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# Variceal Bleeds in Patients with Biliary Atresia

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## Abstract

**Introduction** Portal hypertension often occurs in biliary atresia (BA). The subsequent development of esophageal varices and bleeding from these varices are a well-known complication. We aim to describe the incidence and severity of variceal bleeding in patients with BA. In addition, we describe the characteristics of patients who experienced variceal bleeds.

**Materials and Methods** We included all infants treated for BA at our center between March 1987 and August 2015. Variceal bleeding was defined as hematemesis and/or melena with presence of varices at endoscopy. Findings at endoscopy and ultrasound, laboratory tests, clearance of jaundice, fibrosis-grade at Kasai portoenterostomy, and several varices prediction scores were documented. Routine endoscopies were not performed.

**Results** In this study, 74 patients were included. During follow-up, 18 out of 74 patients (24%) developed variceal bleeding at an age of 9 months (range, 4–111). Twelve patients were listed for liver transplantation at the time of bleeding. Patients who did not clear their jaundice developed variceal bleeds more often and earlier in life. Bleeds were treated with sclerotherapy, banding, or octreotide. Four patients did not receive treatment. No bleeding-related mortality occurred.

**Conclusion** One-fourth of the children diagnosed with BA experience variceal bleeds during follow-up. Most of these children are younger than 1 year and often already listed for transplantation. Major complications did not occur after variceal bleeding.

**Keywords**
- biliary atresia
- variceal bleeds
- portal hypertension
- endoscopy

## Introduction

Biliary atresia (BA) is a rare cholestatic liver disease of infancy. Initial management of BA consists of the Kasai portoenterostomy (KPE) and subsequently, in case of liver failure, a liver transplantation (LTx). During KPE, the obliterated extrahepatic bile ducts are resected and a portoenterostomy is constructed in an attempt to re-establish bile flow. Adequate drainage of bile is achieved in 38 to 75% of patients.[1–4] Even if this procedure is successful, liver fibrosis often progresses, resulting in cirrhosis. Before the age of 20 years, 70 to 80% of the children will need LTx.[5] BA is the main indication for LTx at pediatric age.[6,7]

The progression of fibrosis to cirrhosis is accompanied by the development of portal hypertension. The subsequent

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development of esophageal varices (EVs) and bleeding from these EVs are a well-known complication. In adult patients with cirrhosis, screening for varices is recommended as primary prophylaxis.[8] Previous studies have described several aspects of screening for EVs and the development of bleeding from these varices, and even though the authors suggest endoscopic injection sclerotherapy as primary and secondary prophylaxes,[9,10] evidence for this practice is far from conclusive.[11] Noninvasive methods, such as assessment of platelet counts and spleen size on ultrasound, might be helpful to identify children at high risk of EV bleeding.[12–14] Also, the varices prediction rule (VPR) showed to be a useful tool in identifying patients eligible for endoscopic screening for EVs.[15,16] In the Netherlands, all endoscopies in children are performed under general anesthesia, which in itself is not without risk.

In the present series, we investigated the incidence and severity of EV bleeding during follow-up of children after KPE for BA. In addition, we compared patient characteristics as well as endoscopic, laboratory, and ultrasound findings of children who experienced EV bleeds and those who did not.

## Materials and Methods

This retrospective study was performed in accordance with the guidelines of the Medical Ethical Committee of University Medical Center Groningen, the Netherlands (No. 201600448). We collected data on 74 children (30 boys and 44 girls) who had been treated for BA at our institution between March 1987 and August 2015. In the present series, we focused on the patients who presented with EV bleeding. Our institution is the only pediatric LTx center in the country. The diagnosis of BA was established during intraoperative cholangiogram and/or histopathology of the liver and the biliary remnant. In accordance with the METAVIR criteria,[17,18] we scored liver fibrosis as: (1) no fibrosis, (2) mild fibrosis, or (3) moderate (bridging) fibrosis or cirrhosis. Clearance of jaundice was defined as a total serum bilirubin $< 20$ µmol/L within 6 months after KPE.

We graded EVs as follows: Grade 1, varices defined as small straight varices, Grade 2, defined as enlarged tortuous varices occupying less than one-third of the lumen, and Grade 3, defined as large coil-shaped varices occupying more than one-third of the lumen. Bleeding from EVs was defined as a combination of (1) hematemesis and/or melena and (2) presence of varices during endoscopy. We noted the need for red blood cell (RBC) transfusion separately. A major complication as a result of an EV bleed was defined as hemodynamic instability and/or death. During endoscopy, the presence of gastric varices and hypertensive gastropathy were also recorded. Rebleeding was defined as any novel episode of hematemesis and/or melena after previous sclerotherapy or banding of the varices.

