

Impact of Mild and Moderate Intrapulmonary Shunting in Children with End-Stage Liver Disease Undergoing Liver Transplantation

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Abstract

Aim The aim of this study was to evaluate the impact of mild and moderate intrapulmonary shunting (IPS) in children with end-stage liver disease (ESLD) undergoing liver transplantation.

Materials and Methods A total of 73 patients (38 male, 35 female; mean age 31.5 ± 35.2 months, range 6–180 months) with ESLD and subsequent liver transplantation were enrolled. Based on contrast echocardiography, patients without IPS were assigned to group 1 ($n = 57$), and patients with mild or moderate IPS were assigned to group 2 ($n = 17$). The preoperative age, body weight, O_2 saturation, length of hospital stay, duration of mechanical ventilation, postoperative complications, and 1-year survival rate were compared between groups.

Results The overall incidence of IPS and 1-year survival rate were 23.3% (17/73) and 96% (70/73), respectively. There were significant differences between group 1 and

group 2 patients regarding age at transplant (35.9 vs. 16.6 months, $p = 0.002$) and body weight (12.6 vs. 8.5 kg, $p = 0.002$). There were no other statistically significant differences between the two groups.

Conclusion Although children with mild and moderate IPS were younger at the time of transplantation and had significantly lower body weight than those without IPS, the presence of mild and moderate IPS in children with ESLD did not affect the overall outcome of liver transplantation.

Intrapulmonary shunting (IPS) is common in patients with end-stage liver disease (ESLD), with an estimated incidence of 13% to 47% among adults evaluated for liver transplantation [1, 2]. The etiology of IPS in ESLD remains unclear. In the past, IPS with severe hypoxemia had been considered an absolute contraindication to liver transplantation [3, 4]. However, with improvements in intensive care, surgical techniques, and medical treatments, ESLD patients with IPS-induced severe hypoxemia successfully treated by liver transplantation have been reported [5–11]. In patients with IPS, complications such as pneumonia with respiratory failure or substantial hepatic allograft dysfunction may be encountered after liver transplantation.

To our knowledge, the incidence of IPS in pediatric patients with ESLD has never been reported. In addition, detection of IPS in these patients using contrast-enhanced echocardiography has not been fully evaluated, and the impact of IPS on the overall outcome of liver transplantation has not been elucidated. The objectives of this study were to determine the incidence of IPS in our pediatric patients with ESLD undergoing liver transplantation and to evaluate the impact of mild and moderate IPS on the overall recipients' outcome after liver transplantation.

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Materials and methods

Between January 1998 and December 2003, a total of 140 pediatric patients with ESLD were referred to our institution for possible liver transplantation. All patients underwent transthoracic contrast echocardiography to evaluate the presence and severity (if present) of IPS. The echocardiographic examination was repeated if the data had been obtained more than 3 months before transplantation. Informed consent was obtained from the patients' parents.

The echocardiographic study was performed using a Philips (Andover, MA, USA) SONOS 5500 system and 5- to 8-mHz transducers. Imaging of the right-to-left shunt was performed in an apical four-chamber view. In each patient, a 21- or 23-gauge cannula was inserted via a peripheral vein. IPS was detected using agitated saline as an echocardiographic contrast agent. Contrast echocardiography was performed according to Krowka's method [1]. After connecting two 10-ml syringes to the intravenous cannula in a three-way stopcock, another syringe with 5 ml of saline solution was mixed with 0.2 ml of carbon dioxide and connected to the three-way stopcock. After agitating the saline solution for 10 to 15 seconds, a forceful hand injection was applied, and simultaneous two-dimensional echocardiographic evaluation of the heart in an apical four-chamber view was performed. A simultaneous electrocardiography recording was also obtained to facilitate detection and timing of contrast occurrence in the atria. Two injections were performed in each patient to obtain an optimal contrast effect in the resting state. Contrast echocardiograms were analyzed for time delay (in frames) between the occurrence of microbubbles in the right atrium and the initial occurrence in the left atrium. The examination was performed without sedation in most patients. Oral chloral hydrate (50 mg/kg) was given to uncooperative patients.

