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Acute-on-chronic liver failure in children with biliary atresia awaiting liver transplantation

Rashmi D'Souza[1] | Tassos Grammatikopoulos[1] | Akhilesh Pradhan[2] | Harry Sutton[1] | Abdel Douiri[3] | Mark Davenport[1] | Anita Verma[1,4] | Anil Dhawan[1]

[1]Paediatric Liver, Gastroenterology and Nutrition Centre, King's College Hospital, London, UK

[2]School of Medicine, King's College London, London, UK

[3]Department of Primary Care and Public Health Sciences, King's College London, London, UK

[4]Department of Medical Microbiology, King's College Hospital, London, UK

Correspondence
Anil Dhawan, Paediatric Liver GI and Nutrition Center and MowatLabs, King's College Hospital, London, UK.
Email: anil.dhawan@nhs.net

Abstract

Objectives: Acute-on-chronic liver failure (ACLF) is an acute decompensation of cirrhosis complicated by other organ failure and is associated with increased mortality and morbidity. ACLF has not been studied in children with biliary atresia (BA), which is the commonest indication for pediatric liver transplantation (LT) worldwide. This study aims to evaluate ACLF and outcomes in children with BA while awaiting deceased donor LT.

Methods: This was a subanalysis of the dataset from a prospective cohort study of patients aged 0-18 years who underwent portoenterostomy for BA and were listed for LT at King's College Hospital, London, between 1999 and 2003. Outcomes included the development of ACLF, mortality, and complications.

Results: Ninety-nine (41 male) children were included, and follow-up was 10 [6.0-15.0] years. A total of 20/99 children developed ACLF. ACLF was associated with increased mortality while awaiting LT (20% vs 4%; $P = 0.03$). There were no associations between biochemical parameters at listing and death. Increased bilirubin levels 3 months post-portoenterostomy was predictive of development of ACLF (AUROC = 0.72, $P < 0.01$). Age at LT and time on the waiting list in the ACLF subgroup were both lower compared to the non-ACLF group ($P > 0.05$). Sepsis and gastrointestinal bleeding were the commonest precipitants of ACLF. Complications included ascites, hepatic encephalopathy, and hepatorenal syndrome; the ACLF subgroup required multisystem support and longer intensive care unit stay.

Conclusions: ACLF in children with BA awaiting deceased donor LT carries increased mortality and morbidity. This warrants stratification of patients for earlier wait-listing and prioritization for LT.

KEYWORDS

acute-on-chronic liver failure, biliary atresia, children, liver, transplantation

Abbreviations: ACLF, acute-on-chronic liver failure; AUROC, area under receiver operating characteristic; BA, biliary atresia; BiPAP, bi-level positive airway pressure; CLIF, Chronic Liver Failure consortium score; CMV, Cytomegalovirus; CVVH, continuous veno-venous hemofiltration; FiO_2, fraction of inspired oxygen; GI, gastrointestinal; INR, international normalized ratio; LT, liver transplantation; MAP, mean arterial pressure; NPV, negative predictive value; NS, not significant; PaO_2, arterial partial pressure of oxygen; PELD, pediatric end-stage liver disease score; PICU, pediatric intensive care unit; PLT, platelet count; PPV, positive predictive value; ROC, receiver operating characteristic; RRT, renal replacement therapy; SAPS, simplified acute physiology score; SOFA, sepsis-related organ failure assessment score.

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1 | INTRODUCTION

BA is an obliterative cholangiopathy that occurs in up to 1 in 6000-18 000 children.[1,2] Clearance of jaundice following portoenterostomy is achieved in 55%-60% of infants in England and Wales although the majority will still need LT within 10 years.[3-5] About 70% of patients who undergo successful portoenterostomy (post-operative bilirubin <50 μmol/L at 6 months) will develop fibrosis and cirrhosis, particularly in cases with recurrent cholangitis.[6] Complications of cirrhosis, including portal hypertension, ascites, variceal bleeding, and ACLF, become an indication for LT. In the United Kingdom, BA is the commonest indication for pediatric LT[7] and transplantation is carried out at three national liver centers. Entry onto the waiting list is an individual institutional multidisciplinary team decision as there are no specific national guidelines.

