61
	Esophagus varices	23 (35.4)	8 (22.9)	0.196
Recipient Blood group				0.708
A		13 (25.5)	8 (25.8)	
B		14 (27.5)	12 (38.7)	
O		17 (33.3)	8 (25.8)	
AB		7 (13.7)	3 (9.7)	
Donor Age		23.80 ± 17.29	17.81 ± 18.12	0.332
Donor Gender (male)		16 (51.6)	8 (66.7)	0.373
Donor Blood group				0.941
A		8 (26.7)	4 (40)	
B		9 (30)	3 (30)	
O		11 (36.7)	3 (30)	
AB		2 (6.7)	0 (0)	
Donor Type				0.088
Living		18 (52.9)	4 (26.7)	
Cadaver		16 (47.1)	11 (73.3)	
Percentile+	Height for age	23.81 ± 29.85	14.53 ± 26.38	0.313
	Weight for age	23.51 ± 29.01	16.09 ± 21.25	0.331
	Weight for height	38.45 ± 29.25	39.36 ± 33.63	0.954
	BMI for age	49.52 ± 32.23	55.45 ± 35.86	0.538
PELD*		14.62 ± 9.54	20.33 ± 10.76	0.021
<b>Note:</b> +Mann-Whitney U test was used. *MELD, model for end-stage liver disease.				

The comparison of the lab data is given in Table 3. Based on these results, the two groups showed significant differences in parameters Red Blood Cell (RBC), White blood cell (WBC), Hemoglobin (Hb), Alanine Aminotransferase (ALT), Aspartate

Aminotransferase (AST), Total and direct Bilirubin, Globulin and Gamma-glutamyl Transferase (GGT) ( $p < 0.05$ ). In other lab data, no statistically significant differences were seen between the two groups ( $p > 0.05$ ).

**Table 3.** Comparison of lab data of Children with Progressive Familial Intrahepatic Cholestasis in two living and dead groups.

Variable/Test	Alive (n= 65)	Dead (n= 35)	P value
RBC ( $10^6$ )	4.11 ± 0.84	3.68 ± 0.71	0.018
WBC ( $10^3$ )	8.92 ± 4.93	11.43 ± 5.78	0.028
Hemoglobin	10.88 ± 1.92	9.95 ± 1.90	0.026
Hematocrit	33.76 ± 8.24	30.83 ± 5.28	0.071
MCV	81.55 ± 9.33	84.02 ± 11.92	0.272
MCH	26.78 ± 4.03	27.04 ± 4.40	0.771
Platelet ( $10^5$ )	2.49 ± 1.62	2.74 ± 1.92	0.517
PT	16.56 ± 5.90	18.40 ± 8.39	0.216
PTT	42.86 ± 15.17	42.42 ± 9.91	0.951

INR	1.63 ± 0.96	1.77 ± 0.86	0.475
ALT	125.46 ± 110.42	215.90 ± 202.59	0.022
AST	202.29 ± 189.91	404.97 ± 309.83	0.001
ALP	1060 ± 921	1285 ± 733	0.227
Total Bilirubin	9.32 ± 8.34	16.56 ± 12.73	0.005
Direct Bilirubin	6.00 ± 6.29	10.45 ± 8.68	0.012
Total Protein	6.73 ± 0.97	6.80 ± 1.15	0.753
Albumin	3.84 ± 0.73	3.74 ± 0.77	0.543
Globulin	2.70 ± 0.80	3.32 ± 0.97	0.016
GGT	46.54 ± 54.54	103.86 ± 113.77	0.037

**Note:** Aspartate aminotransferase (AST); Alanine transaminase (ALT); Alkaline phosphatase (ALP); Prothrombin time (PT); Partial thromboplastin time (PTT); International normalized ratio (INR); White blood cell (WBC); Gamma-glutamyl transferase (GGT).

**Multivariate analysis:** At this stage, the variables that were significant in the univariate analysis were entered into the multiple Cox regression model, the forward elimination approach for variable selection and the results of remaining variables are summarized in Table 4. Based on these results, children who were diagnosed at a younger age had a higher risk of death (Hazard ratio (HR)=1.237,  $p < 0.001$ ).

Also, there was a significant and direct relationship between the risk of death and Pediatric End-Stage Liver Disease (PELD) score (HR=1.662,  $P=0.001$ ), WBC (HR=1.001,  $P=0.003$ ), AST (HR=1.014,  $P=0.003$ ) and bilirubin direct (HR=1.383,  $P=0.007$ ).

