Editors' Choice

ORIGINAL PAPER

Nagoya J. Med. Sci. **83**. 765–771, 2021
doi:10.18999/nagjms.83.4.765

Long-term outcomes of the partial splenectomy for hypersplenism after portoenterostomy of patients with biliary atresia

Takahisa Tainaka, Akinari Hinoki, Yujiro Tanaka, Chiyoe Shirota, Wataru Sumida, Kazuki Yokota, Satoshi Makita, Kazuo Oshima, Hizuru Amano, Aitaro Takimoto, Yoko Kano and Hiroo Uchida

Department of Pediatric Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

Massive splenomegaly and hypersplenism in patients with biliary atresia after Kasai portoenterostomy were treated with partial splenic embolization or total splenectomy. We performed partial splenectomy to reduce the complications of partial splenic embolization and avoid overwhelming post-splenectomy infection. This study aimed to evaluate the long-term effects of partial splenectomy for hypersplenism on postoperative liver and spleen function in patients with biliary atresia. Among jaundice-free patients with biliary atresia who underwent Kasai portoenterostomy between January 1992 and December 2012, 15 underwent partial splenectomy for massive splenomegaly and hypersplenism at our institution. Changes in the laboratory data 10 years post partial splenectomy were retrospectively investigated, and these along with the latest data were measured. A total of four patients (27%) required living-donor liver transplantation after partial splenectomy, a proportion similar to those who did not undergo partial splenectomy. Compared to the preoperative baseline, the platelet counts were significantly higher at 1 and 3 years after surgery ($p < 0.05$). Aspartic aminotransferase-to-platelet ratio index was significantly lower at 1, 7, and 10 years after partial splenectomy ($p < 0.05$). No further surgeries were required for hypersplenism after partial splenectomy over 10 years, and there were no cases of overwhelming post-splenectomy infection after partial splenectomy. Partial splenectomy is safe and effective for the treatment of hypersplenism with biliary atresia over a long time period. It could be considered as an alternative to partial splenic embolization as it can suppress hypersplenism for a long time and induces fewer postoperative complications.

Keywords: biliary atresia, partial splenectomy, portal hypertension, splenomegaly, hypersplenism

Abbreviations:
BA: biliary atresia
PSE: partial splenic embolization
PS: partial splenectomy
AST: aspartic aminotransferase
APRI: aspartic aminotransferase-to-platelet ratio index

Received: December 23, 2020; accepted: March 19, 2021
Corresponding Author: Uchida Hiroo, MD, PhD
Department of Pediatric Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-2959, Fax: +81-52-744-2980, E-mail: hiro2013@med.nagoya-u.ac.jp

INTRODUCTION

Biliary atresia (BA), also known as progressive obliterative cholangiopathy, is a rare cholestatic disease of unknown etiology resulting in neonatal biliary obstruction and jaundice.[1] The prognosis of patients with BA has improved since the introduction of Kasai portoenterostomy in 1959.[2,3] Portal hypertension and its associated variceal hemorrhage are common and fatal complications in infants with BA.[1,4,5] BA is a progressive disease, even in the absence of jaundice; thus, majority of patients will develop cirrhosis and portal hypertension. Approximately 49–63% of patients have clinical evidence of portal hypertension as demonstrated by ascites, variceal bleeding, hepatopulmonary syndrome (HPS), splenomegaly, and thrombocytopenia.[4] While liver failure requires liver transplantation, in patients without hepatic insufficiency, the risks related to portal hypertension and hypersplenism justify the symptomatic treatments. Splenomegaly and hypersplenism in patients with biliary atresia have often been treated using partial splenic embolization (PSE) or total splenectomy.[6,7,8] Complications such as fever and abdominal abscess after PSE were frequent.[9] Total splenectomy is known to increase overwhelming post-splenectomy infection (OPSI) caused by encapsulated bacteria such as streptococcus pneumoniae using a capsule.[10] We performed partial splenectomy (PS) to reduce these complications of PSE, normalize splenic function, and avoid OPSI. The long-term effect on the liver and spleen function of BA after PS has not received much scholarly attention. The purpose of this study was to evaluate the effect of PS on postoperative liver and spleen function and the long-term outcomes in patients with BA.