ACLF is recognized to be a distinct condition in adults, where there is an acute decompensation of chronic liver disease, often, but not always preceded by a precipitating event and leading to organ failure.[8,9] There are different definitions for the diagnosis of ACLF in adults.[10,11]

The following criteria for adults were described by the CANONIC study and will be used for the remainder of this paper: an acute decompensation of liver disease, associated with increased one month mortality (>15%) and complicated by organ failure including deranged liver or kidney biochemistry, coagulopathy, hepatic encephalopathy, hypotension, and hypoxia as defined by the Chronic Liver Failure-sepsis-related organ failure assessment (CLIF-SOFA) score.[10]

The prevalence of ACLF has been reported to be around 22.6%-30% in adults.[11] ACLF is associated with significantly increased mortality, with 90-day rates in adults with ACLF of 50%-90%.[11,12] Although there is a paucity of research evaluating ACLF in children, prognosis seems equally poor—short-term mortality rates are reported to be 20%-59%.[13,14] However, there are no data available in children from the Western world on ACLF in general and BA in particular.

The aims of this study were to describe ACLF in the context of BA and characterize its outcome and management in children requiring LT.

2 | METHODS

This was an opportune analysis of a preexisting dataset from a prospective cohort study evaluating the use of biomarkers of inflammation in children with BA.[15] As part of that study, the authors had the opportunity to interrogate the database for the incidence of ACLF in a prospective manner. Participants aged 0-18 years who had undergone portoenterostomy at King's College Hospital, London (KCH) and were subsequently listed for deceased donor LT at KCH between 1999 and 2003 were included. The dataset was collected for the purposes of audit for service development; therefore, ethical approval was not required by our institution.

Baseline data at 1, 3, and 6 months after portoenterostomy, at listing and LT, were recorded. Data collection included demographic characteristics, liver and renal function, INR, serum albumin, total conjugated bilirubin, platelet count, and PELD score at the time of listing.

Primary outcomes were the development of ACLF, precipitating factors and complications. ACLF was defined as acute decompensation of cirrhosis with evidence of organ failure including hyperbilirubinemia, renal failure, hepatic encephalopathy, deranged coagulation, and cardiovascular or respiratory failure as defined by the CLIF-score (Table 1).[10] At our center, patients presenting with ACLF were listed for transplantation within a 7- to 10-day period; therefore, timing of ACLF is equivalent to timing from Kasai to waitlisting. Other outcome measures included mortality, requirement for assisted ventilation, CVVH, time to LT, and length of stay in the PICU post-LT.

Data are shown as median and interquartile range. Chi-square and Fisher's exact tests were used for categorical data, Mann-Whitney *U* tests were used for investigating associations in continuous data, and binomial logistic regression was used for evaluating the association of independent variables to ACLF. Cox regression analysis was used to investigate variables associated with death. Discriminatory powers were assessed with ROC curve analysis. PPV and NPV were calculated. The level of significance was preset at $P < 0.05$. Statistical analyses were conducted using SPSS (version 22.0, IBM).

3 | RESULTS

3.1 | Participants

Ninety-nine (41 male) children were included in the study, with a median follow-up time of 10.0 [6.0-15.0] years. Age at portoenterostomy was 2.4 [1.8-4.1] months. Age at listing was 7.0 [5.0-12.5] months. A total of 43/99 children underwent LT within 6 months of portoenterostomy.

At 3 months after portoenterostomy, 71/99 (72%) were identified with an unsuccessful procedure (bilirubin >50 μmol/L). At the time of LT listing, 92/99 (93%) had a bilirubin level greater than 50 μmol/L.

A total of 20/99 children (20%, 10 male) developed ACLF and, in line with local practice at our center, were listed within 7-10 days of diagnosis. A total of 79/99 (31 male) were listed for transplantation and did not develop ACLF. Of the 79 children without ACLF, 72/79 had a bilirubin greater than 50 μmol/L at listing, 3/79 were listed with hypersplenism (splenomegaly >9 cm and platelet count $<150 \times 10^9$/L) and 2/79 with cholangitis.