Contrast echocardiography was considered negative if microbubbles were not observed in the left atrium. Simultaneous contrast occurrence in the left and right atria or less than three heart cycles indicated the presence of intracardiac shunt, and the patient was excluded from the study. IPS was identified by the initial occurrence of microbubbles in the left atrium beyond three beats of opacification of the right atrium (RA). IPS was diagnosed and classified by contrast echocardiography according to Donovan's method [12]. The opacification of the left atrium (LA) by microbubbles was compared with its counterpart in the right atrium. The degree of opacification of the left atrium by comparing the amount of microbubbles was defined as mild ($LA \ll RA$), moderate ($LA < RA$), or severe ($LA = RA$). The echocardiographic images were reviewed individually by an experienced pediatric cardi-

ologist and a pediatric radiologist. Any disagreement was resolved by consensus.

Two patients with severe IPS by echocardiography were further studied using arterial blood gas analyses, technetium-99m macroaggregated albumin ($^{99m}\text{Tc-MAA}$) scintigraphy, and angiography for confirmation and were excluded from this study. In addition, 15 patients with intracardiac shunt and 50 on-list potential candidates for liver transplantation were excluded. A total of 73 patients with confirmed echocardiographic examinations and who subsequently underwent transplantation were enrolled. Among the 73 patients, 69 underwent living donor liver transplantation, and 4 received deceased donor liver transplants (2 left-split and 2 full-size).

The disease indications for transplantation included biliary atresia (60), neonatal hepatitis (8), glycogen storage disease (4), and Wilson's disease (1) (Table 1). There were 38 boys and 35 girls. The mean age was 31.45 ± 35.25 months (range 6–180 months). Based on contrast echocardiographic findings, the patients were classified into two groups: group 1, without IPS; and group 2, with mild or moderate IPS. The preoperative body weight, Pediatric Model for End-Stage Liver Disease (PELD) score, Child-Turcotte-Pugh (CTP) score, preoperative O_2 saturation, length of hospital stay, duration of mechanical ventilation, occurrence of major complications (including bowel perforation, sepsis, respiratory failure, intracranial hemorrhage), occurrence of minor complications (e.g., wound infection, bile leak, ascites, pleural effusion, rejection), and 1-year survival rate were compared between groups.

Statistical analysis

Continuous variables were expressed as the mean \pm 1 SD and were compared using the unpaired Student's *t*-test. Categorical data were expressed as proportions and were compared using the chi-squared test or Fisher's exact test. The statistical procedures were performed using the Statistics Package for Social Sciences (version 9.0 for Windows; SPSS Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

Results

Fifty-six patients were in group 1, and 17 were in group 2 (13 mild, 4 moderate). The overall incidence of IPS was 23.3%. The demographic and clinical data are summarized in Tables 1 and 2. The data are from the time of the echocardiography study. There were significant differences between group 1 and group 2 patients in terms of age (35.9 ± 38.7 vs. 16.6 ± 11.9 months, $p = 0.002$) and body

Table 1 Baseline patient characteristics

Characteristic	Group 1 (n = 56)	Group 2 (n = 17)	p
Primary liver disease	Biliary atresia (47), neonatal hepatitis (4), GSD (4), Wilson's disease (1)	Biliary atresia (13), neonatal hepatitis (4)	
AST (U/L)	229 ± 248 (19–1874)	281 ± 138 (76–562)	0.964
ALT (U/L)	189 ± 252 (15–1716)	173 ± 93 (51–398)	0.271
Bilirubin (mg/dl)	12.2 ± 10.1 (0.2–37.0)	14.1 ± 7.2 (2.8–30.7)	0.130
Albumin (g/dl)	3.5 ± 0.6 (1.5–4.5)	3.3 ± 0.8 (1.5–4.6)	0.259
TP (g/dl)	6.3 ± 1.0 (3.0–8.1)	5.6 ± 1.0 (3.0–7.1)	0.968
ALK-P (U/L)	643 ± 348 (33–1658)	770 ± 456 (82–1778)	0.167
GGT (U/L)	231 ± 233 (7–947)	387 ± 291 (28–971)	0.339
BUN (mg/dl)	11 ± 4 (5–26)	9 ± 4 (3–18)	0.983
Cr (mg/dl)	0.4 ± 0.2 (0.1–0.9)	0.3 ± 0.1 (0.2–0.5)	0.433
Hgb (g/dl)	10.0 ± 1.7 (6.8–13.4)	10.0 ± 1.8 (6.4–12.6)	0.747
Platelet ($\times 10^4/\text{mm}^3$)	18.8 ± 12.2 (0.9–48.3)	17.9 ± 9.6 (0.8–40.8)	0.118