PATIENTS AND METHODS

Study sample

Among the patients with BA who underwent Kasai portoenterostomy between January 1992 and December 2012, patients who were jaundice-free and had undergone PS for massive splenomegaly and hypersplenism were enrolled in the study. Hypersplenism with thrombocytopenia was defined as a platelet count ≤100,000/μl.

Surgical technique

Laparotomy was performed through a left abdominal transverse incision under general anesthesia without performing platelet transfusion before and during the surgery. First, the spleen was turned out of the wound to expose the splenic hilum. The splenic artery and vein are normally branched into three; hence, the splenic artery and vein were ligated from the side of the lower pole at the splenic hilar. At this time, extra care was taken to not damage the splenic vein. If the vein is damaged, it will be difficult to assess the anatomy of the splenic hilum because of bleeding, and the risk of damaging the splenic vein increases. Regarding the ligation of the blood vessels, the color of the spleen becomes black (Fig. 1a). The splenic artery and vein of the upper spleen are preserved. The border of the middle and lower poles of the spleen whose color had changed was marked with an electric scalpel, and the spleen was cut off using an ultrasonic surgical aspirator system along it. Moreover, it was necessary to observe the blood flow of the left upper spleen using an ultrasound device. After the splenectomy was completed (Fig. 1b), we applied fibrin glue to the stump of the spleen. The volume to be resected was approximately 70% of the total spleen. The collateral circulation around the spleen was not blocked. We were careful not to form portal vein thrombi by administering heparin while paying attention to the increase in platelet count because there had been cases where platelets increased rapidly after surgery.

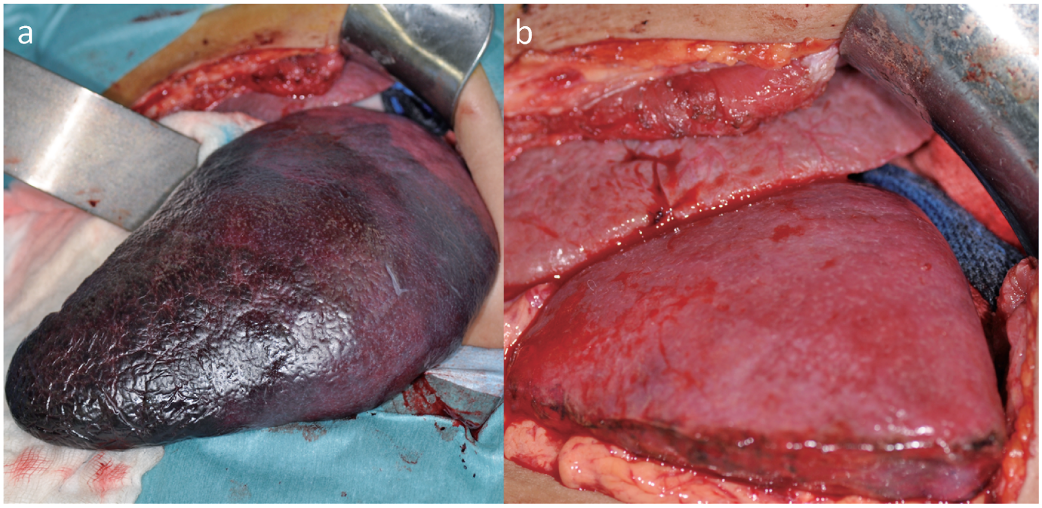

Fig. 1 Intraoperative images
Fig. 1a: The color of the spleen becomes black with the ligation of the blood vessels.
Fig. 1b: Partial splenectomy was completed.

Changes in the laboratory data such as total bilirubin, aspartic aminotransferase (AST), serum albumin, white blood cell (WBC) counts, hemoglobin, platelet counts, and aspartic aminotransferase-to-platelet ratio index (APRI) were retrospectively investigated (before PS at 1, 3, 5, 7, and 10 years after surgery). APRI has been reported as an noninvasive marker which can predict hepatic fibrosis and liver cirrhosis in patients with chronic hepatitis C.[11] In addition, the latest laboratory data were measured.