We recorded the following parameters during surgery and during follow-up at 6 months: platelets, leucocytes, alkaline phosphatase (AP), alanine aminotransferase, aspartate aminotransferase (ASAT), total and conjugated bilirubin, gamma-glutamyltransferase, albumin, activated partial thromboplastin time, and prothrombin time (PT). We applied the VPR[15,16] and calculated the ASAT-to-platelet ratio index (APRI) score.[19–21] The VPR is derived from albumin and platelet levels (albumin $\times$ platelets/1,000). The APRI score is commonly used for staging liver fibrosis and cirrhosis ([ASAT/ULN ASAT] $\times$ 100/platelets; where ULN is upper limit of normal). Using ultrasonography, we investigated signs of portal hypertension (defined by splenomegaly and/or the presence of ascites). Ultrasound findings were noted when the ultrasound was performed within 3 months of the first endoscopy.

Follow-up was standardized with visits to the KPE center at 1 and 6 months after KPE and visits to the shared-care hospital in between. Visits to the KPE center were intensified if necessary on clinical grounds. Initially, we performed routine endoscopies upon listing for LTx. Because of frequent inconclusive results and because of our reluctance to start primary prophylaxis in very young children ($< 3$ years), we now only perform endoscopies in children $> 3$ years with indications of portal hypertension at physical examination or ultrasound (e.g., splenomegaly). Follow-up ended when a patient died, underwent LTx, or when the end of the study period had been reached (February 1, 2016).

Data are expressed as median (range) unless otherwise specified. Continuous variables were compared with the Mann–Whitney's *U* test, categorical data by using the chi-square test or the Fisher's exact test. For survival analyses, we constructed survival curves by using the Kaplan–Meier method. Survival curves were compared using the log-rank test. A $p$-value $< 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0.

## Results

Patient characteristics are depicted in ►Table 1. Age at KPE was 62 days (range, 34–128). Follow-up after KPE was 17 months (range, 0–346). Clearance of jaundice was achieved in 36%. Clearance of jaundice was unknown in eight patients. Seven patients died before LTx. None of these children belonged to the bleeding group. Causes of death were hepatorenal syndrome ($n = 2$), sepsis ($n = 1$), cardiac disease ($n = 1$), and unknown ($n = 3$). Four patients were lost to follow-up. ►Fig. 1 depicts the total survival in the bleeding and nonbleeding groups.

During follow-up, 18 out of 74 patients (24%) developed an EV bleed at an age of 9 months (range, 4–111). None of the patients underwent endoscopy before they suffered EV bleeding. Time between bleeding and endoscopy was 0.5 days (range, 0–36). ►Fig. 2 depicts the bleeding-free survival of patients who cleared their jaundice and those who did not. Three out of 24 (13%) patients who cleared their jaundice developed EV bleeding versus 15 out of 42 patients (36%) who did not ($p = 0.04$). Their age at first EV bleed was 76 months (range, 32–111) versus 7 months (range, 4–75), respectively ($p = 0.03$). Twelve out of 18 patients (67%) who bled from EVs were already listed for LTx at the time of the first bleed. EV bleeding did not diminish their chance for an LTx, since all children remained transplantable.

►Table 2 depicts endoscopy findings. A total of 22 patients were suspected of EV bleeding and underwent diagnostic

**Table 1** Patient characteristics

| | Overall | No EV bleed | EV bleed | *p*-Value No bleed vs. bleed |
|---|---|---|---|---|
| No patients (male) | 74 (30) | 56 (22) | 18 (8) | |
| Gestational age, wk | 39 (31–42) | 39 (31–42) | 39 (36–41) | 0.99 |
| Birth weight, kg | 3.3 (1.7–4.6) | 3.3 (1.7–4.6) | 3.4 (2.6–4.2) | 0.44 |
| Age at KPE, d | 62 (34–128) | 62 (34–120) | 57 (36–128) | 0.22 |
| Transplant-free survival, mo | 26 (4–347) | 30 (4–347) | 14 (5–304) | 0.24 |
| 5-y transplant-free survival, % | 61 | 67 | 39 | **0.04** |
| Clearance, % | 36 | 44 | 17 | **0.04** |
| Fibrosis grade at KPE, 0 no/1 mild/2 moderate/3 cirrhosis | 2 (1–4) | 2 (1–4) | 2 (1–4) | 0.92 |

Abbreviations: EV, esophageal varix; KPE, Kasai portoenterostomy.
Note: Bold values are statistically significant.