GSD: glycogen storage disease; AST: aspartate aminotransaminase; ALT: alanine aminotransaminase; TP: total protein; ALK-P: alkaline phosphatase; GGT: γ -glutamic transaminase; BUN: blood urea nitrogen; Cr: creatinine; Hgb: hemoglobin

Table 2 Clinical data and outcome of the 73 patients after liver transplantation

Parameter	Group 1 (n = 56)	Group 2 (n = 17)	p
Age (months)	35.9 ± 38.7	16.6 ± 11.9	0.002
Sex (F/M)	26/30	9/8	0.638
Body weight (kg)	12.6 ± 8.8	8.5 ± 2.5	0.002
PELD score	15.9 ± 11.2	15.5 ± 11.1	0.921
CTP score	8.7 ± 2.8	7.6 ± 3.3	0.689
O ₂ saturation	95.2% ± 1.3%	94.6% ± 1.5%	0.643
Days on ventilator	2.2 ± 4.7	1.4 ± 1.7	0.506
Complications			
Major	7/56	1/17	0.672
Minor	22/56	8/17	0.568
Length of hospital stay (days)	51.9 ± 20.0	46.8 ± 18.1	0.326
1-Year survival	54/56	16/17	0.554

PELD: pediatric model for end-stage liver disease; CTP: Child-Turcotte-Pugh

weight (12.6 ± 8.8 vs. 8.5 ± 2.5 kg, $p = 0.002$) at the time of transplantation. There were no statistically significant differences between the two groups in terms of their PELD scores (15.9 ± 11.2 vs. 15.5 ± 11.1, $p = 0.921$), CTP scores (8.7 ± 2.8 vs. 7.6 ± 3.3, $p = 0.689$), preoperative O₂ saturation (95.2% ± 1.3% vs. 94.6% ± 1.5%, $p = 0.643$), length of hospital stay (51.9 ± 20.0 vs. 46.8 ± 18.1 days, $p = 0.326$), duration of mechanical ventilation (2.2 ± 4.7 vs. 1.4 ± 1.7 days, $p = 0.506$), occurrence of major complications [7/56 (12.5%) vs. 1/17 (5.9%), $p = 0.672$],

occurrence of minor complications [22/56 (39.3%) vs. 8/17 (47.1%), $p = 0.568$], and 1-year survival rate [54/56 (6.4%) vs. 16/17 (94.1%), $p = 0.554$]. Altogether, 48 of the 56 patients in group 1 were extubated on postoperative day 1, and 4 were extubated on postoperative day 2; the 4 other patients were extubated on postoperative days 8, 18, 22, and 25, respectively. Of the 17 patients in group 2, a total of 16 were extubated on postoperative day 1, and the other patient was extubated on postoperative day 2. All patients were dyspnea-free after extubation, and no patient required reintubation.

The complications were categorized as major or minor. The major complications included bowel perforation (2), pneumonia with respiratory failure (2), sepsis (2), sepsis and left intracranial hemorrhage (1), and portal vein occlusion and hepatic necrosis (1). Five of these eight patients were < 1 year old. Minor complications occurred in 22 of 56 group 1 patients and in 8 of 17 group 2 patients. Overall, the minor complications included ascites (14), rejection (10), pneumonia without respiratory failure (6), wound infection (4), hepatic vein stenosis (4), bile leak (2), cytomegalovirus infection (2), pleural effusion (1), central line infection (1), glomerulonephritis (1), and cholangitis (1). Fourteen patients had more than one complication. Two patients in group 1 died: One patient (biliary atresia) died on postoperative day 43 owing to sepsis and intracranial hemorrhage as a complication of early postoperative portal vein thrombosis, and the other patient (biliary atresia) died of posttransplant lymphoproliferative disorder 9 months after transplant. One patient in group 2 (neonatal hepatitis) died on postoperative day 10 owing to early portal vein thrombosis. None of the mortality was related

to a deceased donor, and there was no difference in post-transplant recovery compared to those who had had a living donor in our study. The overall 1-year survival rate was 96% (70/73).