TABLE 1 Organ failure in ACLF according to the CLIF-score[11]

Variable	Organ failure cutoff
Liver failure	Bilirubin ≥12 mg/dL or 205 μmol/L
Renal failure	Creatinine ≥3.5 mg/dL or use of RRT
Hepatic encephalopathy	West Haven grade 3-4
Clotting abnormalities	INR ≥2.5
Cardiovascular failure	Use of vasopressors
Respiratory failure	PaO_2/FiO_2 ≤200

3.2 | ACLF

Median bilirubin at 3 months after portoenterostomy was significantly higher in children who later developed ACLF compared to those who did not (216 vs 115 μmol/L, $P < 0.05$; Table 2), with an AUROC of 0.72 ($P < 0.05$) (Figure 1). The optimum bilirubin cutoff was 252 μmol/L, which had 50% sensitivity, 82% specificity, 42% PPV, and 13% NPV for predicting ACLF.

This trend was still present at the time of listing ($P = 0.12$; Table 2). ACLF was significantly associated with an increased INR at 6 months post-portoenterostomy (1.04 vs 1.29, $P < 0.01$; Table 2), and at the time of listing for LT (1.2 vs 1.8, $P < 0.001$; AUROC 0.87, $P < 0.01$; Figure 2).

PELD score at listing was significantly higher in patients with ACLF (124 vs 68; $P < 0.01$; Table 2), with an AUROC of 0.85 ($P < 0.01$; Figure 2). The optimal cutoff points at listing were 1.50 for INR and 78.6 for PELD, with the following sensitivity, specificity, PPV, and NPV: INR—80%, 86%, 59%, 94%; PELD—85%, 66%, 39%, 95%. Platelets at LT were significantly lower in those with ACLF (Table 2).

Median age at portoenterostomy was 71 [60-88] days in children who developed ACLF and 73 [55-147] days for children who did not ($P = 0.48$). A total of 13/20 children with ACLF were transplanted within 6 months of portoenterostomy. Although age at wait-listing, time on the waiting list, and age at LT were lower in patients with ACLF, none of these parameters reached statistical significance (Table 2).

3.3 | Mortality

Overall, 15 children died—4/20 (20%) children with ACLF and 3/79 (4%) children without ACLF died before LT ($P = 0.03$; Table 3). After transplantation, a further child without ACLF and

TABLE 2 Baseline characteristics for children with and without ACLF after Kasai portoenterostomy at various time points

Characteristics	Total patients (n = 99)	Patients without ACLF (n = 79)	Patients with ACLF (n = 20)	*P* value
3 months post-portoenterostomy				
Bilirubin (μmol/L)	142 [42-255]	115 [26-212]	261 [138-414]	0.01
Albumin (g/L)	36 [32-41]	38 [32-42]	35 [33-37]	0.11
INR	1.07 [0.98-1.29]	1.06 [0.98-1.26]	1.12 [0.9-1.53]	0.25
Sodium (mmol/L)	137 [135-140]	138 [135-140]	137 [133-139]	0.28
6 months post-portoenterostomy				
Bilirubin (μmol/L)	73 [12-234]	90 [12-227]	31 [11-302]	0.90
Albumin (g/L)	36 [31-40]	36 [32-40]	34 [31-41]	0.84
INR	1.07 [0.98-1.3]	1.04 [0.97-1.23]	1.29 [1.10-1.95]	<0.01
Sodium (mmol/L)	137 [136-139]	137 [136-140]	137 [135-139]	0.51
Listed for LT				
Bilirubin (μmol/L)	230 [146-306]	223 [146-283]	256 [141-428]	0.12
Albumin (g/L)	31 [27-35]	32 [27-36]	30 [28-33]	0.25
INR	1.26 [1.07-1.5]	1.2 [1.03-1.36]	1.8 [1.5-2.08]	<0.01
Sodium (mmol/L)	136 [133-138]	136 [133-138]	136 [133-141]	0.36
Platelets ($\times 10^9$/L)	181 [119-232]	191 [125-257]	136 [104-223]	0.14
PELD score	73 [56-96]	68 [47-85]	124 [85-176]	<0.01
At LT				
Bilirubin (μmol/L)	298 [173-439]	266 [154-397]	444 [305-583]	0.03
Albumin (g/L)	31 [28-34]	32 [28-34]	30 [25-37]	0.16
INR	1.38 [1.17-1.83]	1.3 [1.15-1.53]	2.25 [1.8-2.5]	<0.01
Sodium (mmol/L)	136 [133-139]	136 [134-138]	134 [130-140]	0.64
Platelets ($\times 10^9$/L)	143 [87-226]	161 [95-244]	100 [65-143]	0.04
Timing of LT				
Kasai to wait-listing (mo)	4.0 [1.0-8.0]	4.5 [1.0-8.8]	3.5 [1.3-5.8]	0.91
Age at LT (mo)	11.1 [7.7-17.1]	12.0 [7.7-17.3]	8.8 [6.3-13.8]	0.20
Time on waiting list (mo)	2.6 [1.5-4.7]	2.7 [1.6-4.8]	1.9 [1.0-4.2]	0.36