and possible therapeutic endoscopy. Indications were hematemesis ($n = 9$, 41%), melena ($n = 9$, 41%), or a combination of both ($n = 4$, 18%). In 4 of these 22 patients, no varices were seen at endoscopy and thus, following our definition, did they not bleed from varices. Fourteen patients underwent endoscopy for other indications without suspicion of an active EV bleed. Ten patients underwent endoscopy for LTx assessment at an age of 40 months (range, 5–213), and four patients underwent endoscopy for clinical suspicion of portal hypertension at an age of 36 months (range, 20–127). EV bleeds were treated with sclerotherapy ($n = 6$) or banding ($n = 4$). Two patients received simultaneous octreotide therapy. Four patients received octreotide therapy only. Four patients did not receive treatment because at the time of endoscopy, no active bleeding focus could be identified. Nevertheless, varices were present during endoscopy.

Three out of 18 (17%) patients who experienced an EV bleed had not been assessed for LTx at the time of the first bleeding episode. All were assessed for LTx later in life. Indication for LTx assessment was progression of end-stage liver disease and refractory EV bleeding in the first patient, and progression of end-stage liver disease in the last two. Of the 18 patients who experienced an EV bleed, 15 (83%) ultimately received LTx and 3 (17%) did not. Time between first bleeding episode and LTx was 1 month (range, 0–43).

In total, 14 patients were treated for their EV bleed. Rebleeding occurred in 8 out of 14 (57%) patients after initial sclerotherapy ($n = 5$), banding ($n = 2$), or unknown treatment ($n = 1$). Age at rebleeding was 12 months (range, 6–80). Time between first bleed and first rebleed was 2 months (range, 0–29). One rebleed led to short hemodynamic instability, which was treated promptly without severe consequences. Six of the eight rebleeders underwent LTx within 1 month after rebleeding, and the other two after 6 and 10 months, respectively.

None of the patients succumbed as a result of EV bleeding. Of the 18 patients who suffered an EV bleed, 5 (28%) died. These deaths, however, all occurred after LTx and were therefore not further described in our study. In none of the patients did initial EV bleeding lead to hemodynamic instability. Transfusion of RBCs was needed in 5 out of 18 patients (28%). Altogether, 5 out of 18 patients (28%) were admitted to the intensive care unit, mostly for postendoscopic evaluation.

►**Table 2** depicts laboratory values before surgery and 6 months after KPE, comparing children with and without EV bleeding. Before surgery AP, total bilirubin, conjugated bilirubin, and PT were significantly higher in the bleeding group. Six months after KPE, platelet count, albumin, and thus, the VPR were significantly lower in the bleeding group.