Discussion

Hypoxemia in ESLD patients is usually due to the presence of IPS, which is generally progressive. The prognosis of these patients is guarded even if they have stable hepatic dysfunction [13, 14]. Various methods have been tried to improve oxygenation, but the results are still unsatisfactory [15–18]. Whether IPS is related to a specific mediator remains elusive. The resolution of severe hypoxemia after successful liver transplantation has been reported [5–11]. However, significantly higher morbidity and mortality rates in these patients have also been described [19, 20]. Liver transplantation in patients with severe IPS is still controversial. Most of the previous studies concerning IPS in ESLD patients were done in adults [21, 22]. A prospective evaluation of the impact of mild and moderate IPS in pediatric ESLD patients before and after liver transplantation has not been well addressed. In our study, the overall incidence of mild and moderate IPS was 23.3% (17/73), and the outcome of liver transplantation is excellent, with an overall 1-year survival rate of 96% (70/73).

Hepatopulmonary syndrome usually affects older children or adult patients, but it should be noted that IPS can occur in any age group especially when liver dysfunction progresses quickly. In this series, higher rates of IPS were seen among younger patients without detectable differences in liver disease severity, and the speed of liver function deterioration is a possible contributing factor.

The diagnosis of severe IPS or hepatopulmonary syndrome requires the demonstration of dilated pulmonary vessels, $Pao_2 < 70$ mmHg, or an arterial-alveolar gradient of > 20 mmHg while breathing room air [23]. Several diagnostic methods have been used to study pulmonary vasodilation in hepatopulmonary syndrome, including an A-a Do_2 study, pulmonary angiography, ^{99m}Tc -MAA scintigraphy, and contrast echocardiography [24]. The A-a Do_2 is high when IPS exists; however, it may also show elevated results in many cardiovascular or lung diseases and is not specific for IPS. In addition, most mild and moderate IPS patients have preserved normal gas exchange. Contrast echocardiography is extremely sensitive and can detect a small right-to-left shunt even when the systemic arterial saturation is normal [25]. In our study, only two patients had O_2 saturation of $< 90\%$.

Pulmonary angiography is the gold standard for imaging and localizing pulmonary vascular abnormalities in pa-

tients with hepatopulmonary syndrome. However, in the presence of mild or moderate IPS, the pulmonary vasculature may show no gross abnormality. A disadvantage of angiography is that it is invasive and unsuitable for routine screening.

The severity of mild and moderate IPS may be underestimated. The diagnosis has been greatly improved by lung perfusion scanning and contrast echocardiography, which are now being used as preoperative screening studies. ^{99m}Tc -MAA scintigraphy is a practical method for evaluating the degree of IPS, but this technique does not distinguish between IPS and intracardiac shunting. It may also give a false-positive result if free, unbound ^{99m}Tc passes through normal-size vessels [26]. On the contrary, contrast echocardiography can differentiate between intrapulmonary and intracardiac shunting and can be used to evaluate the severity of IPS by detecting microbubbles immediately or during the delay phase in the left side of the heart after the microbubbles first appeared in the right side of the heart. Contrast echocardiography is a convenient choice because it does not expose the patient to radiation, and it has higher sensitivity and specificity than ^{99m}Tc -MAA scintigraphy in the diagnosis of IPS because microbubbles made of saline are smaller than albumin aggregates and can pass through the IPS [27]. Abrams et al. compared the accuracy of contrast echocardiography and lung perfusion scans in detecting hepatopulmonary syndrome (37.5% vs. 7.5%) [27]. In their study, positive lung scans were present in 3 of 40 ESLD patients who also had positive contrast echocardiogram results. However, 12 of the 40 patients who had positive contrast echocardiogram findings had negative lung perfusion scans. In our study, contrast echocardiography was routinely performed to evaluate patients preoperatively. Other diagnostic modalities, such as pulmonary angiography and ^{99m}Tc -MAA scintigraphy, were used for the evaluation of severe IPS detected on routine contrast echocardiography.