The Wilcoxon rank-sum test for continuous data, Fisher exact test for categorical data, and Dunn test for the change in data over a period of time with the preoperative values as controls were used in the statistical analysis. P values <0.05 were considered as statistically significant. The study protocol was approved by hospital medical ethics committees (approval numbers 2019-0420).

RESULTS

During the study period, 82 patients underwent Kasai portoenterostomy for BA, and 64 patients were jaundice-free. Fifteen out of these 64 patients underwent PS for treatment of massive splenomegaly and hypersplenism. Four patients, who had been previously treated with splenorenal shunt, were included because they showed hypersplenism following splenorenal shunt surgery. The patients' characteristics are summarized in Table 1. The median age at Kasai portoenterostomy was 71 days (47–82). The median age at the PS was 7 years (3.4–10), the median surgery time was 260 min (204–390), and the median amount of bleeding was 194 ml (52–1072). The resection rate was 50–75%. Four patients required blood transfusion, and postoperative complications occurred in two cases. One patient had liver damage and was relieved by conservative treatment. Another patient had portal vein thrombosis; therefore, liver transplantation was performed as planned. There was no case of variceal bleeding after PS. A total of four patients (27%) underwent living-donor liver transplantation after PS (four cases over 3 years after

hepatic portoenterostomy). In contrast, eight (16%) patients who were jaundice-free after hepatic portoenterostomy without PS required living-donor liver transplantation (one case within 1 year, three cases from 1 year to 3 years, and four cases over 3 years after Kasai portoenterostomy). PS did not cause an increase in liver transplantation in comparison with patients who underwent PS.

Table 1 Patient demographics

	Biliary atresia with partial splenectomy (n=15)
Male/Female	8:7
Age at Kasai's operation (day)	71 (47–82)
Biliary atresia type	
Type I	1
Type III	14
Laboratory data at Kasai's operation	
TB (mg/dl)	7.0 (5.2–10.8)
AST (IU/L)	181 (145–516)
ALT (IU/L)	139 (79.8–411)
Jaundice free	15 (100%)
Age at partial splenectomy (year)	7.0 (3.4–10)
Laboratory data at PS	
WBC (10^3/μl)	3.4 (2.8–4.1)
Hb (g/dl)	10.5 (9.0–11.4)
Platelet (10^4/μl)	6.6 (3.9–8.9)
Operation time (min)	260 (204–390)
Amount of blood loss (ml)	194 (52–1072)
Follow-up period after partial splenectomy (year)	14.1 (10.4–14.6)

Changes in the laboratory data after PS are shown in Fig 2. The patient number at 1, 3, 5, 7, and 10 years after PS were 15, 13, 13, 11, and 11, respectively. The values of total bilirubin and serum albumin remained within normal limits after PS surgery. Aspartic aminotransferase (AST) was 83 preoperative and 91, 96, 79, 61, and 53 with no significant differences at 1, 3, 5, 7, and 10 years after PS, respectively. WBC counts were higher after PS, but the differences were not significant. Hb levels tended to increase over time (pre-op: 11.4; 1 year: 11.4; 3 years: 11.8; 5 years: 12.9; 7 years: 13.1; and 10 years: 14.5), but the differences were not statistically significant. The platelet counts were 6.6 before surgery and 14, 12, 9.4, 9.2, and 10 at 1, 3, 5, 7, and 10 years after PS, respectively. Significant increases in the platelet counts were observed at 1 and 3 years after surgery ($p < 0.05$). The value of APRI was significantly decreased at 1, 7, and 10 years after surgery (7.7, 5.0, 6.4, respectively; $p < 0.05$). No further surgeries were required for hypersplenism after PS over 10 years. Additionally, there were no cases exhibiting increased susceptibility to infection or OPSI after PS.