Data given as median and interquartile range. Bilirubin represents total conjugated serum bilirubin.

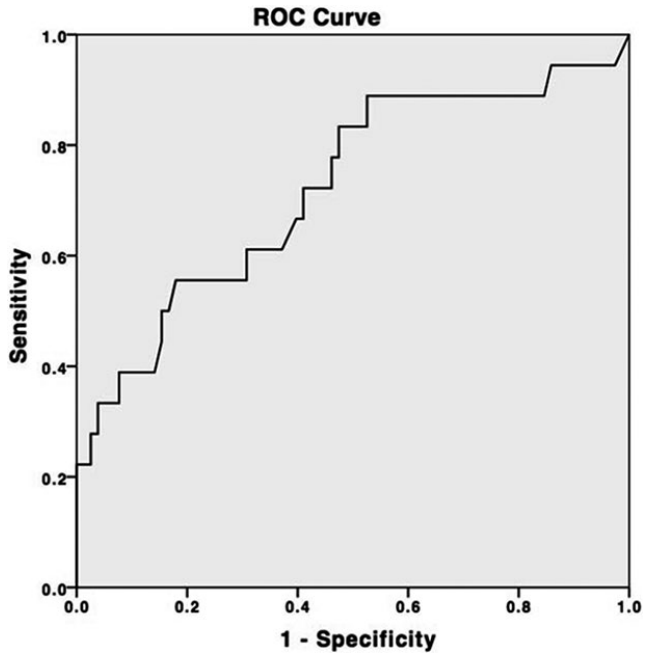

FIGURE 1 ROC curve for bilirubin at 3 mo after Kasai portoenterostomy in the prediction of developing ACLF in children before LT. AUROC = 0.72 ($P < 0.01$)

7/20 children with ACLF died. Overall time to death after LT was 5.4 months [range: 0-5.3 years]. Age at death was lower in children with ACLF—1.5 years in children without ACLF and 0.8 years in children with ACLF. Of the baseline biochemistry, only a minimal difference in serum sodium at 3 months was significantly associated with death (138 [136-140] mmol/L in children who survived vs 136 [131-137] mmol/L in children in died; $P < 0.05$). Survival was not statistically associated with baseline characteristics at listing ($P > 0.05$).

3.4 | Complications

The commonest precipitating factors for ACLF were sepsis (45%) and gastrointestinal bleeding (40%). A total of 9/20 cases with ACLF developed sepsis. Viral causes were identified in 4/9 cases of sepsis, one case each had Parainfluenza and Rhinovirus, CMV, Influenza A, and Adenovirus; bacterial causes were identified in 4/9, including *Streptococcus pneumonia*, *Staphylococcus epidermis*, *Enterococcus faecalis*, *Pseudomonas aeroginosa*; and fungal infection was identified in one child (*Candida albicans*). The following organisms were isolated in the five children with ACLF who died: *Streptococcus pneumonia*, Influenza A, CMV, Adenovirus, and *Candida albicans*.

