Original Article

Pre-operative Serum Albumin Predicts Native Liver Survival in Biliary Atresia

Kakeru Machino, Kotaro Mimori, Seiya Ogata, Yosuke Minami, Hirofumi Shimizu, Michitoshi Yamashita, Hideaki Tanaka

Department of Pediatric Surgery, Fukushima Medical University Hospital, Fukushima, Japan

Abstract

Background: To predict native liver survival (NLS) after Kasai portoenterostomy (KP) for biliary atresia (BA) using pre-operative clinical data. **Materials and Methods:** Pre-operative data were collected from 29 patients with BA who underwent KP at our department between 1989 and 2017 and were analysed including serum albumin, bilirubin, prothrombin time-international normalised ratio, body height, body weight, age at KP, paediatric end-stage liver disease score calculated using the pre-operative data and the period of NLS. **Results:** The 10-year NLS rate of all patients was 51%. A multivariate analysis revealed that among all factors, the pre-KP serum albumin level was the only independent predictor of NLS ($P = 0.04$, hazard ratio = 0.269, 95% confidence interval = 0.077–0.934). The area under the receiver operating characteristic curve for NLS, determined using pre-KP serum albumin was 0.760 and 3.75 mg/dl was selected as the cut-off value. There was a significant difference in NLS between patients with high (≥3.8 mg/dl) and low (≤3.7 mg/dl) pre-KP serum albumin (90.0% vs. 31.5%, $P < 0.01$). **Conclusions:** Decreased pre-KP serum albumin may reflect not only functional impairment of the liver, but also the inflammatory process, which is hypothesized to occur during its advancement. The pre-KP serum albumin level may be a good prognostic factor for NLS in post-KP BA patients.

Keywords: Albumin, biliary atresia, Kasai portoenterostomy, pre-operative, survival

Introduction

There have been numerous reports regarding prognostic factors for children with biliary atresia (BA) who receive Kasai portoenterostomy (KP). The age when the patient underwent KP has been believed to highly influence the post-KP outcome.[1] However, most prognostic factors are measured post-operatively – rather than pre-operatively – such as biochemical markers that reflect the improvement of cholestasis after KP.[2] In the present study, we aimed to verify the usefulness of pre-KP serum biochemical markers for predicting native liver survival (NLS) in children with BA in our institution.

Materials And Methods

All children with BA who underwent KP at Fukushima Medical University Hospital between 1989 and 2017 were identified from our medical database. The following pre-KP variables were collected: age, body height, body weight, serum albumin, total bilirubin, prothrombin time-international normalised ratio (PT-INR), paediatric end-stage liver disease (PELD) score, age in days when KP was performed and period of NLS. The PELD score was calculated using the following equation:[3]

PELD score = 0.436 age (<1 year) − 0.687 loge albumin (g/dl) + 0.480 loge total bilirubin (mg/dl) + 1.857 loge INR + 0.667 growth failure (<2 SD).

The PELD calculator on the website of the Organ Procurement and Transplantation Network[4] was used to simplify the calculation, and the age in days when KP was performed was regarded as 'Date added to the Waiting List' on the website.

Patients who required liver transplantation or who died due to native liver failure were classified into Group F, while those who were followed in an outpatient clinic with NLS without liver transplantation were classified into Group S. The pre-KP

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Address for correspondence: Prof. Hideaki Tanaka, Department of Pediatric Surgery, Fukushima Medical University Hospital, 1 Hikarigaoka, Fukushima 960-1295, Japan. E-mail: tanaka-h@fmu.ac.jp

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clinical data were compared between Group F and Group S with the Mann–Whitney *U*-test, using IBM SPSS Statics ver. 25, Inc., Chicago, IL, USA. Factors with $P < 0.25$ in a univariate analysis were included in a Cox regression analysis to determine independent risk factors for native liver failure. The receiver operating characteristic (ROC) curve and area under the curve were calculated to investigate the reliability of the risk factors and the Youden's index was calculated to determine the optimal cut-off values to maximise both sensitivity and specificity. Survival curves for NLS were drawn for patients whose pre-KP values were more than the cut-off value and those whose were less than the cut-off value and were compared by a Kaplan–Meier analysis. A generalised Wilcoxon test was implemented to compare the survival curves of the two groups. $P < 0.05$ was considered to indicate statistical significance.