## Discussion

This study aimed to assess the demographic characteristics, clinical features and most importantly survival outcomes of pediatric patients with PFIC in Iran, highlighting the importance of early diagnosis and liver transplantation. The findings revealed statically significant differences between living group and deceased group, regarding age at diagnosis and PELD score.

The results demonstrated a mortality rate of 35%, with the majority of deaths occurring in children diagnosed at younger ages; this finding is in line with the systematic review of Baker

et al. which reported mortality rates of 0% up to 87% across 10 studies [1].

Baker et al. reported that common symptoms of the disease appeared at 3 months of age while we found that the first symptoms were present at the age of 11.8 months in the living group and 6 months in the death group [1]. The majority of our study population, 77%, developed jaundice, followed by pruritus, 10% and abdominal swelling, 7% as their first symptom. Pruritus and jaundice were described as early and latent symptoms with different prevalences according to subtypes of PFIC in Baker et al.'s systematic review [1]. Almost half of Saudi patients presented with jaundice, pruritus and 10% with failure to thrive [9]. Sahloul et al., Hang et al., and Aydogdu et al. also reported the same symptoms as the most common [10-12].

A systematic review by Jones-Hughes et al. and other reviews and studies identified the genetic heterogeneity of PFIC as a major challenge in predicting outcomes, particularly in the context of liver transplantation [4,10]. In our study, the high prevalence of consanguinity (70%) likely contributed to the genetic predisposition seen in PFIC, further complicating disease management. This genetic factor has been similarly observed in other studies, such as those by Hassan and Hertel, Agarwal et al. (50% family clustering), which emphasize the need for genetic counseling in regions with high rates of consanguinity [6,13].

**Table 4.** Multiple Cox regression model result cohort study of Children with Progressive Familial Intrahepatic Cholestasis.

Variable/Test	HR	95% CI		P value
		Lower	Upper	
Age in diagnostic	0.81	0.72	0.91	<0.001
PELD	1.662	1.234	2.24	0.001
WBC	1.001	1	1.002	0.003
AST	1.014	1.006	1.023	0.001
Direct Bilirubin	1.383	1.095	1.745	0.007

In contrast, this prevalence of consanguinity was much less (10%), reported by Pfister et al. [14]. The high rate of consanguinity in our cohort suggests that genetic screening and counseling should be integral parts of PFIC management in Iran. As noted in previous studies conducted in countries with similar cultural backgrounds, consanguinity increases the risk of autosomal recessive disorders and early identification of at-risk families could lead to earlier interventions and improved outcomes [9,10]. Hence, it is recommended that susceptible families, be informed about the possible consequences of consanguinity marriage problems.

Biliary diversion surgery was performed in 7 children (7%) in our study. A study report from India included 3 cases (12.5%), 4 children with LT from an American institution (22.2%), one case (1.2%) from Saudi Arabia, about 13% of a Chinese cohort, about a third of cases from a university hospital in Germany and 14.6% of cases with LTx from another Chinese study. 37.5% of children had partial external biliary diversion (PEBD) in a retrospective cohort from Germany. Also, three children (5%) had total internal biliary diversion (TIBD) due to post-LT graft steatohepatitis from Chennai, India [9,11-16].

Liver transplantation was performed in 50% of the cohort and variable survival outcomes. According to Alsohaibani et al., 64.6% of patients had LTx, while this proportion was 46% in Pfister et al., [9,14]. According to our findings, children who underwent transplantation at an older age had worse survival rates, underscoring the major role of early intervention in improving prognosis.

As liver transplantation has been practiced since more than twenty years ago, our data suggest that early diagnosis and timely LTx are important for improving survival in PFIC patients; with an average duration of disease before LTx of 46.1 months. This period is shorter in comparison with 53.9 months, reported by Alsohaibani et al., [9,17]. The inverse relationship between age of enrollment and risk of death highlights the urgency for early intervention. This finding is supported by Kavallar et al., who demonstrated that early liver transplantation in PFIC patients significantly improves long-term outcomes, particularly when combined with biliary diversion surgeries [2]. The higher survival rates among older children in our cohort may reflect delays in diagnosis and access to specialized care, a common issue in resource-limited settings; i.e., the sooner the children are detected and put under management, the higher their chances are to live and get older.