The commonest complications of ACLF were ascites (8/20), hepatic encephalopathy (4/20), and hepatorenal syndrome (3/20). A total of 10/20 cases required bipap ventilation and 4/20 required CVVH. ACLF was associated with a longer interval in PICU post-LT (7 [3-26] days vs 2 [2-5] days; $P < 0.01$).

4 | DISCUSSION

ACLF carries significant mortality in adults and there is an increased awareness of its occurrence and complications. However, it has not been characterized within the pediatric population in the Western world. Therefore, implications on management, including timing of LT, may not be appropriately considered.

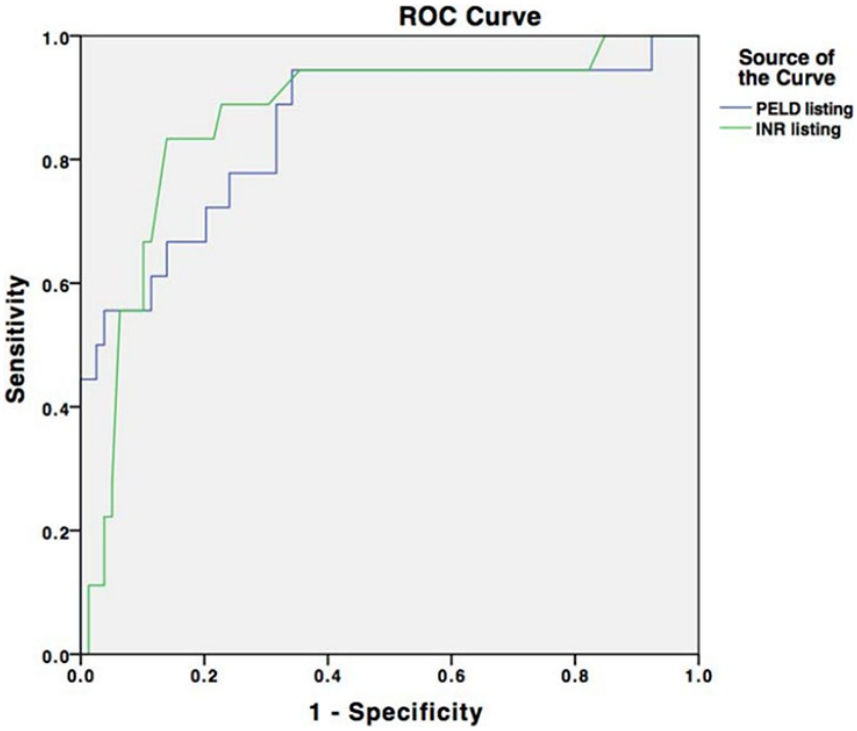

FIGURE 2 ROC curve for INR (green line) and PELD score (blue line) in the prediction of ACLF in children at time of listing for LT. AUROC = 0.85 (PELD) and 0.87 (INR) ($P < 0.01$)

TABLE 3 Mortality in children with and without ACLF after Kasai portoenterostomy

	Total (n = 99)	Children without ACLF (n = 79)	Children with ACLF (n = 20)	*P* value
Died (%)	15 (15%)	10 (13%)	5 (25%)	0.19
Age at time of death (y) [IQR]	1 [0.45-3.2]	1.5 [0.4-4.6]	0.8 [0.7-0.8]	0.81
Death pre-LT	7 (7%)	3 (4%)	4 (20%)	0.03

This is the first study to describe ACLF in children with BA awaiting LT. Our results show that mortality is five times greater in those who developed ACLF before receiving a transplant. Bilirubin levels, INR, and PELD scoring may help to stratify children at risk of developing ACLF and optimize timing of transplantation.