Results

Thirty-five patients were diagnosed with BA (Type 1 in 3 patients, Type 3 in 26, and unknown in 6) and underwent KP at our department between 1989 and 2017. Among these, six patients were excluded from the study due to inadequate clinical data. Groups S and F included 16 and 13 patients, with a median follow-up period of 143.7 (range 15.7–325.3) months and 8.13 (range 5.3–40.0) months, respectively. One patient in Group F who died due to liver failure at 16.1 months after KP did not undergo liver transplantation. Twelve patients underwent living donor liver transplantation at a median of 7.93 (range 5.3–40.0) months after KP. The pre-KP clinical factors in Groups S and F were compared [Table 1] and pre-KP serum levels of albumin (Group S vs. Group F: 3.90 g/dL vs. 3.49 g/dL, $P = 0.016$) and total bilirubin (8.25 mg/dL vs. 6.50 mg/dL, $P = 0.049$) were significantly higher in Group S than in Group F. A multivariate analysis to identify independent prognostic factors for NLS was performed for factors with $P < 0.25$ in a univariate analysis (pre-KP serum albumin, total bilirubin, body height and weight and PELD score). This revealed that the pre-KP albumin level was the only independent predictor of post-KP NLS (hazard ratio: 0.269, 95% confidence interval: 0.077–0.934, $P = 0.04$: Cox regression analysis). An ROC analysis using this variable to predict NLS showed that the area under the curve was 0.760 (moderate accuracy), and the optimal cut-off value of pre-KP serum albumin was 3.75 g/dL with a maximum Youden's index, sensitivity and specificity of 0.529, 0.60 and 0.93, respectively.

The patients were then divided into two groups: those with pre-KP serum albumin levels of ≤3.7 g/dL and ≥3.8 g/dL were assigned to Groups low albumin (LA) and high albumin (HA), respectively. The NLS curves of all 29 patients, Group LA and Group HA are shown in Figure 1. The 10-year NLS rates of the overall population, Group HA and Group LA were 51%, 90.0% and 31.5%, respectively, and the difference of the latter two reached statistical significance ($P < 0.01$).

Table 1: Comparison of pre-Kasai portoenterostomy clinical data (averages) between Groups S and F

Pre-KP data	Group S (*n*=16)	Group F (*n*=13)	*P*
Height (cm)	55.4	53.5	0.247
Weight (kg)	4.51	4.12	0.111
Serum albumin (g/dL)	3.90	3.49	0.016
Serum total billirubin (mg/dL)	8.25	6.50	0.049
PT-INR	1.08	1.02	0.068
Age (day)	67.8	68.1	0.348
PELD score	9.60	8.21	0.226

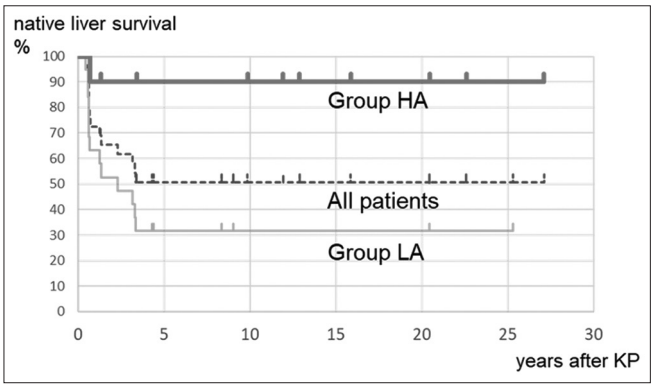


Figure 1: NLS in all the patients, Group HA and Group LA: The 10-year NLS rate in the overall population was 31.5%. The 10-year NLS rate in Group HA (90.0%) was significantly higher than that in Group LA (31.5%) ($P < 0.01$). NLS: Native liver survival, HA: High albumin, LA: Low albumin, KP: Kasai portoenterostomy

Discussion

BA is a destructive inflammatory obliterative cholangiopathy of neonates that affects both the intrahepatic and extrahepatic bile ducts to various degrees. The cause is still unknown, and some factors, including genetic, infective, inflammatory and/or toxic insult may contribute to its development.[1] The incidence rates of BA range from 0.3 to 3.7/10.000 live births.[5] If untreated, atresia of the bile ducts and progressive liver fibrosis leads to cirrhosis, liver failure and death.[1] Hepatic portoenterostomy, first described by Kasai *et al*.,[6] is a surgical procedure – especially for type 3– to uncover small biliary ductules in the fibrous tissue in the porta hepatis, which communicate with intrahepatic bile ducts and establish bile flow.[7] KP has improved the outcomes of children with BA, but their NLS is reported to range from 20.3% to 75.8% at 1–3 years and 24%–52.8% at 10 years in a systematic review.[5] Liver transplantation is often required for children with BA after KP with the indications being failure to establish bile flow, progress to liver cirrhosis, liver failure, gastrointestinal bleeding due to portal hypertension, growth retardation, pruritus, intrapulmonary shunt, hepatopulmonary syndrome and repeated cholangitis.[8]

To the best of our knowledge, this is the first study to identify the pre-KP serum albumin level as an independent risk factor

for NLS in patients with BA after KP. Our literature search revealed a few reports indicating that children with a favourable post-KP outcome tended to have higher pre-KP serum albumin levels in comparison to those with an unfavourable outcome. As early as 1975, Chiba and Kasai[9] first proposed that pre-KP serum albumin seemed to be correlated with good bile excretion after KP. A study conducted by Sun *et al*.[10] showed that the pre-KP serum albumin levels of patients who survived for more than 5 years with a normal liver function and no sign of liver cirrhosis were significantly higher in comparison to those who died from liver failure within 1 year after KP (4.08 ± 0.25 g/dL vs. 3.68 ± 0.36 g/dL, $P = 0.04$), which is similar to our finding. Azarow *et al*.[11] showed that patients in their success group (jaundice cleared after KP) tended to show higher pre-KP serum albumin levels in comparison to patients in their failure group (death or listing for transplant before 1 year of age) (3.73 g/dL vs. 3.01 g/dL), although the difference did not reach statistical significance. Rhu *et al*.[12] reported that native liver failure tended to occur more frequently in patients with pre-operative serum albumin levels of <3.7 in comparison to those with levels of ≥3.7 (76.9% vs. 49.0%), which is close to the cut-off value of pre-operative serum albumin (3.75) that predicted better NLS in our study, although their difference did not reach statistical difference. The above-mentioned data in the previous studies may support our result that high pre-KP serum albumin seems to have a positive impact on the post-KP outcome.