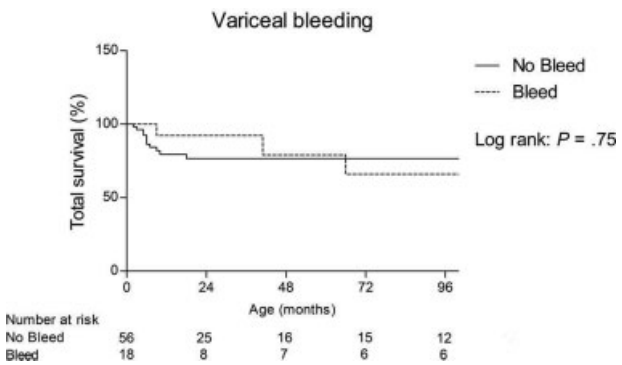


**Fig. 1** Total survival of patients who did and did not bleed from EVs. EVs, esophageal varices.

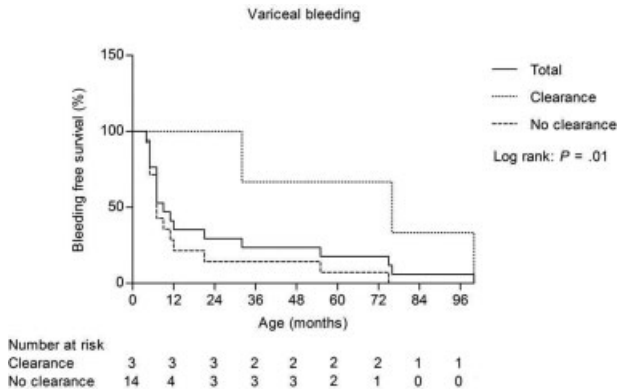


**Fig. 2** Bleeding-free survival of patients who did and did not clear their jaundice.

**Table 2** Laboratory values at KPE and 6-months post-KPE

| Laboratory value | KPE No EV bleed | EV bleed | *p*-Value | 6-mo post-KPE No EV bleed | EV bleed | *p*-Value |
|---|---|---|---|---|---|---|
| Leucocyte count, $10^9$/L | 11 (7–18) | 10 (6–22) | 0.128 | 11 (5–95) | 10 (7–51) | 0.568 |
| Platelet count, $10^9$/L | 425 (43–680) | 349 (118–806) | 0.290 | 205 (23–593) | 138 (64–881) | **0.022** |
| AP, U/L | 440 (88–905) | 600 (33–1,021) | **0.020** | 483 (145–3,475) | 518 (147–1,515) | 0.772 |
| Total bilirubin, μmol/L | 150 (92–430) | 195 (96–418) | **0.015** | 25 (3–520) | 83 (4–483) | 0.139 |
| Direct bilirubin, μmol/L | 124 (68–415) | 162 (78–284) | **0.022** | 17 (0–471) | 65 (1–435) | 0.123 |
| ASAT, U/L | 193 (56–646) | 201 (100–787) | 0.543 | 127 (23–8,342) | 108 (15–424) | 0.500 |
| ALAT, U/L | 147 (29–634) | 125 (78–426) | 0.682 | 100 (25–2,817) | 83 (19–342) | 0.476 |
| G-GT, U/L | 495 (0–2,109) | 559 (121–2,365) | 0.200 | 183 (12–1,119) | 158 (58–668) | 0.502 |
| Albumin, g/L | 38 (26–53) | 37 (20–58) | 0.200 | 37 (10–48) | 28 (3–42) | **0.020** |
| PT, s | 11.6 (2.7–59.6) | 13.0 (10.1–37.4) | **0.038** | 13.1 (10.5–33.3) | 14.0 (10.5–20.4) | 0.323 |
| APTT, s | 34 (25–84) | 37 (28–85) | 0.358 | 30 (22–61) | 33 (19–66) | 0.588 |
| APRI | 1.0 (0.3–5.7) | 1.3 (0.5–6.9) | 0.201 | 1.5 (0.2–772.4) | 1.8 (0.0–6.5) | 0.384 |
| VPR | 15.3 (1.1–27.9) | 12.2 (4.5–29.8) | 0.067 | 6.7 (0.2–23.1) | 4.0 (0.4–35.2) | **0.006** |

Abbreviations: ALAT, alanine aminotransferase; AP, alkaline phosphatase; APTT, activated partial thromboplastin time; APRI, ASAT-to-platelet ratio index; ASAT, aspartate aminotransferase; EV, esophageal varix; G-GT, gamma-glutamyltransferase; KPE, Kasai portoenterostomy; PT, prothrombin time; VPR, varices prediction rule.

We compared ultrasound findings between the bleeding and nonbleeding groups. Ascites was seen in 4 out of 12 patients (33%) in the nonbleeding group versus 8 out of 12 patients (67%) in the bleeding group ($p = 0.001$). ►Table 3 depicts the findings during endoscopy.

At the time of KPE, we were able to determine the fibrosis grades of 60 patients. When differentiating between noncirrhosis (Grade 1, 2, or 3) and cirrhosis, noncirrhotics developed EV bleeding in 14 out of 52 cases (27%) versus 2 out of 7 cases (29%) in cirrhotics ($p = 0.93$).

## Discussion

In this study, we set out to clarify the incidence and severity of EV bleeding in children who had undergone KPE for BA. Our data suggest that one quarter of BA patients undergoing a KPE will develop bleeding from EVs. However, major complications did not occur. The majority will develop EV bleeding while younger than the age of 1 year, with two-thirds already listed for transplantation. Earlier studies established similar results.[22,23] Not surprisingly, children who did not clear their jaundice after KPE appear to be at higher risk of EV bleeding.

Earlier studies reported incidences ranging from 6.6 to 36%.[24–30] Our data showed that 24% of the children with BA developed EV bleeding at a median age of 9 months. The incidence seems comparable to earlier studies, while our cohort bled at a slightly younger age than the cohorts mentioned previously. This might be due to the relatively low clearance of jaundice rate, especially at the beginning of our series.