Fewtrell et al. reported that patients with severe IPS required prolonged ventilation after liver transplantation [11]. In our experience, patients with mild or moderate IPS were characterized by subtle delayed left atrial echogenicity seen on contrast echocardiography. This suggests that only small amounts of microbubbles pass through the lungs during oxygenation, and the hemodynamic status is essentially normal. In addition, there was no statistically significant difference in terms of O_2 saturation or duration of mechanical ventilation between patients with and without mild to moderate IPS. Hence, the presence of mild and moderate IPS had no apparent adverse impact on postoperative respiratory recovery.

Common complications seen after liver transplantation include wound infection, bile leakage, bowel perforation, intestinal obstruction, and portal vein thrombosis [28, 29].

Other complications, such as cholangitis, acute rejection, sepsis, intracranial hemorrhage, respiratory failure, and multiple organ failure, have also been reported [28, 29]. The incidence of surgically related complications in hypoxemia patients with ESLD was 56%, as reported by Uemoto et al. [28]. IPS was believed to be a potential risk factor. Therefore, identifying patients with IPS before liver transplantation is a prognostic variable.

The long-term outcome of liver transplantation in children is dependent on their age. In our institution, the patients with body weight < 10 kg had a higher operative complication rate than patients with body weight > 10 kg [30]. In the study, although the group 2 patients were of younger age and had a lower body weight than the group 1 patients, there was no significant difference in the morbidity and mortality during liver transplantation. Therefore, we conclude that the presence of mild or moderate IPS in patients with end-stage liver disease does not affect the overall outcome of liver transplantation.

Although severe IPS may affect the outcome of liver transplantation, the results in our series showed that the presence of mild or moderate IPS does not increase the morbidity or mortality associated with pediatric liver transplantation. However, there were three limitations in this study. First, the major weakness is that there were few cases of severe IPS (13 mild, 4 moderate), so this does not advance the debate on the selection of such patients for transplantation. Second, 15 patients with intracardiac shunting were excluded. These patients may also have concomitant IPS. Third, the natural history of the development of IPS is unknown, and the duration of progression from mild to severe IPS can hardly be predicated. On the other hand, our study supports the concept that early recognition of IPS in ESLD patients using contrast echocardiography is valuable for facilitating early transplantation in these patients and thus may avoid possible progression to severe IPS. Thus, pediatric ESLD patients of younger age and lower body weight with mild or moderate IPS can undergo liver transplantation with an excellent outcome, and complete regression of the IPS can be attained.

Conclusions

Contrast echocardiography is a good preoperative screening modality for IPS. The presence of mild or moderate IPS has no adverse impact on the outcome of liver transplantation in this subset of patients.