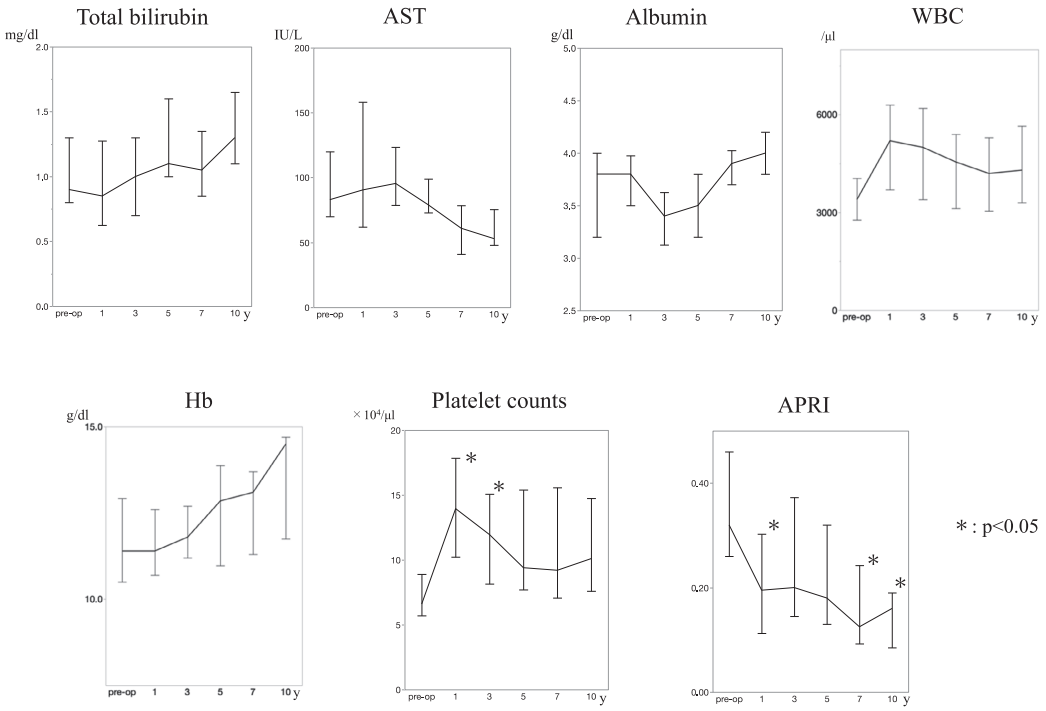

Fig. 2 Changes in laboratory data after the PS (Total bilirubin, AST, Albumin, WBC, Hb, Platelet counts, APRI)

*$p<0.05$, Dunn test.

DISCUSSION

Kasai's portoenterostomy in BA patients aims to improve the rate of survival without liver transplantation by restoring bile flow.[12,13] BA is a progressive disease, even in jaundice-free patients with native liver; thus, majority of patients will develop cirrhosis and portal hypertension.[4] Patients with BA after portoenterostomy had clinical evidence of portal hypertension as demonstrated by ascites, variceal bleeding, hepatopulmonary syndrome (HPS), splenomegaly, and/or thrombocytopenia. Variceal hemorrhage occurs in 24–55% of patients.[14,15] Hypersplenism is a major complication of BA. Nonetheless, the incidence, prevalence, and long-term outcomes of hypersplenism in patients with BA have not been studied.

Liver failure with BA requires liver transplantation. In patients without hepatic failure, the risks are related to portal hypertension, and hypersplenism justifies the symptomatic measures. Severe hypersplenism is often refractory to treatment with PSE or shunt surgery. PSE was introduced as an alternative to splenectomy to avoid the risk of OPSI and to achieve splenic reduction. In patients with BA, the procedure was successful during the early follow-up period. As a result, hypersplenism was controlled, and the frequency in addition to the severity of bleeding from the esophageal varices reduced.[6] Porter reported that the splenic arterial flows decrease whereas the hepatic and superior mesenteric arterial flows increase after PSE.[16] PSE proved to have a long-lasting efficacy in controlling hypersplenism.[6,7] because 70% of the patients had maintained platelet counts greater than 100,000/μl for more than 5 years after PSE. Brandt reported that 10 of 13 patients had no signs of hypersplenism after an average follow-up of more 3 years.[9]

Moreover, we reported that the total bilirubin reduced because of the decreasing turnover in the red blood cell and liver enzyme did not change.[17] However, early complications after PSE such as fever, abdominal pain, abscess surrounding spleen, lung atelectasis, and prolonged ileus were frequent.[9] Furthermore, there were no reports of treatment outcomes after PSE observed for more than 10 years. Our operative PS aimed for satisfactory outcomes such as PSE and to reduce postoperative inflammatory complications due to necrosis of the embolized spleen. After PS procedure, we had no patients suffering from severe infection. PS requires a strict surgical procedure; however, it can be easily achieved. The postoperative course was uneventful in majority of the patients with cystic fibrosis-related liver diseases.[18] We noted one postoperative complication as portal vein thrombosis. Portal vein thrombosis after PSE has been reported to occur in certain cases in adults.[19] After splenectomy, this complication was often described, indicating that we must pay more attention to thrombosis.