Mortality associated with ACLF is largely attributable to multiorgan failure with or without sepsis. The "Predisposition, Injury, Response, Organ" model by Jalan et al[8] suggests that a precipitating event causing injury in the context of predisposing factors can lead to a generalized inflammatory response and organ failure. Immune over-activation results in a relative deficit and inefficient reactions to microorganisms. This explains the greater propensity to sepsis seen in ACLF compared to chronic cirrhosis. Additionally, children diagnosed with a failed portoenterostomy procedure within the first year are at higher risk of sepsis and bacteremia; therefore, suspected infection requires particularly prompt treatment.[16-18]

Although the increased mortality and morbidity associated with ACLF apply to any chronic liver disease, they have not previously been demonstrated in this specific population.

In our population, increased bilirubin at 3 months post-portoenterostomy was associated with subsequent development of ACLF. This association lends weight to the case to consider early LT in children with evidence of jaundice at 3 months after portoenterostomy. Our data did not find a statistical difference in time on the waiting list; however, the median time was lower in children with ACLF which could suggest an institutional prioritization (1.9 vs 2.7 months; $P = 0.36$). Younger children may have to wait longer for a suitable graft size because of their smaller weight; therefore, the degree of prioritization on our institution waiting list may be underestimated because children with ACLF are listed at a younger age.

In the UK, there is no algorithm for prioritization at listing; patients are evaluated on an individual basis according to institutional practice, with no standardized use of clinical scoring systems. The PELD score is widely utilized in the United States for organ allocation by the United States Organ Network[19,20] but is not formally followed in the UK. It has been shown to be less effective, a prognostic marker in BA cases because it incorporates albumin and patient weight—fluid therapy or intravenous infusions could be confounding variables.[21] Additionally, current liver disease scores are limited predictors of the clinical course of ACLF because end-organ failure is a greater factor determining outcome.[8]

The SOFA score and INR have promising predictive powers for mortality in children with ACLF due to hepatitis A (sensitivities, specificities, and NPVs were 76%-100%, and the PPVs were 45%).[11] However, extrapolation of this to our population is difficult due to different disease etiologies, hepatitis A is not prevalent in the UK, where the commonest indication for pediatric LT is BA—the clinical picture of ACLF may therefore differ in the UK because of demographic variation. A minimal difference in serum sodium at 3 months post-Kasai procedure was the only statistical association with death in children in this study (138 vs 136 mmol/L; $P < 0.05$)—this difference is not clinically significant as it is minimal and within the physiological range.

Interestingly, bilirubin at 3 months post-Kasai procedure was significantly higher in children with ACLF; however, there was no difference at 6 months. As almost half the cohort underwent LT within 6 months of Kasai procedure, this may explain why bilirubin at 6 months is not statistically associated with ACLF. Liver function in children with ACLF may have initially been worse; however, there was a non-significant trend toward earlier transplantation in ACLF so therefore it is likely the 6-month bilirubin may be post-operative and therefore improved.

Small study size and low outcome rates limit the power of this study. Our data provide preliminary evidence in favor of stratifying patients into risk categories. Prospective studies evaluating predictive scores in this population are required to identify high-risk groups to appropriately tailor follow-up and aid robust, objective prioritization for pediatric LT. Another limitation is the historic nature of data used for this study—firstly, current outcomes of Kasai procedures and LT may have improved since this cohort, secondly, there was a paucity of data detailing the use of intensive care support including parenteral nutrition, invasive procedures, and ventilation settings. Finally, the nature of this cohort study data collection and the indolent presentation of ACLF make it difficult to investigate predictive markers at specific time points before onset of disease.

This is the first study looking at ACLF in children awaiting LT in the Western world. Our results describe the prevalence and nature of ACLF in children, as a distinct entity to an acute decompensation and the progressive course of liver cirrhosis. The most significant finding is the increased mortality associated with ACLF. This creates a persuasive argument for prioritizing children with ACLF or factors predictive of ACLF for LT.

5 | CONCLUSION

A substantial proportion of children with BA develop ACLF while awaiting LT, with higher mortality and morbidity rates than children without ACLF. ACLF is statistically associated with biochemical

parameters and the PELD score—further work is required to evaluate the use of predictive risk factors to closely monitor children at risk of developing ACLF.