The causal relationship – if any – between high pre-KP serum albumin and favorable post-KP outcomes is uncertain. Serum albumin levels reflect several aspects of general conditions of the patients, including not only the synthetic capacities of the liver, but also malnutrition and loss through enteropathy or proteinuria.[13] Considering that pre-KP INR levels were maintained in our both groups, derangement of the liver synthetic capacity was not the cause of the hypoalbuminemia in our study. The contribution of malnutrition and loss of albumin through enteropathy or proteinuria to hypoalbuminemia was not clear because we could not collect data on these conditions.

Soeters *et al*.[14] recently reviewed the pathogenesis of hypoalbuminemia and the association between hypoalbuminemia and inflammation and reported that inflammation increases capillary permeability and the escape of serum albumin, increasing the distribution volume of albumin. The half-life of albumin has been shown to be shorter in an inflammatory state. Thus, low serum albumin levels seem to be an indication of the severity of inflammation.[14] On the other hand, lymphocyte-mediated biliary inflammation seems to be the most likely mechanism of BA development through which bile duct damage occurs; however, the trigger for this response remains unknown.[1] Various signs of inflammatory reactions have been detected within the liver (periductal infiltration of mononuclear cells, the amplified expression of human leukocyte antigen-DR on the vascular and biliary epithelium, the expression of various intracellular adhesion molecules [e.g., ICAM1 and E selectin]), and in the circulation (increased soluble inflammatory adhesion molecules and cytokines [e.g., interleukin 2, interleukin 18 and tumour necrosis factor α]).[1] Although decreased albumin synthesis in the liver may partly contribute to lowering the serum albumin level in children while the disease process of BA progresses, our hypothesis is that the level of serum albumin declines as the inflammatory process of BA advances; KP may need to be performed and biliary drainage should be restored, while serum albumin level is maintained above a certain level, below which KP is likely to be unsuccessful (the cut-off level was estimated to be 3.75 mg/dl in our study). Serial measurement of serum albumin during the disease process of BA, for example, in cases in which BA is suspected in the perinatal period, should be accumulated and analysed to confirm our hypothesis.

The PELD score is calculated using several objective values (age, growth failure [based on sex, height and weight], albumin, international normalisation ratio and total bilirubin). In the United States, the PELD score has been shown to predict the death of children awaiting liver transplantation and has been used for allocation of liver grafts since 2002.[3] Although several studies – with conflicting results – have investigated whether the PELD score could predict the outcomes after paediatric liver transplantation for BA,[15-17] the PELD score may help optimise the timing of liver transplantation. Cowles *et al*. suggested that a score approaching 10 should trigger discussion about liver transplantation.[18] Rhu *et al*.[12] focused on the pre-KP PELD score as a possible prognostic factor of BA and reported that a PELD score of ≥15 and age at KP ≥60 were significant risk factors for native liver failure. We also analysed these factors, but they did not have the same impact as in their study. The reason for these discrepancies between their study and our own is not clear. In our study, the mean PELD scores in Groups S (NLS) and F (native liver failure) were 9.60 and 8.21, respectively, while those in the study of Rhu *et al.*[12] were 9.4 and 14.9. In our study, the mean age at KP of Groups S and F was 67.8 days and 68.1 days, respectively, while that in the overall population of the study of Rhu *et al.*[12] was 75. Therefore, our patients seemed to undergo KP relatively earlier with less disease progression of BA in comparison to their study, which may explain the relatively better 10-year native-liver survival in our study (50.8% vs. 41.9%). It should be noted again that in their study, native liver failure tended to occur more frequently in patients with pre-operative serum albumin levels of <3.7 in comparison to those with levels of ≥3.7, which is similar to the cut-off value of our study.

Our study was associated with several limitations. This was a retrospective single-institutional study with a relatively small study population. The pre-operative managements of BA patients, including enteral and parenteral nutrition, had not been standardised in this study, which may have influenced the hepatic synthetic capacity for albumin. Prospective, multi-centre studies with unified pre-operative management are deemed necessary to investigate the pre-operative prognostic factors associated with improved NLS after KP.

Conclusion

The pre-KP serum albumin level may be a good prognostic factor for NLS in post-KP BA patients. Decreased pre-KP serum albumin may reflect not only functional impairment of the liver at diagnosis, but also the inflammatory process, which is hypothesized to occur during the advancement of the disease process of BA.

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Conflicts of interest

There are no conflicts of interest.

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