APRI, an indicator of portal vein pressure and hepatic fibrosis,[20] remained low over time although the liver enzymes remained almost unchanged after PS. This study showed that PS had a long-term positive effect on portal hypertension.[21,22] The value of the latest APRI as an index of the hepatic fibrosis are relatively low.[20] There were no cases of variceal bleeding after PS, indicating a clinical effect. Variceal hemorrhage was ameliorated in all patients after PSE,[9] and it is expected to have almost the same effect. The native liver survival rate is about 70% after PS. Four patients required liver transplantation for liver failure in two, gastrointestinal bleeding in one, and recurrent cholangitis in another. These suggest that PS is useful in terms of improving the patient's QOL.

Central shunt surgeries with splenic preservation are successful for reversing mild to moderate hypersplenism[23]; nevertheless, massive splenomegaly is often refractory to such procedures.[24] In our four cases, splenorenal shunt could not improve hypersplenism; hence, we performed PS. Even if the shunt surgery achieved good results in patients without any hepatic failure, they had to follow a low-protein diet. Twenty percent of the patients with BA had hepatic encephalopathy.[25] Therefore, PS, which could not decrease the flow of the portal vein, is an extremely safe procedure and a good surgical indication for splenomegaly and hypersplenism after Kasai portoenterostomy. PS preserved anatomic and vascular relation of the hepatosplenic axis and was not an obstacle to a subsequent liver transplantation; this was confirmed in our liver transplantation patients. In this study, we described the long-term significant outcomes of PS for more than 10 years, which has never been reported.

Several limitations to this study must be considered. First, the number cases in this study was small because BA is a rare disease. Second, this study is retrospective and does not have an appropriate control group with PSE. However, we could show fairly long-term outcomes after PS.

In conclusion, PS is safe and effective for treatment of hypersplenism with BA over a long time period. It could be considered as an alternative for PSE as it could suppress hypersplenism for a long time and induces fewer postoperative complications.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to disclose.

REFERENCES

1 Sokol RJ, Mack C, Narkewicz MR, Karrer FM. Pathogenesis and outcome of biliary atresia: current concepts. *J Pediatr Gastroenterol Nutr*. 2003;37(1):4–21. doi:10.1097/00005176-200307000-00003.