In addition to the identified risk factors for mortality, our study revealed several noteworthy observations. First, the mean age of enrollment in the study was 47.5 months, with a wide range from 2.5 months to 206.63 months. Children, who enrolled in the study at a younger age, had a significantly higher risk of death, indicating the severity of their conditions and symptoms, affecting their survival. Furthermore, survival outcomes varied considerably, particularly after liver transplantation. While the median survival time for those who survived post-transplant was 46.35 months, those who died after transplantation had a median survival of only 1.15 months. This stark difference emphasizes the challenges of post-transplant care and the need

for continuous monitoring and supportive therapies to improve long-term outcomes; confirmed by Sahloul et al. as well [10].

In our study, about 45% of patients undergoing LTx received Live Donor Liver Transplantation (LDLT). In a study from China by Hang et al., 75.6% of patients received the transplanted liver from living donors [11,15]. In Vasudevan et al.'s study though, more than 90% had LDLT [16].

Furthermore, Hang et al. also reported two cases of re-transplantation (4.9%) which is close to our study which is 3%.

The follow-up duration also varied significantly among patients, with a mean of 31.56 months in comparison with about 66 months reported by Hang et al., and 62.8 month by Vasudevan et al., [15,16]. Patients who survived beyond the study period had longer follow-up times compared to those who did not survive, indicating that early and prolonged follow-up care may play a role in improving patient outcomes. These findings suggest that timely enrollment into care and consistent follow-up are essential for optimizing survival in children with PFIC which needs to be considered and improved.

The result of multiple cox regression models showed the PELD score, WBC, AST levels and direct bilirubin levels were significantly increased risk of death among children with PFIC.

The association between high PELD scores and mortality in our study mirrors the findings of previous research, which has established PELD as a reliable predictor of transplant outcomes in pediatric cholestatic liver disease. Elevated AST and direct bilirubin levels, both strong indicators of liver dysfunction, were also significantly higher in death patients. This parallels findings in bile acid studies, such as that of Liu et al., which show that uncontrolled cholestasis is associated with increased levels of toxic bile acids, further exacerbating liver damage [15,18].

These findings emphasize the need for regular monitoring of liver function and early referral for liver transplantation in PFIC patients. Clinicians should be aware of the potential benefits of bile acid profiling to better predict disease progression and assess the efficacy of treatments like Partial Internal Biliary Diversion (PIBD); as mentioned by Pfister et al. [14]. The significant association between liver enzyme levels and mortality highlights the importance of comprehensive biochemical monitoring in PFIC management which could provide deeper insights into patient prognosis and guide clinical decision-making, particularly in resource-constrained environments where genetic testing may not be readily available. This awareness is also demanded in Ruiz-Casas et al.'s study [19].

Our study had some limitations. Lack of genetic subtyping and measuring bile salt levels, prevent us from further elaborating the results. Unfortunately, the costs of these laboratory tests are not affordable for many families in Iran. Future research should aim to incorporate bile acid profiling and genetic subtyping, as these could provide valuable information for monitoring disease progression and treatment response. Meanwhile, a key strength of this study is the providing a

comprehensive representation of PFIC cases from different parts of Iran, with a cohort of 100 patients who are being followed regularly, which enhances the reliability of our findings.

## Conclusion

In conclusion, this study provides valuable insights into the clinical characteristics and outcomes of PFIC in Iran. Early diagnosis and liver transplantation are key to improving survival and the incorporation of bile acid profiling may enhance the management of this complex disease. Further research is needed to develop targeted therapies and improve long-term outcomes for PFIC patients.

## Declarations

### Ethics approval

The protocol of this study approved by Shiraz Ethic Committee (IR.SUMS.REC.1403.091). The SPLCCS initiative commenced in September 2018 after obtaining approval from the ethics committee at Shiraz University of Medical Sciences (IR.SUMS.REC.1398.142). Prior to participation, written consent was secured from the parents or legal guardians of the participants. Patients' follow-ups were extracted from the Shiraz Pediatric Cirrhosis database (IR.SUMS.REC.1399.530).

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests in this section.

### Funding

None of the authors received any sources of funding for conducting this research.

### Authors' contributions

Nasrin Motazedian, Seyed Mohsen Dehghani, Maryam Ataollahi, Alireza Shamsaefar and Kouros Kazemi participated in study design. Ali Ghorbanpour collected the data. Ali Ghorbanpour, Mehrab Sayadi and Nasrin Motazedian wrote and prepared the draft of the manuscript. Nasrin Motazedian, Seyed Mohsen Dehghani, Maryam Ataollahi, Alireza Shamsaefar and Kouros Kazemi commented on the manuscript and finalized it. All authors read and approved the final manuscript.

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