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References

1. Krowka MJ, Tajik AJ, Dickson ER, et al. (1990) Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates: screening by two-dimensional contrast-enhanced echocardiography. *Chest* 97:1165–1170
2. Hopkins WE, Waggoner AD, Barzilai B (1992) Frequency and significance of intrapulmonary right-to-left shunting in end-stage hepatic disease. *Am J Cardiol* 70:516–519
3. Busuttill RW, Goldstein LI, Donovan GM, et al. (1986) Liver transplantation today. *Ann Intern Med* 104:377–389
4. Shaw BW Jr, Wood RP, Kaufman SS, et al. (1988) Liver transplantation therapy for children. Part 2. *J Pediatr Gastroenterol Nutr* 7:797–815
5. Liang CD, Chen CL, de Villa VH, et al. (2001) Successful liver transplantation in a child with biliary atresia and hepatopulmonary syndrome. *J Formos Med Assoc* 100:403–406
6. Stoller JK, Moodie D, Schiavone WA, et al. (1990) Reduction of intrapulmonary shunt and resolution of digital clubbing associated with primary biliary cirrhosis after liver transplantation. *Hepatology* 11:54–58
7. Eriksson LS, Soderman C, Ericzon BG, et al. (1990) Normalization of ventilation/perfusion relationships after liver transplantation in patients with decompensated cirrhosis: evidence for a hepatopulmonary syndrome. *Hepatology* 12:1350–1357
8. McCloskey JJ, Schleien C, Schwarz K, et al. (1991) Severe hypoxemia and intrapulmonary shunting resulting from cirrhosis reversed by liver transplantation in a pediatric patient. *J Pediatr* 118:902–904
9. Schwarzenberg SJ, Freese DK, Regelman WE, et al. (1993) Resolution of severe intrapulmonary shunting after liver transplantation. *Chest* 103:1271–1273
10. Van Obbergh L, Carlier M, de Cleyt SC, et al. (1993) Liver transplantation and pulmonary gas exchanges in hypoxemic children. *Am Rev Respir Dis* 148:1408–1410
11. Fewtrell MS, Noble-Jamieson G, Revell S, et al. (1994) Intrapulmonary shunting in the biliary atresia/polysplenia syndrome: reversal after liver transplantation. *Arch Dis Child* 70:501–504
12. Donovan CL, Marcovitz PA, Punch JD, et al. (1996) Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation* 61:1180–1188
13. Jeffrey GP, Prince RL, Van der Schaaf A (1990) Fatal intrapulmonary arteriovenous shunting in cirrhosis: diagnosis by radio-nuclide lung perfusion scan. *Med J Aust* 152:549–553
14. Krowka MJ, Dickson ER, Cortese DA (1993) Hepatopulmonary syndrome: clinical observation and lack of therapeutic response to somatostatin analogue. *Chest* 104:515–521
15. Krowka MJ, Cortese DA (1987) Severe hypoxemia associated with liver disease: Mayo Clinic experience and the experimental use of almitrine bismesylate. *Mayo Clin Proc* 62:164–173
16. Andrivet P, Cadranet J, Housset B, et al. (1993) Mechanisms of impaired arterial oxygenation in patients with liver cirrhosis and severe respiratory insufficiency: effects of indomethacin. *Chest* 103:500–507
17. Agusti AG, Roca J, Bosch J, et al. (1990) Effects of propranolol on arterial oxygenation and oxygen transport to tissues in patients with cirrhosis. *Am Rev Respir Dis* 142:306–310
18. Krowka MJ, Cortese DA (1990) Hepatopulmonary syndrome: an evolving perspective in the era of liver transplantation. *Hepatology* 11:138–142
19. Hobeika J, Houssin D, Bernard O, et al. (1994) Orthotopic liver transplantation in children with chronic liver disease and severe hypoxemia. *Transplantation* 57: 224–228

20. Mews CF, Dorney SF, Sheil AG, et al. (1990) Failure of liver transplantation in Wilson's disease with pulmonary arteriovenous shunting. *J Pediatr Gastroenterol Nutr* 10:230–233
21. Collisson EA, Nourmand H, Fraiman MH, et al. (2002) Retrospective analysis of the results of liver transplantation for adults with severe hepatopulmonary syndrome. *Liver Transpl* 8:925–931
22. Arguedas MR, Abrams GA, Krowka MJ, et al. (2003) Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* 37:192–197
23. Scott VL, Dodson SF, Kang Y (1999) The hepatopulmonary syndrome. *Surg Clin North Am* 79:23–41
24. Castro M, Krowka MJ (1996) Hepatopulmonary syndrome: a pulmonary vascular complication of liver disease. *Clin Chest Med* 17:35–48
25. Seward JB, Tajik AJ, Spangler JG, et al. (1975) Echocardiographic contrast studies: initial experience. *Mayo Clin Proc* 50:163–192
26. Bank ER, Thrall JH, Dantzker DR (1983) Radionuclide demonstration of intrapulmonary shunting in cirrhosis. *AJR Am J Roentgenol* 140:967–969
27. Abrams GA, Jaffe CC, Hoffer PB, et al. (1995) Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. *Gastroenterology* 109:1283–1288
28. Uemoto S, Inomata Y, Egawa H, et al. (1997) Effects of hypoxemia on early postoperative course of liver transplantation in pediatric patients with intrapulmonary shunting. *Transplantation* 63:407–414
29. Barbe T, Losay J, Grimon G, et al. (1995) Pulmonary arteriovenous shunting in children with liver disease. *J Pediatr* 126:571–579
30. Chen CL, Concejero A, Wang CC, et al. (2006) Living donor liver transplantation for biliary atresia: a single-center experience with first 100 cases. *Am J Transpl* 6:2672–2679