CONFLICT OF INTEREST

The authors declare no conflict of interest or financial recompense as a result of this study.

AUTHORS' CONTRIBUTIONS

Rashmi D'Souza: Drafted the article and contributed to the data analysis; Tassos Grammatikopoulos: Contributed to the concept and critical revision of the article; Akhilesh Pradhan, Mark Davenport and Anita Verma: Contributed to the data collection; Harry Sutton: Contributed to data analysis; Abdel Douiri: Contributed to the data collection and analysis; Anil Dhawan: Contributed to the study concept, design, critical revision, and approval of the article.

ORCID

Rashmi D'Souza https://orcid.org/0000-0002-9690-8288
Anil Dhawan https://orcid.org/0000-0002-4942-0845

REFERENCES

1. McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet*. 2000;355(9197):25-29.
2. Sokol RJ, Mack C, Narkewicz MR, et al. Pathogenesis and outcome of biliary atresia: current concepts. *J Pediatr Gastroenterol Nutr*. 2003;37:4-21.
3. Davenport M, De Goyet J, Stringer M, et al. Seamless management of biliary atresia in England and Wales (1999–2002). *Lancet*. 2004;363(9418):1354-1357.
4. Hung PY, Chen CC, Chen WJ, et al. Long-term prognosis of patients with biliary atresia: a 25-year summary. *J Pediatr Gastroenterol Nutr*. 2006;42:190-195.
5. Davenport M, Ong E, Sharif K, et al. Biliary atresia in England and Wales: results of centralization and new benchmark. *J Pediatr Surg*. 2011;46(9):1689-1694.
6. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet*. 2009;374(9702):1704-1713.
7. Davenport M, Ure BM, Petersen C, et al. Surgery for biliary atresia – is there a European consensus? *Eur J Pediatr Surg*. 2007;17:180-183.
8. Jalan R, Gines P, Olson JC, et al. Acute-on chronic liver failure. *J Hepatol*. 2012;57:1336-1348.
9. Bernal W, Jalan R, Quaglia A, et al. Acute-on-chronic liver failure. *Lancet*. 2015;386:1576-1587.
10. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome developing in patients with acute decompensation in cirrhosis. *Gastroenterology*. 2013;144:1426-1437.
11. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol*. 2014;61(5):1038-1047.
12. Gustot T, Fernandez J, Garcia E Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology*. 2015;62:243-252.
13. Lal J, Thapa B, Rawal P, et al. Predictors of outcome in acute-on-chronic liver failure in children. *Hepatol Int*. 2011;5(2):693-697.
14. Jagadisan B, Srivastava A, Yachha SK, et al. Acute on chronic liver disease in children from the developing world: recognition and prognosis. *J Pediatr Gastroenterol Nutr*. 2012;54(1):77-82.
15. Grammatikopoulos T, Dhawan A, Bansal S, et al. Baseline evaluation of serum markers of inflammation and their utility in clinical practice in paediatric liver transplant recipients. *Clin Res Hepatol Gastroenterol*. 2012;36(4):365-370.
16. Alexopoulos SP, Merrill M, Kin C, et al. The impact of hepatic portoenterostomy on liver transplantation for the treatment of biliary atresia: early failure adversely affects outcome. *Pediatr Transpl*. 2012;16:373-378.
17. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. *Curr Opin Crit Care*. 2011;17:165-169.
18. Kim TY, Kim DJ. Acute-on-chronic liver failure. *Clin Mol Hepatol*. 2013;19:349-359.
19. Wiesner RH, Kamath PS, Malinchoc M, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transpl*. 2001;7:567-580.
20. McDiarmid SV, Anand R, Lindblad AS. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation*. 2002;74(2):173-181.
21. Tessier ME, Harpavat S, Shepherd RW, et al. Beyond the Pediatric end-stage liver disease system: solutions for infants with biliary atresia requiring liver transplant. *World J Gastroenterol*. 2014;20:11062-11068.

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