There was no difference in degree of liver damage at KPE between the bleeding and nonbleeding groups. One would

**Table 3** Endoscopy findings

| | Overall | No EV bleed | EV bleed | *p*-Value No bleed vs. bleed |
|---|---|---|---|---|
| Age at first endoscopy, months | 21 (5–213) | 26 (5–213) | 11 (5–45) | < **0.05** |
| Number of endoscopies | 1 (0–10) | 0 (0–5) | 3 (1–10) | < **0.01** |
| Ascites at the time of first endoscopy[a] | 12/24 | 4/12 | 8/12 | < **0.01** |
| Splenomegaly at the time of first endoscopy[a] | 18/21 | 7/10 | 11/11 | 0.14 |
| Hypertensive gastropathy at the time of first endoscopy | 10/36 | 4/18 | 6/18 | 0.46 |
| Grade of varices at first endoscopy 0/1/2/3/unknown | 8/4/10/10/4 | 8/3/5/2/0 | 0/1/5/8/4 | < **0.01** |
| Gastric varices at the time of first endoscopy | 4/36 | 1/18 | 3/18 | 0.29 |
| Cherry red spots at the time of first endoscopy | 6/36 | 1/18 | 5/18 | 0.07 |

Abbreviation: EV, esophageal varix.
[a]As seen on ultrasound within 3 months of the first endoscopy.

expect patients in the cirrhosis group to present with bleeding from varices more often due to the severity of liver disease. Our results are not in line with a study published by Duché et al in 2006.[31] They found that BA patients with elevated portal pressure at the time of KPE have lower chances of success following this procedure and run a higher risk of developing portal hypertension. On the contrary, Kang et al failed to find a correlation between histologic features of the liver biopsy at KPE, such as fibrosis and the severity of EVs.[32]

Our study compared several ultrasound findings between the bleeding and nonbleeding groups. Ascites was seen more often in the bleeding group. This is an expected result, as ascites is an expression of end-stage liver disease.

Our present data are in accordance with previous reports regarding a generally low mortality of EV bleeding in children. Nevertheless, individual fatalities after EV bleedings have been reported: 2 out of 13 children with an EV bleeding[30] and 4 out of 44 children who died while listed for LTx.[33] Desai et al found a mortality rate of 5% in BA children listed for LTx.[34] Thus, it appears that an EV bleed can certainly be fatal, and this was, however, not demonstrated by our cohort.

In our cohort, patients who would develop an EV bleed later in life presented with higher total and direct serum bilirubin levels at the time of the KPE. Lampela et al found that at 3 months after KPE, a total bilirubin serum level $>$ 40 µmol is a risk factor for bleeding from varices.[22] Miga et al found total bilirubin serum concentration $>$ 4 mg/dL (corresponding to approximately $>$ 68 µmol/L) at the time of bleeding is associated with worse outcome.[24]

In our cohort, three patients (17%) had not been assessed for LTx at the time of the first bleeding episode. All were assessed later in life. In one of these patients, EV bleeding contributed to commencing assessment for LTx. Due to the retrospective nature of our study, determining the main indication(s) for listing for LTx in individual cases was difficult. Our data suggest that patients are often already listed for LTx when subject to an EV bleed and that an EV bleed was not likely the sole indication for LTx.

The VPR is a promising novel predictor of EVs in BA patients at 6 months after KPE[15] and patients with suspected portal hypertension or gastrointestinal bleeding.[16] Our data showed a significantly lower VPR in the bleeding group. Our results suggest the VPR could be useful in identifying those patients who are at highest risk of EV bleeding, and moreover, it might allow for selective endoscopic evaluation of EVs. This should, however, be studied in larger, prospective cohorts.

As BA is a rare disease, we were only able to include 74 patients. Because of these low numbers and even lower absolute (however relatively high) number of bleeding episodes ($n = 18$), constructing a proper prediction model for EV bleeding was therefore inappropriate, as we would only be able to include one or two predictor variables.[35] We realize it is difficult to assure that a gastrointestinal bleeding after KPE is coming from EVs. We, however, aimed to construct a definition in which all EV bleeds were detected as such, based on studies previously reported.[24,36,37] Moreover, due to the 28-year study period, we cannot guarantee that the grading of varices, of gastropathy, and of gastric varices was homogeneous. These are all weaknesses of the study.

This study contributes to our knowledge on the incidence and severity of EV bleeding in BA patients. Our data show that while EV bleeds are relatively common, major complications are not. Nevertheless, despite adequate treatment, recurrent bleeds occurred in a significant number of patients. While ours was a small retrospective series, our findings do offer further data regarding the incidence and severity of EV bleeding. Given the absence of major complications as a result of EV bleeds, the lack of guidelines for prophylactic treatment for EVs, as well as the lack of sufficient clinical evidence on this subject, endoscopic screening of all patients with BA for varices, necessitating general anesthesia, is probably a bridge too far.

## Conclusion

A quarter of the children diagnosed with BA experience an EV bleeding during follow-up, a majority of these children are younger than the age of 1 year, while listed for transplantation. Major complications did not occur after EV bleeding, possibly due to rapid LTx after the first bleeding episode.

### Conflict of Interest

None.

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