2 Kasai M, Suzuki M. A new operation for non-correctable biliary atresia: hepatic portoenterostomy [in Japanese]. *Shujutsu*. 1959;13:733–739.
3 Ando H. A new operation for noncorrectable biliary atresia. *Nagoya J Med Sci*. 1999;62(3–4):107–114.
4 Shneider BL, Abel B, Haber B, et al. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr*. 2012;55(5):567–573. doi:10.1097/MPG.0b013e31826eb0cf.
5 Bijl EJ, Bharwani KD, Houwen RH, de Man RA. The long-term outcome of the Kasai operation in patients with biliary atresia: a systematic review. *Neth J Med*. 2013;71(4):170–173.
6 Kumpe DA, Rumack CM, Pretorius DH, Stoecker TJ, Stellin GP. Partial splenic embolization in children with hypersplenism. *Radiology*. 1985;155(2):357–362. doi:10.1148/radiology.155.2.3885306.
7 Nio M, Hayashi Y, Sano N, Ishii T, Sasaki H, Ohi R. Long-term efficacy of partial splenic embolization in children. *J Pediatr Surg*. 2003;38(12):1760–1762. doi:10.1016/j.jpedsurg.2003.08.050.
8 El-Alfy MS, El-Sayed MH. Overwhelming postsplenectomy infection: is quality of patient knowledge enough for prevention? *Hematol J*. 2004;5(1):77–80. doi:10.1038/sj.thj.6200328.
9 Brandt CT, Rothbarth LJ, Kumpe D, Karrer FM, Lilly JR. Splenic embolization in children: long-term efficacy. *J Pediatr Surg*. 1989;24(7):642–644;discussion 644–645. doi:10.1016/s0022-3468(89)80710-9.
10 Krivit W. Overwhelming postsplenectomy infection. *Am J Hematol*. 1977;2(2):193–201. doi:10.1002/ajh.2830020210.
11 Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518–526. doi:10.1053/jhep.2003.50346.
12 Feldman AG, Mack CL. Biliary Atresia: Clinical Lessons Learned. *J Pediatr Gastroenterol Nutr*. 2015;61(2):167–175. doi:10.1097/MPG.0000000000000755.
13 Sumida W, Uchida H, Tanaka Y, et al. Review of redo-Kasai portoenterostomy for biliary atresia in the transition to the liver transplantation era. *Nagoya J Med Sci*. 2017;79(3):415–420. doi:10.18999/nagjms.79.3.415.
14 Karrer FM, Price MR, Bensard DD, et al. Long-term results with the Kasai operation for biliary atresia. *Arch Surg*. 1996;131(5):493–496. doi:10.1001/archsurg.1996.01430170039006.
15 van Wessel DB, Witt M, Bax N, et al. Variceal Bleeds in Patients with Biliary Atresia. *Eur J Pediatr Surg*. 2018;28(5):439–444. doi:10.1055/s-0037-1603987.
16 Porter BA, Frey CF, Link DP, Lantz BM, Pimstone NR. Splenic embolization monitored by the video dilution technique. *AJR Am J Roentgenol*. 1983;141(5):1063–1065. doi:10.2214/ajr.141.5.1063.
17 Ando H, Ito T, Nagaya M. Partial splenic embolization decreases the serum bilirubin level in patients with hypersplenism following the Kasai procedure for biliary atresia. *J Am Coll Surg*. 1996;182(3):206–210.
18 Louis D, Duc ML, Reix P, et al. Partial splenectomy for portal hypertension in cystic fibrosis related liver disease. *Pediatr Pulmonol*. 2007;42(12):1173–1180. doi:10.1002/ppul.20713.
19 Cai M, Zhu K, Huang W, et al. Portal vein thrombosis after partial splenic embolization in liver cirrhosis: efficacy of anticoagulation and long-term follow-up. *J Vasc Interv Radiol*. 2013;24(12):1808–1816. doi:10.1016/j.jvir.2013.08.018.
20 Mo YH, Chen HL, Hsu WM, Chang CH, Peng SS. A noninvasive index to predict liver cirrhosis in biliary atresia. *Pediatr Radiol*. 2021;51(2):257–264. doi:10.1007/s00247-020-04823-w.
21 Sintusek P, Siriporn N, Punpanich D, Chongsrisawat V, Poovorawan Y. Spleen and Liver Stiffness to Detect Esophageal Varices in Children with Biliary Atresia. *J Pediatr Gastroenterol Nutr*. 2019;69(4):411–415. doi:10.1097/mpg.0000000000002430.
22 Yokoyama S, Ishigami M, Honda T, et al. Spleen stiffness by 2-D shear wave elastography is the most accurate predictor of high-risk esophagogastric varices in children with biliary atresia. *Hepatol Res*. 2019;49(10):1162–1168. doi:10.1111/hepr.13381.
23 Mitra SK, Rao KL, Narasimhan KL, et al. Side-to-side lienorenal shunt without splenectomy in noncirrhotic portal hypertension in children. *J Pediatr Surg*. 1993;28(3):398–401;discussion 401–392. doi:10.1016/0022-3468(93)90239-h.
24 Sharma BC, Singh RP, Chawla YK, et al. Effect of shunt surgery on spleen size, portal pressure and oesophageal varices in patients with non-cirrhotic portal hypertension. *J Gastroenterol Hepatol*. 1997;12(8):582–584. doi:10.1111/j.1440-1746.1997.tb00489.x.
25 Guerin F, Charre L, Jasienski S, et al. The efficacy of surgical shunts to treat severe portal hypertension after a Kasai procedure for biliary atresia. *J Pediatr Surg*. 2019;54(3):531–536. doi:10.1016/j.jpedsurg.2018.06.023.